

Substance P at the Nexus of Mind and Body in Chronic Inflammation and Affective Disorders

Melissa A. Rosenkranz
University of Wisconsin—Madison

For decades, research has demonstrated that chronic diseases characterized by dysregulation of inflammation are particularly susceptible to exacerbation by stress and emotion. Likewise, rates of depression and anxiety are overrepresented in individuals suffering from chronic inflammatory disease. In recent years, substance P has been implicated in both the pathophysiology of inflammatory disease and the pathophysiology of depression and anxiety by 2 parallel fields of study. This review integrates the literature from these 2 parallel fields and examines the possibility that substance P dysregulation may be a point of convergence underlying the overlap of chronic inflammatory disease and mood and anxiety disorders. First, the involvement of substance P in peripheral inflammation and in the immune events associated with chronic inflammatory disease is discussed, with a focus on inflammatory bowel disease and asthma. Next, the function of substance P in the communication of peripheral inflammation to the brain is considered. Finally, to complete the bidirectional loop of brain–immune interactions, substance P expression in anxiety and depression as well as its potential role in the neural regulation of peripheral inflammation is reviewed.

Keywords: substance P, inflammation, stress, mood and anxiety disorders, chronic inflammatory disease

For over a hundred years, scientists have documented that chronic diseases characterized by impaired regulation of inflammation are particularly susceptible to aggravation by stress and emotion. The distillation of this body of work supports the hypothesis that bidirectional communication exists between the brain and body, through which stress and emotion promote inflammation and vice versa. Substance P (SP), a neuropeptide involved in inflammation and in signaling noxious stimulation to the brain, is one factor that plays an important role in mediating this bidirectional pathway but has been largely neglected in human psychoneuroimmunology. The ability of SP to perpetuate inflammation in diseased tissues and to evoke negative mood, fear-, and anxiety-like responses when acting in the brain makes it an interesting target of study when examining the intersection of populations with chronic inflammatory disease and affective disorders. This intersection is evident in the overrepresentation of anxiety and depression¹ in individuals with inflammatory disease. Moreover, the consequences of chronic SP signaling in the brain and in the periphery—signal amplification and a decrease in neuronal response threshold—suggest a possible mechanism for the chronicity and coincidence of these conditions.

Inflammation is an intrinsic part of the body's response to a stressor, whether it is physical or psychological in nature. Indeed,

some have suggested that the bidirectional brain–immune pathways through which the brain carries out what we typically think of as a stress response—fight or flight—evolved first in the service of behavioral and physiological adaptations (e.g., inflammation, fever, lethargy, anorexia) necessary for optimal defense against immune insults (e.g., Black, 2002; Maier & Watkins, 1998). In this respect, the immune system has been likened to a sense organ (Blalock & Smith, 2007) through which the brain can monitor (and respond to) internal threats, just as the eyes and ears scan the external environment for physical danger. It likely was not until later in evolutionary development that these pathways were also employed for the physiological changes necessary to escape or defend against predation and attack. As a result, the immune consequences of activation of stress-related neural circuitry are essentially the same regardless of whether the source of stress is internal or external, psychological or physical. From this perspective it seems clear why stress prevalence and immune function are so interrelated and why balanced regulation in this bidirectional pathway is important.

Neural regulation of immune function, particularly inflammation, in barrier tissues is especially important. Barrier tissues are tissues that interface between the external and internal environments, such as the skin and the gastrointestinal, respiratory, and urogenital tracts. These tissues are the first line of defense against invading pathogens, and the inflammatory response is one of the primary means of resisting infection once a pathogen has circumvented the physical barrier. The susceptibility of these tissues to

Much gratitude goes to my mentor, Richard J. Davidson, for his guidance and unflagging support. Many thanks also to Craig W. Berridge, Margaret Kemeny, Simone Kern, and Brendon Nacewicz for their time, valuable input, and encouragement.

Correspondence concerning this article should be addressed to Melissa A. Rosenkranz, University of Wisconsin—Madison, Department of Psychology, Waisman Laboratory for Brain Imaging and Behavior, A130 Waisman Center, 1500 Highland Avenue, Madison, WI 53705. E-mail: marosenk@wisc.edu

¹ Though there may be important differences in the involvement of SP in the pathophysiology of depression and anxiety, in this review, they will largely be lumped together due to very high comorbidity and overlap in pharmacological treatment.

stress- and emotion-related modulation makes sense in this light, since, evolutionarily speaking, stress represents an increased likelihood for bodily injury and pathogenic exposure. Thus, although SP has been implicated in many stress-related chronic inflammatory diseases such as arthritis and fibromyalgia (reviewed in Lucas, Brauch, Settas, & Theoharides, 2006; and O'Conner et al., 2004), it seems to be most relevant in diseases where inflammation is dysregulated in barrier tissues. Inflammatory bowel disease (IBD) and asthma are of particular interest. The gastrointestinal and respiratory tracts have two of the largest exposed surface areas in the human body, making them considerably vulnerable to pathogenic damage. Both areas have dense sensory innervation and high levels of SP expression, allowing for a quick response to pathogen exposure, a robust signal to the CNS, and intimate neural regulation. Though advantageous in some regards, these characteristics may also increase the vulnerability of these regions to inflammatory dysregulation. As a result, the gut and airways have received considerable attention as sites of stress-related inflammation and will be the focus of the discussion concerning chronic inflammatory disease in the following review.

SP and its primary binding site, the neurokinin-1 receptor (NK-1r), are widely distributed throughout the brain and body, with some of the highest concentrations in the gut and airways (Otsuka & Yoshioka, 1993). In the brain, some of the densest regions of SP and NK-1r expression include those involved in processing and responding to stressful and emotional information, including the amygdala and prefrontal cortex (Hayashi & Oshima, 1986). Under normal circumstances, release of SP in the brain and body typically follows noxious stimulation, such as painful heat, ingestion of bacteria, inhalation of an irritant, or psychological stress (Otsuka & Yoshioka, 1993). The consequences of its release vary greatly but generally function to signal a negative event and neutralize or eliminate the offending stimulus. For example, SP release triggers inflammation—one of the body's most primitive and immediate means of "walling off" an offending agent (Harrison & Geppetti, 2001). In addition to inflammation, SP stimulates evacuation in the gastrointestinal tract to flush out the source of noxious stimulation (Cooke, Sidhu, Fox, Wang, & Zimmermann, 1997; Greenwood et al., 1990; Holzer & Holzer-Petsche, 2001). Similarly, in the airways, SP release causes an expulsive and protective response involving mucus production and a decrease in breathing depth (Baraniuk, Ali, Yuta, Fang, & Naranch, 1999; Carr & Udem, 2001; Sertl et al., 1988; Solway & Leff, 1991). It is important to note that these are normal, protective responses. Disease states, such as those in IBD and asthma, can arise when these very same processes occur inappropriately.

When noxious stimulation occurs in the periphery, the central nervous system (CNS) is alerted via SP release from sensory nerves in the spinal cord and brain stem (Kuraishi et al., 1989). This signal is then propagated to brain regions that process the information and coordinate a response, such as the amygdala (Konsman, Luheshi, Bluthé, & Dantzer, 2000). When noxious stimulation is psychological, SP is released in these same brain regions (e.g., Boyce et al., 2001; Brodin, Rosen, Schott, & Brodin, 1994; Ebner, Rupniak, Saria, & Singewald, 2004). This leads to both biochemical and behavioral changes that, like inflammation, function to isolate or neutralize the offending stimulus (e.g., Gregg & Siegel, 2001; Han, Shaikh, & Siegel, 1996; Shaikh, Steinberg, & Siegel, 1993).

It is widely accepted that stress and negative emotion are associated with flare ups in many chronic inflammatory diseases, including IBD (e.g., Solmaz, Kavuk, & Sayar, 2003) and asthma (e.g., Lehrer, Isenberg, & Hochron, 1993). Conversely, inflammation in the periphery results in mood and behavioral patterns similar to those observed in anxiety and depression, which may be reflected in the increased rates of mood and anxiety disorders in these conditions (e.g., Lydiard, 2001; Mrazek, 2003). Combined with what we know about the effects of SP release in the brain (see *Emotion, Stress, and Diseases of Chronic Inflammation: SP Evokes Anxiety- and Fear-Like Responses*), this suggests that inflammation-related events, including increases in SP neurotransmission, carry negative emotional salience. This, in turn, results in similar neural, biochemical, and behavioral consequences as those of psychological stress, including symptoms of anxiety and depression in some cases, when inflammation is chronic. In fact, SP expression is elevated in the cerebral spinal fluid (CSF) of at least a portion of depressed and anxious individuals, and increased release has been associated with expression of depressive and anxious symptoms (Geraciotti et al., 2006; Lieb et al., 2002; Rimón et al., 1984). Further, NK-1r antagonists have shown antidepressant efficacy commensurate with that of modern conventional antidepressant drugs (e.g., Kramer et al., 2004). Although not significant in all studies (Herpfer & Lieb, 2005; McLean, 2005; Rupniak & Kramer, 1999; see below for further discussion), these latter observations suggest that chronic inflammatory diseases and mood and anxiety disorders may share a common underlying pathology—SP dysregulation—in at least a subset of individuals. The importance of SP in chronic inflammation and depression was initially proposed and was extensively developed by Paul H. Black in 2002. This review will examine and extend the current evidence for this hypothesis through a discussion of the roles of SP in the brain and periphery. The consequences of its dysregulation will be discussed in the context of two chronic inflammatory diseases that are highly susceptible to stress and emotion—asthma and IBD.

SP is just one of many molecular mediators and factors that contribute to the relationship between inflammation, brain activity, and emotion. For example, pro-inflammatory cytokines (chemical signals of the immune system) have been shown to activate neural stress response circuitry and evoke symptoms of depression (Capuron et al., 2003; Dunn, Wang, & Ando, 1999). Likewise, immune cells in the periphery produce, release, and express receptors for multiple neurotransmitters and neuropeptides in addition to SP, such as adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH), and endorphin (reviewed in Blalock & Smith, 2007). Thus, the mediators involved in the inflammatory response are numerous, interdependent, and highly redundant. However, given the relative youth of the field, it seems essential to initially focus on identification of the individual components involved in periphery–brain interactions as they relate to inflammation and affective state. Because the roles of other inflammatory mediators in emotion have been extensively reviewed elsewhere (e.g., Anisman, Merali, Poulter, & Hayley, 2005; Dantzer & Kelley, 2007; Schiepers, Wichers, & Maes, 2005), and because the role of SP in linking chronic inflammatory disease and psychopathology may be distinct, this is the primary focus of this review. A comprehensive review of other contributors to the relationship between inflammation and emotion, such as pro-inflammatory

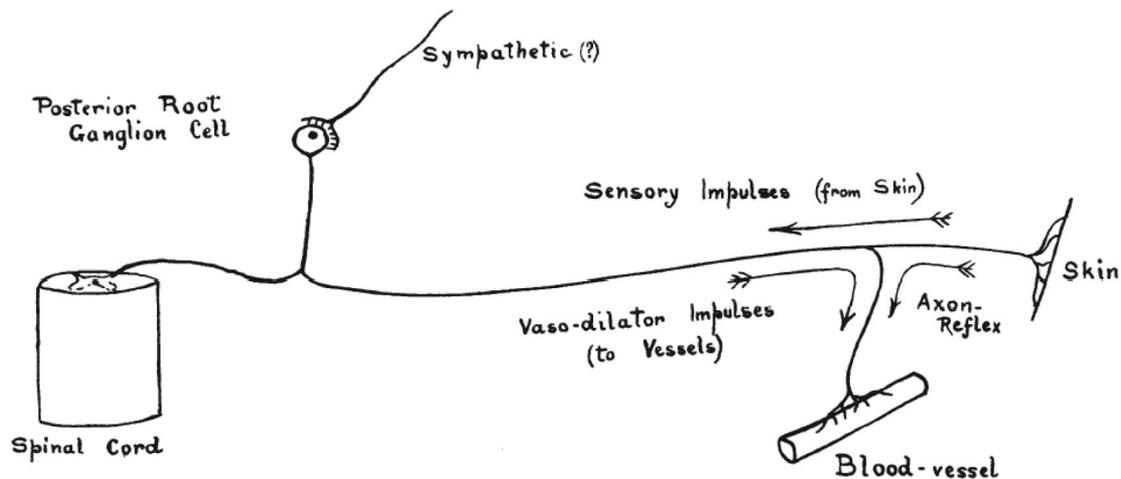


Figure 1. A graphic illustration of antidromic stimulation of nerve terminals. Antidromic stimulation occurs when an impulse is carried by a nerve fiber in the direction reverse of what is normal for that fiber. For example, when stimulation of a sensory nerve at its central terminal results in vasodilation at its peripheral terminal, the signal is said to be antidromic. From A. N. Bruce, "Vaso-Dilator Axon-Reflexes," *Experimental Physiology*, 6, p. 352. Copyright 1913, The Physiological Society. Reprinted with permission from Blackwell Publishing.

cytokines, can be found elsewhere, and citations in the current article point interested readers to sources for more information.

The Basics of SP

SP is an 11 amino acid neuropeptide belonging to the tachykinin family of neuropeptides (Harrison & Geppetti, 2001). Tachykinins are derived from the preprotachykinin-A gene (Carter & Krause, 1990; Harrison & Geppetti, 2001; Pennfather et al., 2004). SP exerts its actions predominantly via the NK-1r, but can also bind to neurokinin-2 (NK-2) and neurokinin-3 (NK-3) receptors with lower affinity. Activation of an NK-1r leads to rapid internalization of the peptide-receptor complex, followed by recycling of the receptor and its return to the cell surface within 30 minutes (Mantyh et al., 1995; Southwell, Woodman, Murphy, Royal, & Furness, 1996). Both SP and NK-1r are distributed widely throughout the brain and body of many species, and together they compose one of the most substantial neuropeptide systems in the central and peripheral nervous systems (Patacchini & Maggi, 2001; Pernow, 1981; Severini, Improta, Falconieri-Erspamer, Salvadori, & Erspamer, 2002). In the periphery, SP is found predominantly in the end terminals of capsaicin-sensitive² primary afferent nerves (Mazzone, 2004). The cell bodies of these afferent nerves can be found in various ganglia (groups of nerve cells). Their central projections synapse in the spinal cord or brain stem nuclei, and peripheral projections innervate most tissues and physiological systems of the body (Pernow, 1981). When these neurons are activated, they release SP both centrally, into the spinal cord and brain stem, and peripherally, into organs and other areas of somatic innervation (Lecci, Giuliani, Tramontana, Carini, & Maggi, 2000; Pernow, 1981). The peripheral release of SP occurs as a consequence of *antidromic stimulation*, which is when a nerve impulse travels in a direction contrary to its fiber type (i.e., an impulse travels toward the periphery via an afferent nerve; see Figure 1; Baluk, 1997; Otsuka & Yoshioka, 1993; Pernow, 1981).

Though the major source of SP in the periphery is primary afferent neurons, it is also synthesized in and released from nonneuronal cell types, including several types of immune cells (e.g., granulocytes, monocytes, and activated lymphocytes; De Giorgio, Tazzari, Barbara, Stanghellini, & Corinaldesi, 1998; Lai, Douglas, & Ho, 1998).

Conditions and Consequences of SP Release

Release of SP typically follows exposure to noxious stimuli under normal circumstances. Indeed, it is considered essential in the transmission of pain to the CNS (Ueda, 1999). A wide range of stimuli is capable of eliciting SP activity. In the airways, its release is stimulated by inhalation of allergens and irritants, such as cigarette smoke (nicotine), acidic substances, and cold air (Patacchini & Maggi, 2001; Solway & Leff, 1991). In the gastrointestinal tract, endogenous stimulation from distention or pressure, stomach acidification, and excitation of the vagus nerve trigger its release (reviewed in Holzer & Holzer-Petsche, 1997a; Lecci et al., 2000). Likewise, noxious psychological stimulation, such as immobilization stress or social isolation, results in release of SP in the brain (Brodin et al., 1994; Ebner et al., 2004; Kramer et al., 1998).

Generally speaking, the consequences of activating NK-1rs, the preferential binding site for SP, are consistent with its proposed role in protecting local tissues from the source of noxious stimulation and alerting the CNS of the encounter. As with the stimuli that evoke SP release, the effects of NK-1r binding range widely from smooth muscle contraction to recruitment and activation of immune cells, depending on where the receptor is located (Gerard, Bao, Xiao-Ping, & Gerard, 1993; Maggi, 1995; Pernow, 1981; van

² *Capsaicin* is the naturally occurring chemical in hot peppers that imparts the "hotness" and has been used to classify this type of sensory afferent fiber. It is a potent activator of these fibers and evokes SP release.

Hagen et al., 1999). The development of NK-1r agonists, antagonists, and knockout models has dramatically increased our understanding of the role of SP as it functions in many physiological systems. There are now NK-1r-specific peptide and nonpeptide agonists and antagonists, which allow the determination of both peripheral and central effects of NK-1r activation. These effects are described in more detail below.

Regulation is a crucial component of any discussion regarding the role of an endogenous biomolecule. SP activity is regulated, in large part, through the enzymatic inactivation processes of neutral endopeptidase (NEP) and angiotensin-converting enzyme. Angiotensin-converting enzyme inhibitors and NEP inhibitors and knockout models have been illustrative in defining the functional significance of SP throughout the brain and body. For example, NEP knockout mice display many of the symptoms observed in diseases of dysregulated inflammation, including increased levels of plasma leaking from blood vessels into the tissues of the gut (IBD) and airways (asthma; Lu et al., 1997; Solway & Leff, 1991).

Synergy Between the Immune System and SP

Although SP-containing primary afferent nerves innervate most tissues and physiological systems of the body (Mazzone, 2004), discussion of the distribution of SP and NK-1r in the periphery will be mostly limited to the regions relevant to IBD and asthma—the gut and the airways, respectively. However, the implication of SP in chronic inflammatory disease is partially seated in its interaction with the immune system, which is synergistic in nature (see below). Therefore, SP expression in and its interaction with the immune system will be addressed first.

Typically, inflammation occurs when immune cells recognize something as foreign to the organism or “nonself” (e.g., an invading virus or bacteria). The inflammatory response that occurs following this type of recognition is called *immunogenic*. Inflammation can also be *neurogenic*, meaning that it is triggered by the release of mediators (e.g., neuropeptides like SP) from nerve endings. In the immune system, SP-containing primary afferents innervate the blood vessels and follicles of the primary and secondary immune organs, including the thymus, spleen, lymph nodes, and bone marrow (Bellinger et al., 1990; Goto & Tanaka, 2002; Imai, Tokunaga, Maeda, Kikkawa, & Hukuda, 1997; Jurjus, More, & Walsh, 1998; Lorton, Bellinger, Felten, & Felten, 1990). During both immunogenic and neurogenic inflammation, blood vessels dilate to allow more blood to flow into the area. At the same time, blood vessels become “leaky,” allowing plasma to accumulate in tissue, which causes swelling. Immune cells (e.g., neutrophils) migrate to the area and move from the blood into tissue (extravasation), where they engulf invading pathogens (phagocytosis) and release mediators that attract (chemotaxis) and activate other immune cells (e.g., macrophages, eosinophils). These immune cells further promote inflammation through their release of proinflammatory cytokines, which amplify the aforementioned processes and facilitate the movement of immune cells into tissue (Goldsby, Kindt, & Osborne, 2000).

The coordination of the inflammatory response involves a complex milieu of cytokines and other proteins that varies temporally and by stimulus type. SP interacts intimately with this cast of characters. Several classes of immune cells, such as macrophages and activated lymphocytes, synthesize and release SP and express

NK-1rs (De Giorgio et al., 1998; Lai et al., 1998). SP binding to NK-1rs on immune cells can contribute to and amplify most of the inflammatory processes described above (see Figure 2). Macrophage and lymphocyte activation, for instance, up-regulates self-expression of SP and NK-1r (Bost, Breeding, & Pascual, 1992; De Giorgio et al., 1998; Saria, 1999). Release of pro-inflammatory cytokines from activated macrophages causes expression of SP and NK-1r in cells where they were previously absent (Goode et al., 2003) as well as release of SP from nerve terminals (Inoue et al., 1999; Perretti, Ahluwalia, Flower, & Manzini, 1993). Release of SP enhances immune cell activation (Marriott & Bost, 2001) and recruitment (Feistritzer et al., 2003), leading to further release of pro-inflammatory cytokines (Berman, Chancellor-Freeland, Zhu, & Black, 1996; Lotz, Vaughan, & Carson, 1988) and amplification of the inflammatory response. Conversely, a lack of SP release in response to pathogen exposure causes a suppression of macrophage pro-inflammatory cytokine synthesis and release as well as a suppression of the response of neutrophils to pro-inflammatory cytokines (Ahluwalia, De Felipe, O'Brien, Hunt, & Perretti, 1998; C. Dickerson, Udem, Bullock, & Winchurch, 1998). This suggests that SP is necessary for the macrophage to mount a full defense against the pathogen. The synthesis and release of SP in activated macrophages, in combination with the expression and up-regulation of NK-1r suggests *autocrine stimulation* (Bost et al., 1992). Autocrine stimulation is a process by

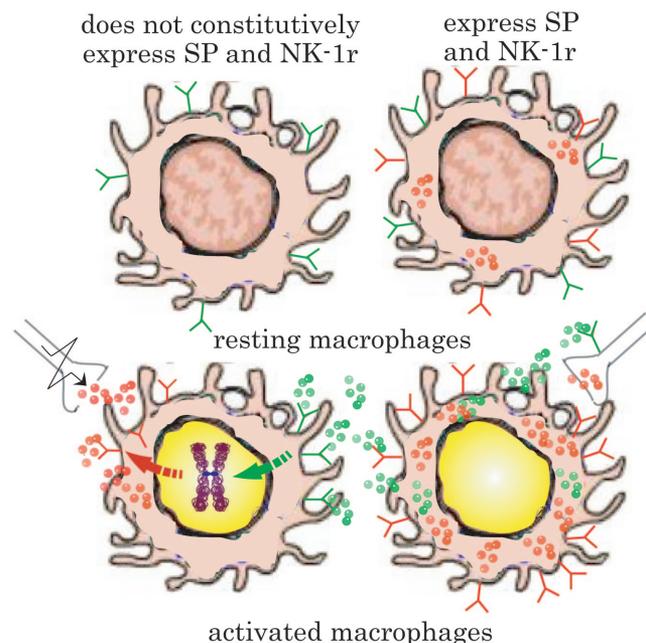


Figure 2. As shown in the top two macrophages: Some macrophages constitutively express substance P (SP) and neurokinin-1 receptors (NK-1r; right) and some do not (left). When activated, macrophages that express SP constitutively (bottom right) up-regulate self-expression of SP and NK-1r (in red). Activated macrophages also release pro-inflammatory cytokines (green), which cause expression of SP and NK-1r in cells where they were previously absent (bottom left). Activation of pro-inflammatory cytokine receptors on nerve terminals also stimulates their release of SP (bottom right). This interaction illustrates one way in which substance P synergizes with the immune system and may perpetuate chronic inflammation.

which a cell is stimulated by a substance it releases when it binds to a receptor on its own surface. Through the interaction of SP and immune cells, therefore, amplification of inflammatory processes can ensue in the absence of further injury or pathogenic exposure. Moreover, SP stimulates the production of new immune cells in bone marrow (Imai et al., 1997) and may influence the lineage direction of stem cells, with a bias toward those that will go on to participate in an ensuing inflammatory response (Maggi, 1997; Rameshwar & Gascón, 1995).

The role of SP in mounting a full inflammatory response is not limited to the regulation of macrophages (Chavolla-Calderón, Bayer, & Fontán, 2003; Perretti et al., 1993). Chavallo-Calderón and colleagues (2003) elegantly demonstrated the requirement for both primary afferent and nonneuronal (originating from bone marrow) cell sources of SP for the manifestation of inflammatory damage in the lungs. In this study, mice lacking the gene that encodes SP (preprotachykinin A) and wild-type mice were irradiated, and their bone marrow was reconstituted with cells from either knockout or wild-type mice. They were subsequently subjected to lung injury. Wild-type mice reconstituted with wild-type cells suffered severe pulmonary inflammation resulting from lung injury, whereas wild-type mice reconstituted with cells from SP knockout mice (i.e., devoid of nonneuronal SP but primary afferent intact) received the same protection from inflammation that their knockout counterparts received. Likewise, the knockout mice whose bone marrows were reconstituted with wild-type cells (i.e., devoid of neuronal SP but nonneuronal capacity restored) were also protected from excessive inflammation. Similarly, symptoms of experimentally induced arthritis in animal models can be blocked by site-specific afferent C-fiber degeneration, thus eliminating neuronal input (Cruwys, Garrett, & Kidd, 1995; Lorton et al., 2000). These studies highlight the potential importance of SP in the pathophysiology of many diseases characterized by chronic or dysregulated inflammation, through its participation in both immunogenic and neurogenic inflammation.

Mast cells, part of the innate immune system, play an integral part in the relationship between SP and inflammation, especially when inflammation is chronic (reviewed in Marshall & Wasserman, 1995). They can be found in many different tissues throughout the body and contain histamine, a potent mediator of inflammation. Histamine is the primary factor in the development of allergies and hypersensitivities (Bachert, 1998). Mast cell degranulation (release of its contents) can stimulate resident neurons in the periphery, which in turn release SP (McKay & Bienenstock, 1994). SP, in turn, can cause further mast cell degranulation. There is some debate as to whether local SP can degranulate mast cells in normal, healthy tissue (Janiszewski, Bienenstock, & Blennerhassett, 2003). However, it is clear that in chronically inflamed or atopic tissue, SP evokes release of histamine from mast cells via a receptor-independent process³ (Järvikallio, Harvima, & Naukkarinen, 2003; Lorenz et al., 1998; Raithel, Schneider, & Hahn, 1999). Further, larger numbers of mast cells and increased levels of histamine are present in the afflicted compartment in chronic inflammatory disease: for example, colon (He, 2004), lung (Sun et al., 1998), and joint (Woolley & Tetlow, 2000). Thus, the interaction between SP and mast cells displays the same synergy discussed above and likely contributes to the ongoing inflammation observed in chronic inflammatory diseases.

Distribution of SP and NK-1r

Expression of SP and its receptor, as well as its effects on target cells, are exaggerated in several inflammatory diseases such as rheumatoid arthritis (Keeble & Brain, 2004; Lambert et al., 1998; Westermark, Rantapää-Dahlqvist, Wållberg-Jonsson, Kjöll, & Forsgren, 2001) and atopic dermatitis (Katsuno et al., 2003; Kim, Park, Chung, & Choi, 2003). However, as mentioned earlier, discussion here will be limited to SP activity in the brain, as well as in IBD and asthma, which affect systems with some of the highest constitutive levels of SP in the periphery.

Gastrointestinal system. The major site of SP innervation in the periphery is the gut—the site where SP was first discovered. Within the gut, the primary source for SP is the enteric nervous system (Costa, Brookes, & Henning, 2000; Furness, 2000; Holzer & Holzer-Petsche, 1997a). The enteric nervous system is a network of neurons located in the wall of the digestive tract that rivals the complexity of the spinal cord and secretes a number of different neurotransmitters and neuropeptides to control digestive tract activity. Neurons of the enteric nervous system supply the majority of SP to the gastrointestinal tract (Costa et al., 2000; Lecci et al., 2000; Rettenbacher & Reubi, 2001; Severini et al., 2002). In addition to these intrinsic gut neurons, SP-immunoreactive primary afferent fibers (originating outside the gastrointestinal tract) supply blood vessels of the intestinal wall and connective tissue (Holzer & Holzer-Petsche, 1997a). Not all of the SP found in the gastrointestinal tract comes from neuronal sources, however. Epithelial, endocrine, and immune cells of the intestinal mucus lining also synthesize and release SP (Severini et al., 2002; Simon, Portalier, Chamoin, & Ternaux, 1992). These nonneuronal sources may be important in the perpetuation of inflammation in IBD, in which SP immunoreactivity is increased (Mazumdar & Das, 1992; Mimoda, Kitamura, Hondo, & Yamada, 1998; Simon et al., 1992).

NK-1r-mediated activity plays an important role in protecting the gut from damage by noxious stimuli. As such, NK-1rs are activated in circumstances ranging from pathogenic exposure and intestinal pressure to changes in stomach pH (reviewed in Holzer & Holzer-Petsche, 1997a; Lecci et al., 2000). NK-1r-specific antagonists have been instrumental in understanding the protective role of the NK-1r in the gastrointestinal tract, showing, for example, that NK-1r blockade inhibits contractile activity of smooth muscle and prevents the inflammatory and fluid secretion effects caused by bacterial infection (Pothoulakis et al., 1994; Venkova, Sutkowski-Markmann, & Greenwood-Van Meerveld, 2002). Though the role of the SP–NK-1r system is typically discussed in the context of a threat, when the gut is insult free these receptors modulate normal gastrointestinal processes, including blood flow, peristalsis, fluid secretion, and secretory reflexes (Cooke et al., 1997; Greenwood et al., 1990; Holzer & Holzer-Petsche, 2001). The widespread action of SP in the gut is reflected in the number of different types of cells to which it can bind. NK-1r expression is observed on cells of the smooth muscle and blood vessels throughout the gut, neurons of the enteric nervous system, mucosal (mucus membrane) cells, and on endothelial cells of the small intestine (Cooke et al., 1997; Goode et al., 2000; Rettenbacher &

³ A receptor-independent process, in this case, involves direct interaction of the peptide with signaling proteins (G-protein α -subunit).

Reubi, 2001; V. C. Smith, Sagot, Wong, & Buchan, 2000). Localization of NK-1r and its messenger RNA (mRNA) to phagocytic immune cells located in diverse gut tissues, together with the anti-inflammatory effects of NK-1r antagonists, provide evidence of immunomodulation by SP in the intestines (Berman et al., 1996; Cutrufo et al., 1999; Goode et al., 2000; Pothoulakis et al., 1994). This is discussed in more detail below.

Respiratory tract. The respiratory tract is another major peripheral site of SP synthesis and release (Lecci et al., 2000). Here, SP containing sensory fibers have been identified in the smooth muscle layers of the bronchi and trachea, airway epithelium, and larynx (Kraneveld & Nijkamp, 2001; Mazzone, 2004; Tseng, Tsao, Ko, & Huang, 2001). SP-immunoreactive nerve fibers have also been shown to surround blood vessels of the lower airways (Martling, Matran, Alving, Hökfelt, & Lundberg, 1990). The cell bodies for these sensory fibers reside in several different ganglia (Solway & Leff, 1991). Like the intrinsic neurons of enteric nervous system, the airways contain resident neurons, which are located in the bronchial ganglion and provide a local, constitutive source of SP (Dey, Altemus, & Michalkiewicz, 1991; Pérez Fontán et al., 2000). In addition, inflammatory immune cells in the airway release SP, with levels of SP and its precursor preprotachykinin-A mRNA expressed at higher levels in asthmatic patients (Chu, Kraft, Krause, Rex, & Martin, 2000; Germonpre et al., 1999).

As in the gastrointestinal tract, SP release in the respiratory system is widespread and results in physiological changes, mediated by NK-1r, that protect the airways from harmful irritants. NK-1r has been observed in both the upper and lower airways of humans and other species with the use of several different methods (e.g., immunohistochemistry, Mapp et al., 2000; in situ hybridization, Shirasaki, Asakura, Narita, & Kataura, 1998, and Mapp et al., 2000; autoradiography, Sertl et al., 1988; Castairs & Barnes, 1986, and Walsh et al., 1994). Activation of NK-1r in the airways has been shown to cause a variety of effects that are protective but, when exaggerated, can lead to airway obstruction (reviewed in Joos, De Swert, Schelfhout, & Pauwels, 2003). These effects include increases in vascular dilation and permeability, extravasation (Sertl et al., 1988), mucus exudation in the trachea and bronchi, recruitment and stimulation of inflammatory cells in the airways, sneezing, and changes in the depth and rhythm of breathing (Baraniuk et al., 1999; Carr & Udem, 2001; Sertl et al., 1988; Solway & Leff, 1991). In addition, NK-1r agonists and antagonists have been shown to exacerbate and inhibit these responses, respectively (Advenier, Lagente, & Boichot, 1997; Phillips, Hey, & Corboz, 2003; van der Kleij, Kraneveld, et al., 2003).

CNS. Though SP and NK-1r are widely distributed throughout the CNS (see Figure 3), their distribution is only briefly summarized here, where brain regions involved in processing or respond-

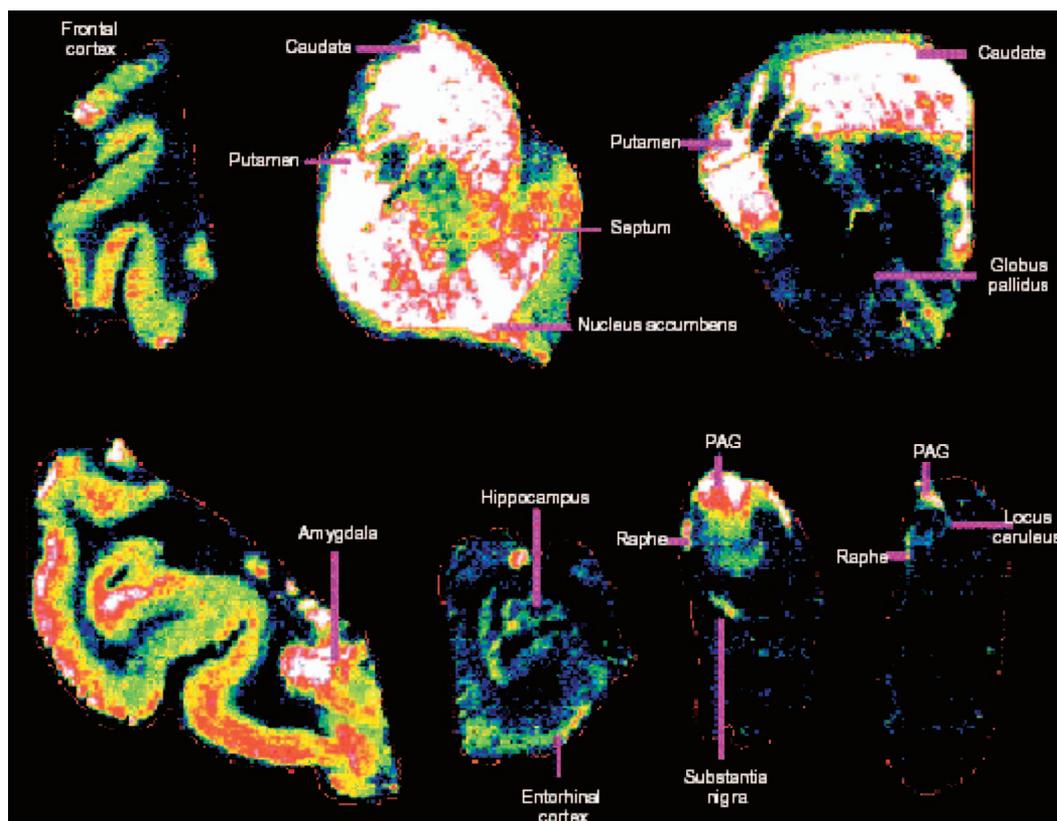


Figure 3. Distribution of neurokinin-1 (NK-1) receptors in the human brain, as determined by autoradiographic studies using [125 I]substance P. PAG = periaqueductal gray. From R. Hargreaves, "Imaging Substance P Receptors (NK-1) in the Living Human Brain Using Positron Emission Tomography," *The Journal of Clinical Psychiatry*, 63, p. 20, 2002. Copyright 2004, Physicians Postgraduate Press. Reprinted by permission.

ing to stressors will be the focus. A more detailed description is provided by Shults, Quirion, Chronwall, Chase, and O'Donohue (1984) and others (Ribeiro-da-Silva & Hökfelt, 2000), who have extensively mapped the distribution of SP and its receptor in the rat CNS, monkey CNS (Hayashi & Oshima, 1986; Nagano et al., 2005), and human CNS (Cooper, Fernstrom, Rorstad, Leeman, & Martin, 1981). Among the brain regions with the highest concentrations are the medial and central amygdalar nuclei (D. W. Smith et al., 1999). These nuclei are of particular importance because of their prominent role in mediating the expression of threat- and anxiety-related behaviors as well as the associated biochemical changes (Davis & Whalen, 2001; Kalin, Shelton, & Davidson, 2004). In addition, several other regions show prominent SP expression, representing both fibers and cell bodies, that include the striatum, bed nucleus of the stria terminalis, hypothalamus (especially preoptic regions), substantia nigra, nucleus of the solitary tract (NTS), diagonal band, lateral septal nucleus (especially rich in SP cell bodies), and the dorsal horn of the spinal cord.

Autoradiography (Dam & Quirion, 1986; Shults et al., 1984; Wolf, Moody, Quirion, & O'Donohue, 1985), immunohistochemistry (Nakaya, Kaneko, Shigemoto, Nakanishi, & Mizuno, 1994; Shigemoto et al., 1993), in situ hybridization (Maeno, Kiyama, & Tohyama, 1993; Otsuka & Yoshioka, 1993), and, more recently, positron emission tomography (PET; Hargreaves, 2002) have been used to map the distribution of NK-1r and/or NK-1r mRNA in the CNS across multiple species. Both the distribution of NK-1r and the consequences of central NK-1r activation are consistent with a role of SP in signaling aversive events and mediating the appropriate behavioral and physiological responses (reviewed in Rupniak & Kramer, 1999; see Table 1). As with its ligand, NK-1r density is highest in the amygdaloid nuclei and the regions these nuclei project to or receive projections from, including the ventral and medial prefrontal cortex (PFC), bed nucleus of the stria terminalis, hippocampus, hypothalamus, periaqueductal grey, raphe nuclei, lateral septal nucleus, striatum, nucleus accumbens, locus coeruleus, and NTS. Activation of NK-1r by SP in the CNS has been implicated in a wide range of processes. Special emphasis will be placed on those processes that are related to responding to noxious stimulation, summarized in Table 1. Relatedly, SP antagonists have received much attention for their potential therapeutic role in treating everything from neurogenic pain and nausea to depression and anxiety. The effects of NK-1r activation and antagonism will be discussed in more detail below.

Role of SP in Diseases of Chronic Inflammatory Disease

Through its synergistic relationship with the immune system in both immunogenic and neurogenic inflammation, sensory neuropeptide activity is an important factor in the pathophysiology of many diseases characterized by chronic or dysregulated inflammation. In some inflammatory diseases like arthritis and psoriasis, disease expression requires primary afferent innervation (Dewing, 1971; Glick, 1967). This is illustrated in cases where unilateral nerve loss, consequent to paralysis on one side of the body or nerve section, has been shown to protect tissue on the affected side from SP-related chronic inflammation and destruction (Veale, Farrell, & Fitzgerald, 1993). In addition, SP and NK-1r expression, as well as its effects on target cells, are exaggerated in several inflammatory

Table 1
Substance P and NK-1r Activity in the Brain During Noxious Stimulation

Region	Response	Reference
Amygdala	Aversive conditioning	Ebner et al., 2004
	Physiological stress response	Boyce et al., 2001 Smith et al., 1999
	Separation anxiety	Steinberg et al., 2002 Hwang et al., 2005
Hippocampus	Facilitation of long-term potentiation	Langosch et al., 2005
Hypothalamus	Coordination of stress response	Faria et al., 1991 Gregg and Siegel, 2001
	Defensive behavior	Han et al., 1996 Shaikh et al., 1993
Periaqueductal grey	Conditioned place aversion	Aguiar and Brandão, 1994
	Aggression	De Araújo et al., 2001
	Antinociception	Gregg and Siegel, 2001 Aguiar and Brandão, 1996 Rosén et al., 2004
Raphe nuclei	Serotonergic neurotransmission	R. Liu et al., 2002
Lateral septal nucleus	Cardiovascular regulation	Gradin et al., 1992 Guiard et al., 2004
	Behavioral inhibition/anxiety	Gavioli et al., 2002 Gavioli et al., 1999
Nucleus accumbens	Avoidance behavior	Gaffori et al., 1984
	Dopaminergic neurotransmission	Kalivas and Miller, 1984
Nucleus of the solitary tract	Cardiovascular regulation	Mutoh et al., 2000 Mazzone and Geraghty, 2000
		Pickering et al., 2003 Cowan et al., 2000
Locus coeruleus	Noradrenergic neurotransmission	Hwang et al., 2005

Note. The table indicates select brain regions in which substance P (SP) or its receptor (NK-1r) have been implicated in physiological or behavioral changes appropriate in a response to noxious stimulation. Citations reflect representative studies in which SP has been directly implicated in evoked changes.

diseases such as rheumatoid arthritis (Keeble & Brain, 2004; Lambert et al., 1998; Westermarck et al., 2001) and atopic dermatitis (Katsuno et al., 2003; Kim et al., 2003). Likewise, SP activity in the gut and lungs is exaggerated in IBD and asthma, respectively.

SP in Chronic IBDs

In addition to its contributions to the physiological regulation of normal digestive processes, SP is involved in mediating pathophysiological processes in the gastrointestinal tract, such as gastrointestinal hyperalgesia (increased magnitude of response to a painful stimulus), mucosal inflammation and injury, and diarrhea (reviewed in Holzer & Holzer-Petsche, 1997b, 2001). These pathological processes are associated with irritable bowel syndrome (IBS) and chronic IBD, a term that refers to Crohn's disease and ulcerative colitis, which are diseases characterized by pathological inflammation, of unknown origin,

of all or part of the gastrointestinal tract.⁴ Dramatic up-regulation of NK-1r in the upper and lower intestine is the most striking indication of the involvement of SP in the pathophysiology of IBD (reviewed in Holzer & Holzer-Petsche, 2001). Cells of the enteric nervous system and colon (including connective tissue, mucosa, and epithelium) display the most elevated levels of NK-1r and NK-1r mRNA expression. In addition to these cells, increased numbers of immune cells expressing NK-1r in gut tissue have been observed in patients with active IBD as well (Goode et al., 2000; Renzi, Pellegrini, Tonelli, Surrenti, & Calabro, 2000).

Similarly, SP expression itself is aberrant in these conditions. In animal models of IBD, SP levels in the intestine are initially decreased, likely reflecting SP release (reviewed in Sharkey & Kroese, 2001). However, a gradual and sustained increase in SP innervation and expression follows. The increased innervation originates first from intrinsic neurons of the gut, followed by afferent sensory neurons (Miller et al., 1993). In humans with IBD, most studies have reported greater quantities of SP in intestinal tissue as well as a greater density of SP-containing nerve fibers (reviewed in Evangelista, 2001, and Quartara & Maggi, 1998; Mantyh et al., 1995), relative to healthy intestinal tissue. However, there are conflicting reports, indicating decreased levels of both SP expression and innervation, especially in Crohn's Disease (Kimura, Masuda, Hiwatashi, Toyota, & Nagura, 1994; Koch, Carney, & Go, 1987). These discrepancies likely reflect heterogeneity in the stage of disease, disease type, and the region of intestine sampled.

Mast cells and nerves are found in close proximity in the gastrointestinal tract (Stead et al., 1987), suggesting that mast cells may be important in neurogenic inflammation in the gut. In tissue of the normal colonic mucosa, SP does not cause mast cell degranulation. However, in both inflamed and unaffected colonic mucosal tissue, SP evokes release of histamine from mast cells in IBD patients, causing exacerbation and initiation, respectively, of a self-amplifying inflammatory response. In addition to histamine, mast cells contain SP and pro-inflammatory cytokines, expression of which is increased in inflamed IBD tissue (Lilja, Gustafson-Svard, Franzen, & Sjobahl, 2000; Stoyanova & Gulubova, 2002). Moreover, an increase in intestinal mast cell numbers in IBD may represent enhanced SP-induced recruitment (Raithel et al., 1999). Interestingly, SP release does not have to occur in the diseased area to affect inflammation. Erin and colleagues (Erin, Ersoy, Ercan, Akici, & Oktay, 2004) reported that stress or SP infusion in the CNS can cause mast cell degranulation in the periphery that is blocked by an NK-1r antagonist.

Up-regulation of the SP-NK-1r system likely plays a part in the chronic intestinal inflammation that is characteristic of IBD via promotion of the immune processes discussed previously, such as vasodilation, recruitment of inflammatory immune cells, and their enhanced migration from blood into tissues. Indeed, interference with NK-1r activity reduces symptoms of and processes underlying pathophysiology in IBD in both animals and humans. For example, in a double-blind, placebo-controlled pilot study, IBS patients reported symptom amelioration following treatment with an NK-1r blocker (O. Y. Lee, Munakata, Naliboff, Chang, & Mayer, 2000). In fact, partial denervation of the intestine (thus eliminating primary afferent innervation) was once used as a management strategy for IBD (reviewed in Sharkey & Kroese,

2001). In animal models of IBD, both capsaicin⁵ and NK-1r antagonists inhibit intestinal inflammation (Di Sebastiano et al., 1999), fluid secretion (Moriarty, Goldhill, Selve, O'Donoghue, & Baird, 2001), and mucosal permeability (Tough, Lewis, Fozard, & Cox, 2003). Increased colonic secretion, the process that underlies diarrhea, is stimulated by SP or NK-1r selective agonists and is abrogated by NK-1r antagonists (Moriarty et al., 2001). Some debate has been raised, however, concerning the efficacy of NK-1r antagonists in completely blocking the inflammatory effects of SP, likely due to the NK-1r-independent effects on mast cells (Wallace, McCafferty, & Sharkey, 1998).

SP in Asthma

Asthma, like IBD, is a chronic inflammatory disease and is characterized by bronchial hypersensitivity, leading to bronchoconstriction, inflammation, and, ultimately, obstruction of the airways. SP has been implicated in the pathophysiology of asthma because it evokes many of the processes underlying asthma symptoms (reviewed in Joos et al., 2003) and because its release is stimulated by many of the same triggers that cause exacerbation of asthma symptoms, such as cold air and inhaled irritants (Patacchini & Maggi, 2001). Although SP does participate in bronchoconstriction, it affects inflammatory processes most dramatically.

Accumulating evidence has indicated an increase in expression of SP and NK-1r as well as SP-containing fiber density in the lungs of asthmatics (Adcock et al., 1993; Chu et al., 2000; Nieber et al., 1992; Ollerenshaw, Jarvis, Sullivan, & Woolcock, 1991). Both at baseline and following respiratory challenge, SP content in sputum is reportedly higher in asthmatics than in nonasthmatics (Tomaki et al., 1995). In addition to pulmonary SP levels, patients hospitalized for an acute asthma exacerbation show higher plasma SP levels than control subjects (Cardell, Uddman, & Edvinsson, 1994). Moreover, level of SP expression is associated with measures of disease severity and lung function impairment (Chu et al., 2000; Tomaki et al., 1995).

The evidence for an increase in SP expression in asthma is not indisputable, however. Though bronchoscopic and postmortem samples have demonstrated an up-regulation of SP-containing primary afferent fibers in asthmatic airways (Ollerenshaw et al., 1991), others have shown no difference (Howarth et al., 1995), or even a decrease, relative to samples from nonasthmatics (Lilly, Bai, Shore, Hall, & Drazen, 1995). Conflicting results, in this case, may be a consequence of the area of the respiratory tract sampled, as the difference in SP distribution between asthmatics and nonasthmatics may be localized to specific tissues. For example, Chu et al. (2000) showed that SP expression is up-regulated in the airway epithelium in asthmatics but not in the underlying mucosa. In addition, heterogeneity in disease severity may lead to conflicting results since SP dysregulation is more dramatic in severe than

⁴ Although IBS is not officially classified as an IBD, it does involve SP dysregulation and is included in the term IBD for the purposes of this review.

⁵ Treatment with capsaicin causes temporary depletion of SP from nerve terminals. Repeated or long-term exposure to capsaicin, or exposure neonatally, can cause permanent neuronal loss of SP (Jessell, Iversen, & Cuello, 1978; L. C. Russell & Burchiel, 1984; Zhao, Yang, Zhang, & Zhuang, 1992).

in mild asthma (Mukaiyama, Morimoto, Nosaka, Takahashi, & Yamashita, 2004). Finally, the rapid degradation of SP by NEP may yield misleading results in some studies.

Despite the conflicting reports in humans, evidence from animal models of asthma overwhelmingly supports a role for increased expression of SP in airway inflammation. In sensitized animals, airway SP can increase fourfold following allergen inhalation challenge, in addition to a 25% increase in numbers of SP-expressing neurons in the ganglia (Fischer, McGregor, Saria, Philipin, & Kummer, 1996). An increase in the degree of CNS innervation of the lung has also been shown to mimic the inflammation observed in the asthmatic respiratory tract. For example, the genetically induced increase in sympathetic and SP-containing sensory fiber innervation of the lung (indicating increased potential for neurogenic inflammation) produces mice with a decreased sensory fiber threshold, increased neutrophilic infiltration, and increased airway resistance, all of which are diagnostic criteria for asthma (Graham, Friedman, & Hoyle, 2001; Hoyle et al., 1998).

NEP is one potential mediator of the increased SP level observed in asthmatics (reviewed in Di Maria, Bellofiore, & Geppetti, 1998). The cleaving activity of NEP is the primary method of SP inactivation in the periphery. Under normal conditions, asthmatics and nonasthmatics do not differ with respect to NEP activity in the lungs (van der Velden et al., 1999). Following inhalation of an allergen, however, NEP levels are substantially reduced in asthmatics (Tudoric et al., 2000). Inhibition of NEP causes an accumulation of SP in lung tissue, leading to the potentiation of its inflammatory effects and an exaggerated response to allergen in the airways (Bertrand, Geppetti, Baker, Yamawaki, & Nadel, 1993; Umeno, Nadel, Huang, & McDonald, 1989). Consistent with a role for NEP as a mediator of SP activity in chronic inflammatory diseases, NEP knockout mice show increased levels of SP across many organ systems (Lu et al., 1997) and manifest symptoms that mimic those observed in chronic inflammatory diseases such as dermatitis (Scholzen et al., 2001) and IBD (Sturiale et al., 1999).

In asthma, increased expression of the SP–NK-1r system has consequences for many aspects of airway function. The most notable effects are the development of airway hypersensitivity and increased infiltration and activation of immune cells. In humans, this increase can be illustrated by a simple test often used to diagnose asthma—degree of lung function decline following inhalation of the bronchoconstricting agent methacholine. SP inhalation has been shown to increase airway responsiveness to methacholine 24 hours later (Cheung, Van Der Veen, Den Hartig, Dijkman, & Sterk, 1994). Moreover, in the airways of normal subjects, inhalation of SP fails to induce the dose-dependent decrease in lung function seen in asthmatic patients (Cheung et al., 1994; Crimi et al., 1988, 1990; Joos, 1989), suggesting that asthmatic airways are hypersensitive to SP itself, perhaps due to the up-regulation of NK-1r (Adcock et al., 1993). Unfortunately, there are currently no reports on the neural, cognitive, or behavioral effects of inhaled SP.

Accumulation and activation of eosinophils (a type of immune cell commonly involved in allergic reactions) is crucial to the development of airway hyperresponsivity and inflammation in asthma (reviewed in Busse & Sedgwick, 1992). SP stimulates prolonged infiltration and degranulation of eosinophils in airway walls (Kroegel, Giembycz, & Barnes, 1990; Tibério et al., 2003).

Indeed, Tomaki and colleagues (1995) have shown that the level of SP expression in sputum predicts the number of eosinophils in the sputum of asthmatic patients but not in that of healthy control subjects. Among the mediators released by eosinophil degranulation is eosinophil cationic protein (Iwamoto et al., 1993), which may contribute to the increased SP in tissues through its inhibition of NEP activity (O'Byrne, 1988). Moreover, eosinophil cationic protein can stimulate primary afferents (Garland et al., 1997; L. Y. Lee, Gu, & Gleich, 2001), causing antidromic release of SP and the mutual amplification observed in the interaction of SP with other immune cells involved in the inflammatory process.

Inhibition of SP activity, through ablation of SP-containing sensory neurons or receptor antagonism, provides evidence for an important role for SP in the generation of airway hypersensitivity and inflammation in asthma. Permanent or reversible long-term loss of SP-containing afferent fibers can be achieved through pretreatment with high doses of capsaicin (Scheerens, Buckley, Muis, Van Loveren, & Nijkamp, 1996). Loss of sensory fibers, in this respect or as a consequence of severing the thoracic branch of the vagus nerve, blocks the development of airway hypersensitivity and neurogenic inflammation in the lower airways (Buckley & Nijkamp, 1994; Ladenius & Nijkamp, 1993; Tseng et al., 2001). Selective antagonists to the NK-1r have also been shown to prevent development of airway hyperresponsivity, airway obstruction, and cough (reviewed in Advenier et al., 1997). Increased mucus secretion, plasma extravasation, and infiltration of inflammatory cells are among the processes that mediate airway obstruction in asthma, which NK-1r antagonists have demonstrably blocked (Joachim et al., 2004; Phillips et al., 2003; Schuilting, Zuidhof, Zaagsma, & Meurs, 1999a, 1999b). These findings have also been replicated in NK-1r knockout mice (van der Kleij, Kraneveld, et al., 2003). Consistent with the idea that SP and NK-1r are primarily involved in promoting inflammation, Schuilting and colleagues (1999b) reported that NK-1r antagonists have little impact on the immediate airway response to allergen challenge, which is characterized by bronchoconstriction, whereas development of hyper-sensitivity, late-phase inflammation, and recruitment of inflammatory cells are dramatically reduced.

Despite the successful use of NK-1r antagonists in preventing airway hypersensitivity and inflammation in animal models of asthma, little research has examined their efficacy for treatment of humans with asthma. Of the work that has been done, the results have been disappointing (reviewed in Advenier, Joos, Molimard, Lagente, & Pauwels, 1999). Only one published report demonstrated benefit of SP antagonists to asthma symptomatology, and it found that the NK-1r selective antagonist, FK-888, dramatically reduced recovery time following an episode of exercise-induced asthma but improved maximum lung function decline in only a subset of the sample (Ichinose et al., 1996). In contrast, CP-99,994—another NK-1r antagonist—had no effect on bronchoconstriction following hypertonic saline inhalation, though measures of inflammation were not reported (Fahy et al., 1995). One additional study used the nonspecific tachykinin receptor antagonist FK-224 and reported no benefit, compared with placebo, to asthma symptoms after 4 weeks of administration. However, this antagonist was unable to block the airway effects of tachykinin administration—a situation potentially affecting the results of other studies as well—which suggests the likelihood of functional SP activity (Lunde, Hedner, & Svedmyr, 1994). Given the success

of NK-1r antagonists in treating symptoms in animal models of asthma and in humans with other maladies (e.g., emesis, de Wit et al., 2004; diarrhea, Moriarty et al., 2001), this area clearly warrants more research. In fact, clinical trials are currently underway that investigate the efficacy of new NK-1r antagonists, as well as drugs that block other neurokinin receptors, in asthma treatment.

Neural Control of Inflammation: Ascending and Descending Communication

The role of the CNS is critical in mounting an appropriate response to a physiological disturbance, such as inflammation, and in maintaining balance and homeostasis in brain-immune communication pathways. Inflammation leads to changes in neural activity primarily through the central release of SP and pro-inflammatory cytokines. Conversely, neural activity modulates inflammatory processes through descending fibers of the autonomic nervous system and through products of the endocrine system. The role of SP, in this regard, seems largely to sensitize neurons and amplify both afferent and efferent signals. This reciprocal influence has important implications for chronic inflammatory diseases and affective disorders.

Ascending Pathways

Primary afferent neurons reside in various ganglia and send projections to the periphery, which innervate almost every tissue in the body. In addition to their peripheral projections, primary afferent neurons send projections to the CNS. The central projections synapse for the first time on second order neurons in the spinal cord and brain stem. These second order neurons project both collaterally (branches at the same or lower level) and to higher brain centers that coordinate and control behavior and homeostasis (Otsuka & Yoshioka, 1993).

Perhaps the most interesting and compelling aspect of SP's involvement in the pathophysiology of diseases like IBD and asthma lies in its association with the sensitization and plasticity that occur during chronic inflammation. In this way, SP may perpetuate inflammation and hypersensitivity during chronic inflammation. SP-containing fibers, for example, become physically closer to inflammatory immune cells, exhibiting membrane to membrane contact in some cases (reviewed in McKay & Bienstock, 1994; Stead et al., 1987). The characteristics of sensory fibers have also demonstrated plasticity during chronic inflammation. Under normal circumstances, SP-containing sensory nerves are almost exclusively of the capsaicin-sensitive, C-fiber type, which are relatively inefficient, have a high-threshold, and are activated by noxious stimuli. Another class of sensory nerves is the relatively efficient, low-threshold A β -fiber type that responds to mechanical stimulation but not to irritants; these neurons do not produce SP (Hunter, Myers, & Udem, 2000). During inflammation, however, a portion (approximately 10%–30%) of A β fibers exhibit phenotypic plasticity such that they begin to express SP and NK-1r (Hunter et al., 2000; Myers, Kajekar, & Udem, 2002; Neumann, Doubell, Leslie, & Woolf, 1996; Udem et al., 1999; Xu & Zhao, 2001). Thus, the number of total fibers capable of releasing SP, as well as the efficiency of those fibers, is increased, both in the periphery and the CNS. Although pro-inflammatory

cytokines do communicate inflammation to the brain via sensory fibers, this type of amplification is unique to SP.

Primary afferent neurons of both types (C and A β) can also become sensitized during inflammation, in which peripheral terminals respond to formerly benign stimuli with the release of SP (reviewed in Carr & Udem, 2001, and Woolf & Salter, 2000; Torebjörk, Lundberg, & LaMotte, 1992; Udem, Kajekar, Hunter, & Myers, 2000; Xu & Zhao, 2001). This sensitization has been observed in both asthma (Joos, 1989) and IBS (Al-Chaer, Kawasaki, & Pasricha, 2000; Sharkey, 1992). In addition to sensitization of peripheral terminals, increased SP and pro-inflammatory cytokine release from central projections into the spinal cord and brain stem has been shown to sensitize second order neurons to excitatory neurotransmitters, which increases the signal of noxious stimulation to the brain and may amplify the brain's defensive response (Chen et al., 2001; Hermann, Holmes, & Rogers, 2005). Increased release into the dorsal horn, for example, may account for the persistent hyperalgesia and allodynia (ordinarily nonpainful stimuli evoke pain) observed in some diseases of chronic inflammation (Galeazza et al., 1995; Neumann et al., 1996; Sommer & Kress, 2004). Brain stem neurons have likewise displayed SP-mediated plasticity during inflammation. In a primate model of chronic inflammation, increased excitability of NTS neurons was shown, following prolonged exposure to noxious stimulation (Chen, Bonham, Plopper, & Joad, 2003). Similarly, chronic exposure to passive cigarette smoke can lead to NK-1r-mediated NTS sensitization and an increased pulmonary response to an inhaled irritant (Joad et al., 2004).

Taken together, these findings indicate that during chronic inflammation, sensory fibers become more easily activated and, in addition to C fibers, A β fibers can participate in the sensitization of second order neurons. Consequently, the signal of noxious stimulation to the brain may be potentiated even further. Magnitude of activation of second order neurons is communicated to other regions of the CNS, leading ultimately to coordinated behavioral and physiological responses. Therefore, an increase in sensitivity of second order neurons may transmit an amplified message to other brain regions (e.g., amygdala; Otsuka & Yoshioka, 1993), resulting in an exaggerated behavioral and physiological response that contributes to the pathophysiology observed in some diseases of chronic inflammation (Udem et al., 2000).

Descending Pathways

The descending pathways through which the CNS coordinates behavioral and physiological responses to noxious stimulation and restoration of homeostatic balance are also sensitized by SP activity. The most immediate descending response to noxious stimulation and C-fiber activation of second order neurons occurs through an autonomic reflex, in which neurons in brain stem nuclei (e.g., NTS) activate the sympathetic and parasympathetic preganglionic neurons (neurons that send projections to the ganglia) to stimulate descending efferents (Myers, 2001; Udem et al., 2000). Above, it was established that SP increases the excitability of NTS neurons. This SP-induced increase in excitability is propagated in the autonomic reflex output (Mazzone & Geraghty, 2000; Mutoh, Bonham, & Joad, 2000; Pickering, Boscan, & Paton, 2003). Preganglionic neurons release acetylcholine onto peripheral neurons of

the autonomic ganglia, which function as a gate to either terminate or propagate the signal, depending on its strength (Myers, 2001). Both SP and NK-1r are expressed in the autonomic ganglia (including those ganglia that innervate the airways and gastrointestinal tract) and function to increase the gain of the preganglionic signal by sensitizing the neurons to acetylcholine, thus increasing the likelihood that the signal gets propagated further to the target organ (S. J. Baker, Morris, & Gibbins, 2003; Messenger, Anderson, & Gibbins, 1999; Myers, 2001; Ribeiro-da-Silva & Hökfelt, 2000).

In part, SP in the autonomic ganglia comes from innervation by collateral afferent C fibers, which release SP during inflammation (Elfvin, Lindh, & Hökfelt, 1993). In addition, large numbers of mast cells reside in the autonomic ganglia (Albuquerque, Leal-Cardoso, & Weinreich, 1997; Weinreich & Udem, 1987). As discussed earlier, SP and mast cells act synergistically to amplify both SP neurotransmission and mast cell release of histamine and other mediators during inflammation. Histamine has been shown to mediate short-term increases in synaptic strength (Weinreich & Udem, 1987; Weinreich, Udem, Taylor, & Barry, 1995). Other mast cell mediators, such as prostaglandin D₂ and platelet-activating factor, evoke a sustained increase in synaptic transmission efficacy that is referred to as *long-term potentiation* (Albuquerque et al., 1997; Weinreich et al., 1995). Therefore, SP, both alone and in conjunction with mast cell products, functions to increase the signal strength in the autonomic ganglia and thus increases the magnitude of the effector mechanisms that the signal encodes.

Propagation of the descending response to noxious stimulation, via the autonomic ganglia, results in the release of neurotransmitters in the target tissue, which can also be potentiated during inflammation (Fryer & Wills-Karp, 1991; Udem et al., 2000). Further, the release of autonomic neurotransmitters (acetylcholine or norepinephrine) can stimulate and sensitize sensory afferent terminals and thus evoke neurogenic inflammation (Banik, Sato, Yajima, & Mizumura, 2001). Thus we have a completed loop of bidirectional communication and amplification of SP signaling and inflammation. Banik (2001) and colleagues have shown that during chronic inflammation, primary afferent terminals are, in fact, sensitized to norepinephrine, resulting in both a local amplification of SP and inflammation and a propagation of the ascending signal, possibly contributing to the chronicity of inflammation.

In addition to neural reflex output, descending responses from other brain regions can also modulate inflammation. The NTS and other brain stem and spinal cord nuclei send projections to higher brain regions (e.g., hypothalamus, substantia nigra, amygdala; Otsuka & Yoshioka, 1993). Higher brain centers integrate information and respond by sending descending output through the brain stem and spinal cord nuclei (Otsuka & Yoshioka, 1993), as well as through systemic release of humoral mediators (i.e., endocrine activation). This activity is subject to the same modulation as the neural reflex output but also to modulation occurring at each synapse in between. In particular, neural circuitry underlying stress and emotion is rich in SP and NK-1r expression and has been shown to modulate efferent activity relevant to inflammation and chronic inflammatory disease (Donahue, LaGraize, & Fuchs, 2001; Erin et al., 2004; Kawashima, Fugate, & Kusnecov, 2002).

Emotion, Stress, and Diseases of Chronic Inflammation

Beyond the second order neurons of the spinal cord and brain stem nuclei, inflammatory signals are transmitted to the same neural circuitry involved in responding to emotional and stress-related information (reviewed in Black, 1994, and Eskandari, Webster, & Sternberg, 2003; Maier & Watkins, 1998). Indeed, the CNS and the immune system work closely in tandem to coordinate stress responses and to keep them from overshooting. Inflammation is an essential, and perhaps the original, response to a stressor. It protects an organism from potential exposure to pathogens encountered during fight or flight (reviewed in Black, 2003, and Eskandari et al., 2003). As was discussed earlier, neural responses to stressors may have actually evolved from and co-opted the machinery of the inflammatory response (Black, 2002; Maier & Watkins, 1998), and central SP activity during neural responses to stressors may reflect this relationship. In healthy humans, little research has examined central SP activity in response to stress. However, serum levels following stress have been studied. The available data have indicated that in healthy individuals acute stress does not affect serum SP levels (Rohleder et al., 2006; Schedlowski et al., 1995) but that during sustained stress (Weiss et al., 1996) chronic inflammation (Anichini et al., 1997; Cardell et al., 1994; Fusayasu, Kowa, Takeshima, Nakaso, & Nakashima, in press) or, in individuals with mood disorders, serum SP levels may be elevated (see below). The major peripheral output systems of the brain's stress responses are the hypothalamic–pituitary–adrenal axis and the sympathetic–adrenal–medullary axis.

Hypothalamic–Pituitary–Adrenal Axis (HPA-Axis)

The HPA-axis is activated by both physiological (e.g., inflammation) and psychological (e.g., social threat) stressors (reviewed in Black, 2003; S. S. Dickerson, & Kemeny, 2004; Maier & Watkins, 1998). Activation of neurons in the paraventricular nucleus (PVN) of the hypothalamus evokes release of CRH into pituitary portal blood. CRH stimulates neurons in the anterior pituitary, evoking the systemic release of ACTH. ACTH stimulates cells in the adrenal cortex to release glucocorticoids (GCs). Inflammation activates hypothalamic PVN neurons through the action of pro-inflammatory cytokines (Sapolsky, Rivier, Yamamoto, Plotsky, & Vale, 1987; reviewed in Maier, 2003) and through ascending sensory afferent activation (see *Ascending Pathways* above). Because of the immunomodulatory actions of GCs, the HPA-axis is considered one of the primary pathways through which the CNS regulates peripheral inflammation. Thus, HPA-axis hypoactivity has been a popular candidate mechanism underlying the pathophysiology of chronic inflammatory disease. Though a compelling body of evidence does suggest that during chronic inflammation or chronic social stress HPA-axis activity is impaired (Buske-Kirschbaum, Geiben, Hollig, Morschhauser, & Hellhammer, 2002; Chrousos, 1998; reviewed in Eskandari et al., 2003, and Lorton, Lubahn, & Bellinger, 2003; Albeck et al., 1997), a number of observations are in apparent contradiction of this hypothesis (for a discussion, see Harbuz, Chover-Gonzalez, & Jessop, 2003; Jessop, Harbuz, & Lightman, 2001; and Shanks et al., 1998). Several studies, for instance, have shown normal or increased ACTH and GC levels in animal models of chronic inflammation despite decreased expression of hypothalamic CRH

(Chowdrey, Larsen, Harbuz, Jessop, et al., 1995; Chowdrey, Larsen, Harbuz, Lightman, & Jessop, 1995; Harbuz et al., 1992; reviewed in Harbuz et al., 2003). In assessing these latter observations, it is important to acknowledge the complex mechanisms involved in the regulation of the HPA-axis. This system is regulated by a variety of neurotransmitters, including both CRH and arginine vasopressin (AVP). Moreover, it is under the tight control of regulatory input from other brain regions (reviewed in Herman, Ostrander, Mueller, & Figueiredo, 2005; Urry et al., 2006), in addition to input from the periphery, that influences both basal and stress-related activity of the axis. To illustrate, a compensatory shift from CRH to AVP as the primary driver of pituitary ACTH release during chronic inflammatory stress may be responsible for the lack of an alteration in basal levels of GCs in certain chronic inflammatory conditions (Chikanza, Petrou, & Chrousos, 2000; Chowdrey, Larsen, Harbuz, Jessop, et al., 1995; Harbuz et al., 1995, 1992). This shift has been associated with relatively normal basal GC levels but with a loss of circadian rhythm and a reduced ability to mount a GC response to a stressor (Albeck et al., 1997; Harbuz et al., 2003; Lightman et al., 2002; Windle et al., 2001). Further, as mentioned, pro-inflammatory cytokines exert an activating influence on CRH neurons. Combined, this makes it difficult to predict what the net effect of an inflammatory condition will be on both basal activity and stressor-evoked activity of the HPA-axis. Of importance for future studies on this topic will be the examination of basal and stress-evoked interactions between SP, as well as other inflammatory mediators, and HPA-axis function.

Both SP and its receptor are found in abundance in the human hypothalamus (Cooper et al., 1981; Culman, Itoi, & Unger, 1995; Hargreaves, 2002). In animal models of chronic inflammatory stress, but not acute stress (Hwang, Katner, & Iyengar, 2005), SP expression in the hypothalamus is increased (Chowdrey, Larsen, Harbuz, Lightman, & Jessop, 1995; Jessop, Renshaw, Larsen, Chowdrey, & Harbuz, 2000; Faria, Navarra, Tsagarakis, Besser, & Grossman, 1991; Sergeev et al., 2005). However, the significance of this increase is currently unclear. Some evidence suggests that SP may act to inhibit hypothalamic CRH expression, consistent with the decreased CRH expression observed during chronic inflammation (Chowdrey, Larsen, Harbuz, Jessop, et al., 1995; Chowdrey, Larsen, Harbuz, Lightman, & Jessop, 1995; Harbuz et al., 1992; reviewed in Harbuz et al., 2003). For example, in an animal model of rheumatoid arthritis, Chowdrey, Larsen, Harbuz, Lightman, and Jessop (1995) showed a dramatic increase in PVN SP levels compared with those of a control group. In the same study, SP signaling in the hypothalamus was blocked via an intracerebroventricular-administered NK-1r antagonist, causing increased CRH message in the PVN as well as increased plasma levels of ACTH and adrenal production of GCs. The potentiating effect of SP antagonists on hypothalamic CRH has been observed in multiple studies (e.g., Larsen, Jessop, Patel, Lightman, & Chowdrey, 1993; Jessop et al., 2000). However, a significant decrease in PVN CRH has not been demonstrated in the presence of elevated SP levels. This may reflect an indirect effect of SP, perhaps via inhibition of serotonin neurons (Culman et al., 1995). Alternatively, SP may have a tonic inhibitory effect on hypothalamic CRH in normal conditions (Jessop et al., 2000), with an increase in the magnitude of inhibition during chronic inflammation (Chowdrey, Larsen, Harbuz, Lightman, & Jessop, 1995). This idea is consistent with the results from Siegel, Düker, Pahnke, and Wuttke's (1987)

investigation addressing the effects of hypothalamic SP activity during acute stress, which suggest that SP may be inhibited initially and thus, permissive of CRH expression and increased GC release, followed by a recovery of SP levels when stress persists. The initial inhibition of SP may be due to NK-1r autoregulatory mechanisms. A similar phenomenon has been observed in the medial amygdala where Ebner and Singewald (2005) observed that basal levels of SP were tonically self-inhibiting, whereas during stress, NK-1r activation potentiated SP release. Therefore, in contrast to basal conditions or acute stressors, increased SP activity in the hypothalamus during chronic inflammation or psychological stress may lead to increased CRH inhibition, a shift from CRH- to AVP-induced ACTH stimulation (Chowdrey, Jessop, & Lightman, 1990; Culman et al., 1995), and subsequent dysregulation of the HPA-axis. An AVP-driven HPA-axis profile, in this scenario, is in accord with previous work showing that normal basal GC levels are insufficient to prevent an excessive inflammatory response and that stress levels of GCs are necessary (Mason, MacPhee, & Antoni, 1990; Morrow, McClellan, Conn, & Kluger, 1993; for an extensive review, see Sapolsky, Romero, & Munck, 2000).

The anterior pituitary of both the rat and primate (including human) also contains SP and NK-1r (Larsen, Mikkelsen, & Saermark, 1989; S. Liu, 1995; Vanhatalo & Soynila, 2001). The primary source of SP in the anterior pituitary is from sensory vagal fibers that originate in the nodose ganglia (lower ganglia of the vagus nerve; Vanhatalo & Soynila, 2001). Cell bodies in this ganglion are activated by sensory afferents during inflammation and likely propagate the signal to the pituitary, causing SP release. The effects of SP-induced activation of NK-1r in the anterior pituitary, however, are even less well understood than those in the hypothalamus. Jessop et al. (2000) reported increased ACTH mRNA following central administration of an NK-1r antagonist. Yet, this increase most likely reflects effects occurring at the hypothalamic level. Indeed, Chowdrey et al. (1990) failed to find any effect of SP on ACTH release from anterior pituitary cells *in vitro*. The paucity of information regarding the importance of SP in the anterior pituitary is surprising given its ubiquity in responses to stress and represents a fertile direction for future research.

In the adrenal gland, both afferent and efferent SP-containing fibers are present, the proportions of which differ among species (reviewed in Nussdorfer & Malendowicz, 1998; Heym, Braun, Shuyi, Klimaschewski, & Colombo-Benkmann, 1995). These fibers are present in both the adrenal medulla and cortex. SP has also been observed in chromaffin cells (neuroendocrine cells that release norepinephrine and epinephrine) of the medulla, and stress-induced increases in SP release from these cells have been demonstrated (Vaupel, Jarry, Schlömer, & Wuttke, 1988). Evidence for NK-1r in the adrenal glands, however, is limited. Otsuka and Yoshioka (1993) reported an absence of NK-1r, but others have observed receptors in the medulla (Nussdorfer & Malendowicz, 1998) and on chromaffin cells in particular (Kodjo et al., 1995). Although there is no clear indication that SP directly impacts GC production or release in the adrenal glands, the pattern of innervation and receptor expression suggests that the release of norepinephrine and epinephrine from medullary chromaffin cells stimulates the activation of SP-containing sensory afferent fibers and further activates the ascending SP pathway. Indeed, as was discussed earlier, catecholamines can sensitize C-fiber terminals (Banik et al., 2001). Interestingly and consistent with the above

observations, release of norepinephrine is increased in diseases of chronic inflammation where stress-induced HPA-axis activation is blunted (Buske-Kirschbaum et al., 2002; Straub & Cutolo, 2001).

Taken as a whole, the reports of the interactions between SP and the HPA-axis suggest that SP has minor influence on basal function. During stress, however, the effect of SP on HPA-axis activity seems to vary according to the duration of the stress—preventing excessive HPA-axis activity when stress persists while permitting the necessary GC activity to prevent an excessive inflammatory response when stress is short lived (Black, 1994; Jessop et al., 2000; Malendowicz, Andreis, Nussdorfer, & Markowska, 1996; Nussdorfer & Malendowicz, 1998). NK-1r knockout models, on the other hand, provide some conflicting data. Santarelli et al. (2001; Santarelli, Gobbi, Blier, & Hen, 2002) reported that mice lacking the NK-1r show a decrease in stress-induced markers of neuronal activity in the PVN and a smaller rise in GCs compared with their wild-type counterparts. These observations illustrate that we do not fully understand this relationship at this time, and more research in this area, in both healthy and chronic inflammation populations, would be of value.

When predicting the net effects of SP–HPA-axis interactions on inflammation, it is important to acknowledge the complexity of the factors and regulatory mechanisms acting on these systems. SP acts in concert with a number of other neurotransmitters, cytokines, and other proteins, both centrally and in the periphery. For example, HPA-axis activation is typically viewed to exert an anti-inflammatory action. However, HPA-axis activation has pro-inflammatory effects that are less widely recognized, including the induction of an increase in expression of pro-inflammatory cytokine receptors (reviewed in Wieggers & Reul, 1998). Even within the domain of GCs, the effects on immune function vary from suppressive to stimulating, depending on concentration and temporal factors (see Figure 4; for recent comprehensive reviews of this material, see Yeager, Guyre, & Munck, 2004, and Sapolsky et al., 2000). Moreover, the ability for GCs and other neuropeptides to interact with immune cells is dynamically regulated and contributes significantly to the ultimate outcome (Heijnen, 2007). Thus, the balance and interplay of pro- and anti-inflammatory influences is most critical in maintaining health and homeostasis as well as the ability to respond appropriately to threats. Likewise, it is this balance that may be perturbed during chronic stress rather than an absolute increase or decrease in the biomolecules involved.

Sympathetic–Adrenal–Medullary Axis (SAM-Axis)

As described above (see *Descending Pathways*), the most immediate descending response to stress occurs through the autonomic reflex. The consequences of this reflex include increase in heart rate and blood pressure and release of norepinephrine and epinephrine from peripheral nerve terminals (McDougall, Widdop, & Lawrence, 2005). SP release can sensitize brain stem neurons (generators of the autonomic reflex) to excitatory neurotransmitters, thus increasing the frequency of autonomic reflex output (Mazzone & Geraghty, 2000; Mutoh et al., 2000; Pickering et al., 2003). In addition, SP acts to increase the strength of the reflex by increasing its gain in the autonomic ganglia (S. J. Baker et al., 2003; Messenger et al., 1999; Myers, 2001; Ribeiro-da-Silva & Hökfelt, 2000). From the autonomic ganglia, descending sympathetic fibers project to the adrenal medulla. In the adrenal medulla,

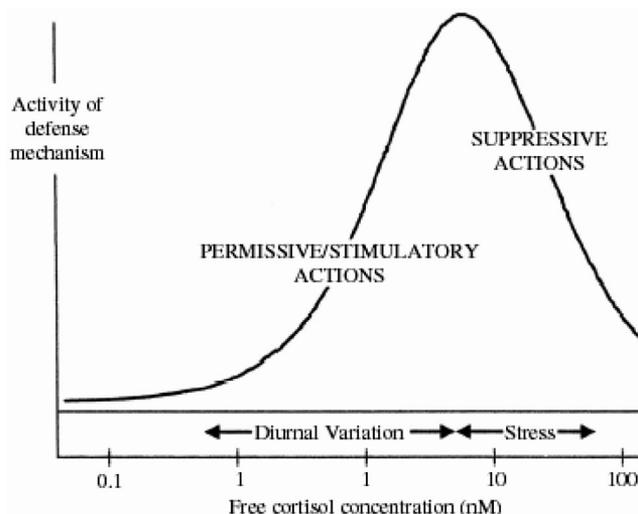


Figure 4. A proposed model of glucocorticoid (GC) action that helps to explain both the enhancing and inhibiting effects of GCs. At low concentrations, GCs exert primarily permissive effects. As the GC concentration increases up to a peak that is close to plasma cortisol levels observed during normal diurnal variation, GCs are stimulatory. At high stress levels, GCs inhibit or suppress defense responses to prevent injury caused by overactivity of the stress-induced response. Note that concentrations are “free” cortisol and that time is not a feature of this model. From M. P. Yeager, P. M. Guyre, and A. U. Munck, “Glucocorticoid Regulation of the Inflammatory Response to Injury,” *Acta Anaesthesiologica Scandinavica*, 48, p. 802, 2004. Copyright 2004, Acta Anaesthesiologica Scandinavica. Reprinted with permission.

they stimulate chromaffin cells to release the catecholamines epinephrine and norepinephrine (Miao, Janig, & Levine, 2000).

These catecholamines modulate inflammation through interaction with sensory nerves and through interaction with receptors on immune cells. The actions of catecholamines are traditionally considered to be anti-inflammatory due to their direct inhibitory effects on immune cells and their ability to activate CRH neurons in the hypothalamus (reviewed in Besedovsky & del Rey, 2007; and Chrousos, 2000). On the other hand, they can contribute to neurogenic inflammation locally, through the noradrenergic sensitization of peripheral primary afferent fibers described previously. In addition, when HPA-axis activity is deficient, epinephrine acts as a potent inflammatory agent (Karalis, Kontopoulos, Muglia, & Majzoub, 1999), perhaps by stimulating the release of pro-inflammatory cytokines (DeRijk, Boelen, Tilders, & Berkenbosch, 1994).

Catecholamines have also been shown to alter the balance of particular classes of cytokines that are released from T-helper (Th) immune cells. Th1 cytokines (e.g., interferon-gamma and interleukin [IL]-2) are dominant in the response to intracellular pathogens (e.g., viruses or intracellular bacteria), whereas Th2 cytokines (e.g., IL-5, IL-6, and IL-10) are dominant in the response to extracellular pathogens. The relative ratio of Th1 to Th2 cytokines is important in mounting an immune response that is most appropriate and effective for a given immune challenge. Catecholamines have been shown to shift the balance of Th1/Th2 cytokines toward that of Th2 dominance (Elenkov, Papanicolaou, Wilder, & Chrou-

sons, 1996). While Th2 cytokines suppress some types of inflammation (phagocyte-dependent), they encourage inflammation involving recruitment and degranulation of eosinophils and mast cells (Romagnani, 2000). This type of response stimulates primary afferent fibers, causing release of SP, and has been associated with chronic inflammatory diseases like asthma (reviewed in Ray & Cohn, 1999) and IBD (Berrebi et al., 2003; Carvahlo et al., 2003).

Other Central Components of the Responses to Stress and Emotion

The amygdala and PFC are two additional brain regions activated by and critical in regulating responses to emotional and stress-related information. In primates, both regions express high levels of SP (Hargreaves, 2002; Hayashi & Oshima, 1986). Activation of these areas, which are known to be involved in detection of threat, by inflammation (Kawashima et al., 2002; Konsman et al., 2000; Nolan, Conner, Kelly, & Leonard, 2000; Tkacs & Li, 1999) has a measurable impact on emotion-related behavior. Konsman et al. (2000) demonstrated activation of the central nucleus of the amygdala (CeA), via sensory afferent (vagal) stimulation of the NTS, during inflammation and showed that CeA activation mediates behavioral symptoms of illness such as reduced social interaction. In addition, SP activity in this pathway has been shown to partially mediate the development of food allergy and immune-induced flavor aversion (Basso, Costa-Pinto, Britto, de Sá-Rocha, & Palermo-Neto, 2004; Basso, de Sá-Rocha, & Palermo-Neto, 2001). Although the neurotransmitter system(s) involved in communication between the NTS and CeA was not determined in these studies, Tkacs and Li (1999) showed that projections to the CeA that mediate its activation during inflammation likely originate in the lateral parabrachial nucleus, acting as a relay between the NTS and the CeA. The terminals of the lateral parabrachial nucleus that terminate in the CeA contain SP (Yamano et al., 1988), suggesting that SP may mediate the inflammation-induced CeA activation.

Activation of the SP–NK-1r system in the CNS is responsive not only to physiological stimuli, it is stimulated also by psychological stressors and emotion. For example, significant increases in SP levels, as measured by *in vivo* microdialysis, have been observed in the rodent amygdala and periaqueductal gray (PAG) following elevated platform exposure, immobilization stress (Boyce et al., 2001; Ebner et al., 2004), and social isolation (Brodin et al., 1994). In addition, Kramer and colleagues (1998) reported that a brief period (approximately 5 minutes) of maternal separation resulted in a dramatic increase in NK-1r internalization (a proxy for local SP release) in the basolateral amygdala in guinea pig pups. Likewise, the magnitude and location of this effect were replicated by D. W. Smith et al. (1999) with immobilization stress. When stress is chronic, observed increases in SP expression are consistent with those following acute stress, with notable mRNA increases seen in the medial amygdala and ventromedial, dorsomedial, and lateral hypothalamic nuclei (Sergeyev et al., 2005). Interestingly, the magnitude of stress intensity is reflected in levels of SP release in these brain regions (Allen et al., 1997; Ebner et al., 2004; Mönikes et al., 2003).

SP Evokes Anxiety- and Fear-Like Responses

The consequences of microinjection of SP into individual components of emotional neural circuitry provide additional support for the involvement of SP neurotransmission in stress and emotion. In the medial amygdala, SP infusion facilitates feline defensive rage behavior and aggression through projections to the lateral hypothalamus (Gregg & Siegel, 2001; Han et al., 1996; Shaikh et al., 1993). In rodents, increasing SP activity in the medial amygdala, dorsal PAG, or lateral septum increases anxiety-related behavior, such as a reduction in time spent in the open arm of an elevated plus maze (Aguiar & Brandão, 1996; Ebner et al., 2004; Gavioli, Canteras, & De Lima, 1999; Teixeira et al., 1996). Increased action of SP in the PAG also mediates conditioned place aversion (Aguiar & Brandão, 1994; De Araújo, Huston, & Brandão, 1998; De Araújo, Huston, & Brandão, 2001) and fear conditioning (Rupniak, Webb, Fisher, Smith, & Boyce, 2003). Although SP cannot be applied to the CNS in humans, it does cross the blood brain barrier (Freed, Audus, & Lunte, 2002) and, when injected into the bloodstream, evokes a rapid decline in mood (Lieb et al., 2002).

Interference with SP activity in the brain, by administration of NK-1r antagonists or gene deletion, inhibits many of the stress- and anxiety-like behaviors discussed above. For instance, several different NK-1r antagonists, administered intracerebroventricularly, essentially abolish stress-induced vocalizations evoked by maternal separation or by an SP agonist (Boyce et al., 2001; Kramer et al., 1998; Rupniak, Carlson, et al., 2003). In the medial amygdala, NK-1r antagonism blocks both stress- and SP-induced defensive rage (Gregg & Siegel, 2001; Han et al., 1996; Shaikh et al., 1993) as well as behavioral anxiety in the elevated plus maze (Ebner et al., 2004; Teixeira & De Lima, 2003). Amygdala-dependent fear conditioning is also abolished by blockade of NK-1rs (Rupniak, Webb, et al., 2003). Likewise, NK-1r antagonist infusion into the lateral septum prevents SP-induced anxiogenic responses to the elevated plus maze (Gavioli, Canteras, & De Lima, 2002), and SP-induced place aversion is prevented by NK-1r antagonism in the dorsal PAG (De Araújo et al., 2001). In NK-1r knockout mice, stress-induced analgesia and response to maternal separation and danger are diminished (De Felipe et al., 1998). In combination, these observations indicate that SP activity in emotional neural circuitry occurs in aversive contexts and that release of SP in these brain regions is itself sufficient to evoke aversion-associated behaviors.

Reciprocal Modulation of Emotional Neural Circuitry and Peripheral Inflammation

Activation of neural circuitry associated with stress and emotion also has “top-down” influence on inflammation (Donahue et al., 2001; Teixeira & De Lima, 2003). The output of this circuitry, as it pertains to inflammation, is likely through the actions of the HPA-axis and descending autonomic nervous system (Dayas, Buller, & Day, 2004) where, for example, norepinephrine release leads to the potentiation of neurogenic inflammation by sensitizing afferent fibers (Banik et al., 2001). In addition, research has indicated that epinephrine and norepinephrine can downregulate expression of GC receptors (Maccari et al., 1992). In the immune system, this would result in the loss of a critical means of regu-

lating inflammatory processes. Thus, it has been suggested that psychological stress or emotion alone can activate SP systems, triggering inflammation in the absence of an immunogenic stimulus (e.g., an invading pathogen or chemical irritant; Black, 2002). Activation of inflammatory processes through psychological means has, in fact, been demonstrated. Both immobilization stress and central SP administration can evoke mast cell degranulation in the periphery, a process which can be blocked with administration of an NK-1r antagonist (Erin et al., 2004). In addition, MacQueen, Marshall, Perdue, Siegel, and Bienenstock (1989) showed that allergen exposure paired with an audiovisual cue could produce Pavlovian conditioning of mast cell degranulation when the cue alone was presented. Therefore, it seems that in terms of inflammation, the consequences of the neural response to physiological or psychological threats may be strikingly similar. Moreover, in an individual in whom low levels of inflammation are ubiquitous, the CNS may already be primed to hyperrespond to threat signals originating peripherally or centrally. This priming may partially underlie the increase in vulnerability to symptom exacerbation by stress and emotion observed in diseases of chronic inflammation.

Inflammatory processes also influence stress and emotion. *Sickness behavior* is a term that refers to a constellation of symptoms such as weakness, malaise, difficulty concentrating, lethargy, and depressed mood. These symptoms can be triggered by peripheral inflammation (Dantzer, Bluthé, Layé, et al., 1998) and have significant overlap with symptoms typical of major depression. A large body of work implicates the actions of pro-inflammatory cytokines, particularly IL-1 β , tumor necrosis factor- α , and IL-6 in the mediation of sickness behavior (e.g., Besedovsky & del Rey, 2007; Dantzer, Bluthé, Gheusi, et al., 1998; Dantzer & Kelley, 2007). SP may also play a role through its synergy with pro-inflammatory cytokines. Additionally, there is evidence that SP itself acts on emotional neural circuitry to produce depression- and anxiety-like symptoms, as is discussed above. Therefore, it is possible that chronic inflammation, via sensitized and hyperactive ascending SP pathways, can lead to hyperactivation of emotional neural circuitry (e.g., amygdala) and consequent psychopathology.

Can Dysregulated SP Signaling Lead to Psychopathology?

There is a well-documented link between exposure to stressful conditions and depression. The above-reviewed information suggests that SP may participate in stress-related alterations in CNS activity and affective state. The idea that immune processes participate in psychopathology is not a new one; the implication of pro-inflammatory cytokines in the initiation and exacerbation of depression has a long history (reviewed in Anisman et al., 2005). The increased expression of SP in individuals suffering from depression and anxiety disorders (Bondy et al., 2003; Geraciotti et al., 2006; Rimón et al., 1984), coupled with the limited evidence for an antidepressive action of NK-1r antagonists (discussed in more detail below), and the normalization of SP levels during remission from depression (Bondy et al., 2003; Husum, Jiménez Vasquez, & Mathé, 2001; Lieb et al., 2004; Olsson, Regnéll, Träskman-Bendz, Ekman, & Westrin, 2004; Shirayama, Mitsu-shio, Takashima, Ichikawa, & Takahashi, 1996) are consistent with the hypothesis that dysregulated SP signaling may contribute to psychopathology in at least a subset of individuals (for a review,

see Herpfer & Lieb, 2005). Recently, Geraciotti and colleagues (2006) demonstrated elevated levels of SP in the CSF of depressed individuals compared with those of healthy control subjects. In this same study, combat veterans with posttraumatic stress disorder (PTSD) showed similarly elevated basal CSF levels of SP as well as a dramatic increase in CSF SP levels while viewing a combat video compared with levels obtained while viewing a neutral video. In animal models of depression and anxiety, blockade of SP receptors mimics the inhibitory effects on stress-induced behavior that are shown with drugs currently used to treat anxiety and depression in humans (Kramer et al., 1998; Santarelli et al., 2002).

Attempts to alleviate depression through the blockade of NK-1rs have yielded both positive and negative results. A recent review of the literature (McLean, 2005) showed that six major clinical trials have examined the efficacy of NK-1r antagonists in the treatment of depression. Two of these multisite trials compared MK-869 (Kramer et al., 1998) and CP-122,721 (Chappell, 2002; reported in McLean, 2005) with placebo and either paroxetine or fluoxetine, respectively; both NK-1r antagonists decreased symptoms of depression significantly more than placebo. Moreover, the effects of MK-869 and CP-122,721 on depressive symptoms were commensurate with those of the active comparator, while causing fewer adverse side effects. A third NK-1r antagonist, L-759,274, successfully reduced symptoms of depression compared with placebo (Kramer et al., 2004) with no active comparator.

In contrast, in two other large multisite trials, the NK-1r antagonists MK-869 (Rupniak & Kramer, 1999) and L-759,274 (Kramer, 2002) failed to outperform placebo. Of importance, in these studies neither of the standard antidepressants, paroxetine and fluoxetine, proved more effective than placebo. Thus, given the well-documented antidepressive actions of these latter drugs, it is difficult to interpret the negative results of the SP antagonists in these studies. Additionally, in a separate large, multisite, phase III trial MK-869 appeared to have modest antidepressant effects that were not statistically different from those of placebo. This was in contrast to the significant antidepressant effects of the standard antidepressant, paroxetine (Keller et al., 2006).

The mixed results of the NK-1r antagonists in these clinical studies is not all that different from the larger body of research on antidepressant actions. Indeed, response to pharmacological treatment for depression is currently insufficient in a significant portion of depressed individuals (reviewed in Souery et al., 2006). In this context, it is important to recognize that available evidence has indicated that depression is not a single, unitary disorder. Rather, this disorder is highly heterogeneous and is likely comprised of many subtypes, differentiated by the etiology and sensitivity to different pharmacological treatments. For example, it has been widely demonstrated that some individuals with depression respond well to SSRIs, whereas others respond better to antidepressants that possess norepinephrine reuptake blocker activity. Of particular relevance to the current discussion, recent studies have indicated that prior stressful experiences may contribute to the development of depression, but only in those individuals carrying a particular allele for the serotonin transporter (Caspi et al., 2003). Given this, it may be the case that SP dysregulation contributes to the development of depression in only a subpopulation of depressed individuals. Thus, careful investigation of the characteristics of those individuals that do respond well to treatment with

NK-1r antagonists is likely to contribute to more accurate and targeted pharmacological interventions in the future.

In addition to depressive symptoms, anxiolytic effects of NK-1r antagonists have been examined. Furmark and colleagues (2005) tested the impact of treatment with GR-205,171 on symptoms of social phobia and reported efficacy similar to that of citalopram. Similarly, Glaxo Smith Kline reported that its NK-1r antagonist, GW-597,599, reduced symptoms of CO₂-induced panic (described in McLean, 2005; Ebner & Singewald, 2006). Furthermore, the patient population in which occurred the positive outcome of the clinical trials reported by Kramer et al. in 1998 had moderately high comorbid anxiety, and both MK-869 (Kramer et al., 1998) and L-759,274 (Kramer et al., 2004) reduced anxious symptoms in these depressed populations.

The contribution of NK-2 and NK-3 receptors to psychopathology should also be considered, since endogenous SP can bind, with varying affinity, to all three neurokinin receptors. NK-2 receptors (NK-2r) and NK-3 receptors (NK-3r) are the preferred binding sites for neurokinin A and neurokinin B, respectively. While NK-1 and NK-3 receptors are widely distributed in the CNS, NK-2 receptors are located primarily in the periphery with much more limited expression in the brain. Though NK-2 receptors are located in the PFC and select hippocampal nuclei, which are areas important in stress and emotion, densities in these regions are very low (Bensaid et al., 2001). Compared with the central effects of NK-1r signaling, much less is known about NK-2r and NK-3r. Selective activation of central NK-2r in animal models produces behavior very similar to that of selective NK-1r agonists (Juszczak, 2005; Teixeira et al., 1996). NK-3 receptors have a very similar central distribution as NK-1r, however the available reports have suggested that selective activation of NK-3r has antidepressant- and anxiolytic-like effects in animal models (Ribeiro, Teixeira, Calixto, & De Lima, 1999; reviewed in Massi, Panocka, & de Caro, 2000). Therefore, it is unlikely that SP-induced activation of NK-3r contributes to anxious or depressive symptoms. It is possible that SP is acting centrally at both NK-1 and NK-2 receptors to evoke stress-associated behaviors, though SP's relatively low affinity for and the limited CNS expression of NK-2r reduces the significance of this possibility.

Development of drugs that act at neurokinin receptors has not ended with the compounds described above. In addition to several new NK-1r antagonists, NK-2 and NK-3 receptor blockers are also currently being developed for the treatment of a wide range of diseases (comprehensively reviewed in Giardina, Gagliardi, & Martinelli, 2003; Czeh, Fuchs, & Simon, 2006; Quartara & Altamura, 2006). Interestingly, drugs that selectively block NK-2r are in advanced phases of clinical trials for treating asthma and IBS, as well as depression. NK-3r antagonists have been developed to a similar extent for treating IBS and schizophrenia (Evangelista, 2005). Furthermore, drugs that block multiple and varying combinations of neurokinin receptors are being developed for therapeutic applications in myriad inflammatory and psychiatric disorders (Giardina et al., 2003). At this point, these drugs are still in the preclinical phase of testing, but the results in animal models are encouraging. Thus, it may prove to be more effective to block multiple neurokinin receptors than to block NK-1r selectively; support for this hypothesis would suggest that SP is acting at multiple receptors and/or that several neurokinins have the potential to modulate mood and inflammation.

As a whole, the clinical results have suggested that drugs that block the NK-1r (and possibly multiple neurokinin receptors) have potential to treat depression and anxiety. Out of eight reported studies, five have found NK-1r antagonists clearly effective in the treatment of depression and/or anxiety; one study has found them clearly ineffective; and two studies have resulted in failed trials, due to a significant placebo response. The one clearly negative trial indicated that NK-1r antagonists are not universally effective in treating depression, however. This is consistent with the failure of some studies to detect differences in CSF levels of SP between depressed individuals and healthy control subjects as well as the failure to detect a change in CSF SP following successful pharmacological treatment (Deuschle et al., 2005; Martensson, Nyberg, Toresson, Brodin, & Bertilsson, 1989). Additional research is necessary to determine which subsets of depressed individuals may benefit most from these drugs. The efficacy of NK-1rs in reducing depressive symptoms in individuals with moderately high anxiety (Kramer et al., 1998) combined with NK-1rs' anxiolytic effects (Ebner & Singewald, 2006; Furmark et al., 2005) suggest a place to begin. In addition, assessing the utility of NK-1r antagonists in treating individuals with comorbid mood disorders and chronic inflammatory disease is warranted, given the high coincidence of these conditions, coupled with the activity of SP in inflammatory disease, stress, and emotion.

Psychopharmacology of NK-1r Antagonists

As is the case with conventional antidepressants, the mechanism through which NK-1r antagonists alleviate symptoms of depression and anxiety is unclear. Given the high levels of SP and the consequences of its activity in the medial temporal lobe, particularly the amygdala and hippocampus, it has been postulated as a likely site of action. Indeed, in a PET study of social phobia, the NK-1r antagonist GR-205,171 decreased amygdalar and hippocampal activity in response to a public speaking challenge when compared with pretreatment activity levels and posttreatment levels of a placebo group (see Figure 5). Moreover, the magnitude of decreased activity predicted the decline in self-reported anxiety symptoms (Furmark et al., 2005). While it may be the case that NK-1r antagonists act on these regions to modulate mood and anxiety independently, in reality the mechanisms are likely much more complex, involving interactions with other neurotransmitter systems and neuropeptides.

Most conventional antidepressants modulate monoaminergic availability (reviewed in Shelton, 2004). It has been suggested that the antidepressant action of NK-1r antagonists is also achieved through interaction with monoaminergic systems (Adell, 2004). First, SP-containing cell bodies and terminals and NK-1rs have a high degree of spatial homology with those of monoamines (K. G. Baker et al., 1991; Cooper et al., 1981; reviewed in Otsuka & Yoshioka, 1993). Second, antidepressant actions of NK-1r antagonists follow a similar time course to that of standard antidepressants, and the chronic effects of NK-1r antagonism on monoaminergic neurons is also similar (Guiard, Froger, Hamon, Gardier, & Lanfumey, 2005; Maubach et al., 2002). For instance, SP increases the firing rate of noradrenergic neurons in the locus coeruleus, and chronic treatment with an NK-1r antagonist or genetic NK-1r deletion increases the burst firing rate while decreasing the level of spontaneous firing (Maubach et al., 2002). The increase in burst

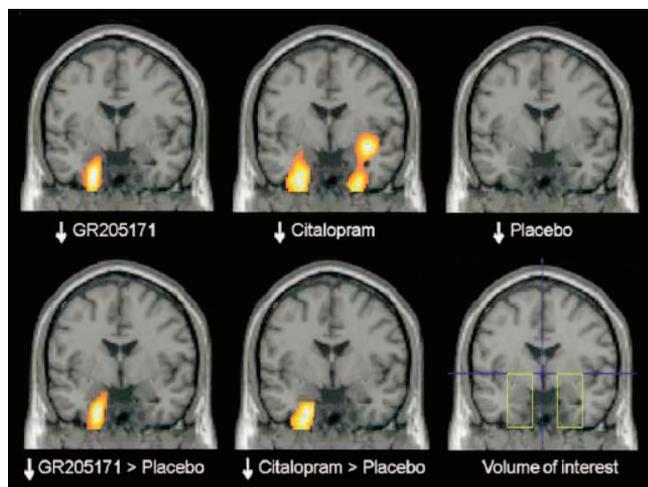


Figure 5. Coronal positron emission tomography (PET) images of patients with social phobia showing clusters of significantly reduced regional cerebral blood flow in the medial temporal lobe during public speaking, after as compared with before treatment, within the neurokinin-1 antagonist GR205171 (top left), citalopram (active comparator; top central), and placebo (top right) groups. Between-groups comparisons revealed a significantly larger reduction of regional cerebral blood flow (rCBF) in subjects treated with GR205171 ($n = 12$; bottom left) and citalopram ($n = 12$; bottom middle) compared with placebo ($n = 12$). Bottom right panel illustrates the volume of interest used for all hypothesis-driven analyses of rCBF changes in the left and right medial temporal lobe. This figure was published in *Biological Psychiatry*, 58, T. Furmark, L. Appel, A. Michelgård, K. Wahlstedt, F. Åhs, S. Zancan, et al., “Cerebral Blood Flow Changes After Treatment of Social Phobia With the Neurokinin-1 Antagonist GR205171, Citalopram, or Placebo,” p. 136. Copyright, Society of Biological Psychiatry (2005). Reprinted with permission from Elsevier.

firing should be associated with an increase in norepinephrine release in terminal fields, which has been observed in both conditions of NK-1r pharmacological inactivation (cortex and hippocampus; Millan, Lejeune, De Nanteuil, & Gobert, 2001) and genetic deletion (cortex; Herpfer, Hunt, & Stanford, 2005). Though genetic or pharmacological inactivation of NK-1r increases the firing rate of dorsal raphe serotonergic neurons as well (Conley et al., 2002; Haddjeri & Blier, 2001), a similar increase in serotonin release in the cortical projection fields of these neurons has not been observed (Kramer et al., 1998; Zocchi et al., 2003). Moreover, the effects of NK-1r antagonists on serotonin neurons in the dorsal raphe are thought to be indirect (perhaps via alterations in noradrenergic activity) because NK-1rs on these neurons are virtually absent (Conley et al., 2002); thus, the effects of NK-1r on dorsal raphe neurons are likely the result of actions in other brain regions and/or effects on other neurotransmitter systems. Additionally, there are some noteworthy differences between the actions of NK-1r antagonists and standard antidepressants—namely that their efficacy is not achieved by altering activity at reuptake sites (Adell, 2004; Conley et al., 2002; Kramer et al., 1998; Lieb et al., 2005; Maubach et al., 2002). Partially in response to this knowledge, novel drugs have been developed that have dual action in blocking both NK-1rs and serotonin reuptake (Ryckmans et al., 2002).

The relationship between SP and monoamines is not unidirectional. Monoamines, especially norepinephrine, influence SP neurotransmission (reviewed in Ebner & Singewald, 2006, and McLean, 2005). Iontophoretic application of norepinephrine or activation of the locus coeruleus-cortical pathway reduces the effects of SP on cortical cells (Jones & Olpe, 1984a, 1984b). In the cortex, evidence has suggested that NK-1r activation potentiates gamma-aminobutyric acid (GABA) release, which functions to inhibit pyramidal neurons and output from the frontal cortex (Jakab, Goldman-Rakic, & Leranath, 1997; Stacey, Woodhall, & Jones, 2002). Thus, both NK-1r antagonists and many standard antidepressants (i.e., those that increase noradrenergic expression in the cortex) decrease NK-1r activity and may remove pyramidal cells from tonic inhibition, resulting in increased frontal cortical output (McLean, 2005). Frontal cortical output has been shown to be crucial in regulating negative mood and neural responses to stress, both of which are important factors in the development of and recovery from depression (reviewed in Gold & Chrousos, 2002; Mayberg et al., 1999).

In addition to the “monoaminergic” hypothesis of antidepressant action, stimulation of hippocampal neurogenesis has also been examined. On the basis of emergent findings of chronic stress-induced suppression of adult neurogenesis (Margariños, McEwen, Flugge, & Fuchs, 1996; reviewed in McEwen & Margariños, 1997) and findings of enhanced neurogenesis after chronic fluoxetine treatment, Jacobs, Praag, and Gage (2000) proposed a model of antidepressant activity in which restoration of normal levels of hippocampal neurogenesis mediated recovery from depression. This hypothesis was supported by the finding that chronic administration of antidepressants from all major classes enhanced hippocampal neurogenesis (Malberg, Eisch, Nestler, & Duman, 2000). Both genetic and pharmacological inactivation of NK-1rs are associated with increased hippocampal neurogenesis and synaptic remodeling (Guest et al., 2004; Morcuende et al., 2003)—perhaps the best evidence that NK-1r antagonists have antidepressant actions. Indeed, though both NK-1r antagonists and standard antidepressants can protect hippocampal interneurons from the damaging effects of chronic stress, the effect of an NK-1r antagonist has shown to be more pronounced and pervasive (Czeh et al., 2005; Margariños, Deslandes, & McEwen, 1999).

Although the specific antidepressant mechanism of NK-1r antagonists is still debated and the evidence is not without dispute (Berrettini et al., 1985; Martensson et al., 1989), it does point to SP dysregulation in at least some forms of depression. Both central and peripheral levels of SP are elevated in some depressed patients (Bondy et al., 2003; Geraciotti et al., 2006; Rimón et al., 1984), and successful antidepressant activity of several classes of antidepressants has been associated with a reduction in these levels (Bondy et al., 2003; Husum et al., 2001; Lieb et al., 2004; Olsson et al., 2004; Shirayama et al., 1996). In addition, antidepressant treatment has been shown to downregulate NK-1r expression in the brain (Herpfer, Fiebich, et al., 2005) and may attenuate stress-induced increases in SP levels in some brain regions (described in Ebner & Singewald, 2006). More general claims about the impact of antidepressants on the central SP–NK-1r system are difficult to make because the data are inconsistent (see Ebner & Singewald, 2006, for a review). These observations, combined with the evidence for a significant role of SP activity in the pathophysiology of chronic inflammation and the high degree of overlap between

diseases of chronic inflammation and depression and anxiety, suggest further examination of the potential for SP as one link between these pathologies.

Stress, Emotion, and IBD

IBD is one of many inflammatory conditions exacerbated by stress and emotion (Collins, 2001; Levenstein et al., 1994; Maunder, 2000; Mulak & Bonaz, 2004; Solmaz et al., 2003). In animal models of IBD, stress increases many of the processes modulated by SP that underlie disease symptomatology (reviewed by Collins, 2001), such as diarrhea, epithelial permeability (Saunders, Kosecka, McKay, & Perdue, 1994) and colonic hypersensitivity (Bradesi, Eutamene, Garcia-Villar, Fioramonti, & Buéno, 2002; Schwetz et al., 2004). In addition, patients with IBD tend to be more responsive to stress, and symptom onset and magnitude are highly associated with perceived stress (reviewed in Stam, Akkermans, & Wiegant, 1997). Therefore, it may be the case that, in patients with IBD, overexpression of SP results in an amplified descending signal from neural circuitry responding to stress and emotion, leading to exacerbation of gastrointestinal inflammation and increased symptomatology.

The pathological relationship between psychological distress and peripheral disease activity in IBD is not limited to peripheral expression. IBD is associated with a much higher incidence of depression and anxiety than would be expected in a healthy population (Kurina, Goldacre, Yeates, & Gill, 2001; Lydiard, 2001). Moreover, stimulation of peripheral disease sites, which evokes SP activation of sensory afferents, produces activation in brain areas implicated in affective disorders. For instance, both anticipated and actual rectal distention increase activation of the right PFC in IBD patients when compared with distention in control subjects (Naliboff et al., 2001; Chang et al., 2003). In an animal model of IBD, noxious colonic distention increased *c-fos* expression in the NTS, hypothalamus, and amygdala (Mönnikes et al., 2003). Thus, it is equally plausible that disease activity in the gastrointestinal tract of IBD sufferers results in increased SP activity in emotional neural circuitry, leading to an increased prevalence of depression and anxiety.

Stress, Emotion, and Asthma

Asthmatic individuals also experience symptom exacerbation consequent to stress and emotion (for a review, see Lehrer et al., 1993). Several studies have shown stress-induced perturbations of asthma symptoms that mimic those evoked by SP activity. In an investigation of the association between stress and inflammation, L. Y. Liu and colleagues (2002) demonstrated that undergraduate asthmatic subjects had greater airway inflammation and a larger decrement in lung function in response to allergen challenge during final examination week—a period of significantly heightened stress—compared with their response to an identical challenge during a relatively stress-free period. Others have shown that immune cell cytokine profiles shift toward the promotion of an allergic response (Th2 dominant) during prolonged stress (Cieslewicz et al., 1999; Matalaka, 2003). In addition, experimental exposure to emotional stimuli has also been shown to increase respiratory resistance in asthma (Ritz, Steptoe, DeWilde, & Costa, 2000).

As is the case with many diseases of chronic inflammation, depression and anxiety prevalence is higher in asthma populations (Mrazek, 2003; Ortega, McQuaid, Canino, Goodwin, & Fritz, 2004), and asthma symptoms are worse in asthma patients with depression (Krommydas et al., 2004). Remission from depression, on the other hand, is associated with improvement in asthma symptoms and decreased usage of asthma medication (Brown et al., 2005). Activation of emotional neural circuitry associated with anxiety and depression has been reported during physiological events related to disease exacerbation. In two similar studies, functional magnetic resonance imaging (fMRI) was used to reveal activation of the insular cortex in response to the experience of breathlessness (Banzett et al., 2000; Liotti et al., 2001). In addition, fMRI data from our own laboratory have revealed a relationship between activity in the anterior cingulate and insular cortices and markers of pulmonary inflammation (Rosenkranz et al., 2005). In this study, asthmatic subjects were challenged with inhaled subject-specific allergen. During a subsequent brain imaging session, subjects viewed asthma-related, general negative, and valence-neutral words. The degree to which activity in the anterior cingulate and insula changed in response to viewing asthma-related words, compared with neutral words, strongly predicted the magnitude of inflammatory cell influx in the lungs and lung function decline. The anterior cingulate and insula are components of neural circuitry critical in processing and responding to stress- and emotion-related information. Although we cannot determine whether the neural activity captured in these studies reflects afferent or efferent modulation, it is clear that a relationship exists between physiological events in the lungs and activity of brain regions underlying stress and emotion.

Conclusions

The activity of the SP neuropeptide system facilitates the most primitive mechanisms of the immune system in protecting an organism from harm through its promotion of inflammatory processes. SP activity stimulates inflammation directly by modulating the activity of cells locally and indirectly by modulating the afferent and efferent activity of the central nervous system. During chronic inflammation, SP activity is increased through sheer quantity of the peptide released and through increases in its signaling capacity due to plasticity and long-term sensitization that occur in the afferent and efferent pathways. This phenomenon provides one possible mechanism for the chronicity of inflammation and its propagation in the absence of a discernible stimulus. Further, SP activity, in at least some cases, is required for the development of hypersensitivity and diseases of chronic inflammation, and successful treatment decreases SP expression (Adcock et al., 1993). In the two diseases reviewed here, asthma and IBD, dysregulation of SP activity is apparent and predicts symptom severity. Taken together, these observations indicate a crucial role for SP in the pathogenesis of chronic inflammation in barrier tissues and perhaps other tissues as well.

SP activity is also aberrant in at least some individuals with anxiety and depression. Depressed patients in multiple studies have shown increased serum and CSF levels of SP. Moreover, when applied to components of emotional neural circuitry critical in regulating stress and emotion, SP evokes behavioral indications of anxiety, fear, and aversion. This observation is not surprising

when considering that the stress responses of the central nervous system likely evolved from the immune system's innate response in protecting an organism from harm, perhaps even utilizing some of its machinery (for the proposal of this idea, see Black, 2002; Maier & Watkins, 1998). Indeed, noxious peripheral stimulation (e.g., pain, inflammation, tissue damage) stimulates SP signaling in the CNS, especially in regions that regulate stress and emotion (e.g., amygdala, hypothalamus). Regulation of SP activity has effectively been used in the treatment of anxiety and depression. NK-1r antagonists have efficacy commensurate with that of currently available antidepressants in some individuals, and the ability of an antidepressant to lower SP levels has predicted its ability to successfully decrease symptoms of depression. Therefore, dysregulation of SP may underlie the pathophysiology in a subset of anxiety and depression sufferers.

Diseases characterized by dysregulated and chronic inflammation, such as asthma and IBD, have a high co-incidence with anxiety and depression. Stress and negative emotion have also been shown to trigger and exacerbate symptoms in these diseases. Further, SP plays an integral role in determining the magnitude of the signal strength of communication between the viscera and the brain and evokes symptoms of both types of pathology. Thus, symptoms of depression and anxiety and diseases of chronic inflammation in the periphery may reflect a common underlying pathophysiology. In this scenario, perturbations of either end of this bidirectional system would result in perturbations of the other.

Limitations of the Current Literature

Although the evidence is strong for significant involvement of SP in the pathophysiology underlying chronic inflammatory disease and affective disorders, it no doubt acts in concert with the myriad other neurotransmitters and neuropeptides present in the same signaling pathways. Indeed, SP is frequently colocalized with and released from the same nerve terminals as several other neurotransmitters and neuropeptides (for a review, see Otsuka & Yoshioka, 1993; Quartara & Maggi, 1997; Hökfelt, Pernow, & Wahren, 2001). Unfortunately, the data available describing the interactions between these molecules are sparse. The data that are available do suggest that this interplay is important to the nexus between chronic inflammatory disease and psychopathology as well as to the treatment of these conditions. For example, Beaujouan, Torrens, Saffroy, Kemel, and Glowinski (2004) described SP modulation of dopamine and serotonin transmission in the basal ganglia. These interactions, as well as the interactions between SP and norepinephrine (discussed in more detail above, in the context of the antidepressant mechanisms of NK-1r antagonists), highlight the fact that SP does not act in isolation.

SP also interacts intimately with immune system products, such as pro-inflammatory cytokines and histamine, and the individual contribution of these molecules is difficult, if not impossible, to define. Attributing the relationship between chronic inflammation and depression to a single mediator would be a gross oversimplification since these disorders are heterogeneous and the factors that regulate them are complex and redundant. Future research aimed at understanding these interactions should be a priority and will undoubtedly prove useful in more precisely defining SP's role in the overlap of chronic inflammation and affective disorders.

Most of the evidence implicating SP in the pathophysiology of chronic inflammatory disease comes from studies of chronic inflammation of barrier tissues, such as the respiratory tract, gastrointestinal tract, and skin. Evidence for SP involvement in arthritis (Keeble & Brain, 2004; Lambert et al., 1998; Westermarck et al., 2001) and fibromyalgia (De Stefano et al., 2000; I. J. Russell et al., 1994) does exist, but it is limited. On the other hand, chronic inflammatory conditions like cardiovascular disease clearly have an association with stress and depression, yet evidence has suggested that SP does not contribute significantly to inflammation in this context. Rather, SP seems more involved in modulating coronary artery tone and heart rate (Hoover, Chang, Hancock, & Zhang, 2000). In contrast, other inflammatory mediators including C-reactive protein and pro-inflammatory cytokines have been directly linked to the pathogenesis and progression of inflammation in cardiovascular disease (Reiss & Glass, 2006). Moreover, these inflammatory mediators can participate in the stress-induced cardiovascular conditions that lead to atherosclerosis and have been implicated in the association between cardiovascular disease and depression (Black & Garbutt, 2002; Elenkov, Iezzoni, Daly, Harris, & Chrousos, 2005; Musselman, Evans, & Nemeroff, 1998). Thus, it is likely that multiple mechanisms underlie the association between chronic inflammatory disease and affective disorders. It may be the case that the importance of SP in this regard is limited to inflammation occurring in barrier tissues.

Future Directions

The drugs currently available for treating depression are not an option for a significant number of individuals because either they are not effective or they are accompanied by intolerable adverse effects. Hence, there is a need for new classes of antidepressant drugs that work through novel mechanisms, as well as a need for a more detailed system for categorizing subtypes of depression. Drugs acting at neurokinin receptors show promise in this regard. At this point, knowledge concerning the antidepressant mechanism of NK-1r antagonists is very limited. Together with the mixed results of the clinical trials, these observations speak to the need for future work to focus on a more precise understanding of how SP contributes to psychopathology and which neural processes NK-1r antagonists specifically affect. As a complement to research at the molecular and cellular levels, neuroimaging tools such as PET and fMRI provide the potential to address these types of questions relatively noninvasively. SP radioactive tracers are currently being developed and tested for use in PET, which will allow investigation of *in vivo* central SP activity (Solin et al., 2004; reviewed in Hargreaves, 2002). This technology will prove invaluable and should be used in determining under what circumstances neural SP activity changes and if SP expression is aberrant in depressed populations or subpopulations. Combined, this information would hopefully lead to a more targeted approach to pharmacological treatment of depression and the identification of subtypes of depression that would benefit from neurokinin receptor (NK-1, NK-2, and/or NK-3) blockade, either alone or in combination with other available drugs.

At the same time, a closer look should be taken at the composition of the groups of depressed individuals included in the successful NK-1r antagonist antidepressant trials. It has been suggested that individuals whose depression is more severe or accom-

panied by moderate to high anxiety are more likely to respond to NK-1r antagonists (Kramer et al., 1998; Rupniak & Kramer, 1999). Individuals with elevated serum or CSF levels of SP may also be likely to benefit. In addition, the information reviewed here suggests that both symptoms of chronic inflammatory disease and mood and anxiety disorders may respond to blockade of one or more neurokinin receptors. Thus, individuals in whom these conditions are comorbid are another logical target.

If symptoms of psychopathology and chronic inflammation reflect a common underlying pathophysiology—dysregulation of SP—either central or peripheral normalization of SP levels might be expected to ameliorate symptoms in the other. Indeed, Krommydas and colleagues (2005) suggested that antidepressants actually reduce expression of inflammatory mediators and discussed their utility in treating asthma and other inflammatory diseases. This is consistent with the reports, discussed above, showing that SP levels normalize following successful antidepressant treatment (Bondy et al., 2003; Husum et al., 2001; Lieb et al., 2004; Olsson et al., 2004; Shirayama et al., 1996). However, few reports in the literature have addressed this question in the context of peripheral inflammation. Lechin et al. (1998) reported that the antidepressant tianeptine (a selective serotonin reuptake enhancer) was very effective in treating asthma in a double-blind and randomized, placebo-controlled study. In a more recent investigation, Brown et al. (2005) reported a decline in corticosteroid use in depressed asthmatics treated with the antidepressant citalopram (an SSRI) compared with corticosteroid use in a group treated with placebo, despite similar improvements in self-reported functional impairment and quality of life related to asthma symptoms in the two groups. However, this study did not report the effect of citalopram on any objective measures of lung function. The efficacy of citalopram was recently evaluated in a group of nondepressed IBS patients (Tack et al., 2006). In this study, citalopram significantly reduced gastrointestinal symptoms and improved overall well-being compared with placebo. Similarly, both psychotherapy and paroxetine treatment were evaluated in IBS patients with and without depression and anxiety (Creed et al., 2005). The efficacy of paroxetine and psychotherapy was similar to that of citalopram in reducing gastrointestinal and psychological symptoms. Interestingly, the reduction in gastrointestinal symptoms was determined to be partially independent of the reduction in psychological symptoms. Nevertheless, all of these studies assessed subjective measures of symptom improvement. Future research should include objective measures of disease progress as well. Further, whether or not SP signaling was normalized as a result of antidepressant treatment in these studies is unknown. The neuroimaging techniques previously discussed would be useful to this end in determining the actions of SP in the brain in the context of comorbid inflammation and mood and anxiety disorders. fMRI is currently being used to study the effects of manipulating peripheral physiological function, relevant to chronic inflammatory disease, on activity in emotional neural circuitry in patients and healthy populations (Banzett et al., 2000; Liotti et al., 2001; Mertz et al., 2000; Rosenkranz et al., 2005). A subsequent step in this line of inquiry will be to investigate the effect of SP signaling in these paradigms through the use of NK-1r antagonists and agonists, as well as SP radioactive tracers.

References

- Adcock, I. M., Peters, M., Gelder, C., Shirasaki, H., Brown, C. R., & Barnes, P. J. (1993). Increased tachykinin receptor gene expression in asthmatic lung and its modulation by steroids. *Journal of Molecular Endocrinology*, *11*, 1–7.
- Adell, A. (2004). Antidepressant properties of substance P antagonists: Relationship to monoaminergic mechanisms? *Current Drug Targets—CNS & Neurological Disorders*, *3*, 113–121.
- Advenier, C., Joos, G., Molimard, M., Lagente, V., & Pauwels, R. (1999). Role of tachykinins as contractile agonists of human airways. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology*, *29*, 579–584.
- Advenier, C., Lagente, V., & Boichot, E. (1997). The role of tachykinin receptor antagonists in the prevention of bronchial hyperresponsiveness, airway inflammation and cough. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology*, *10*, 1892–1906.
- Aguiar, M. S., & Brandão, M. L. (1994). Conditioned place aversion produced by microinjections of substance P into the periaqueductal gray of rats. *Behavioral Pharmacology*, *5*, 369–373.
- Aguiar, M. S., & Brandão, M. L. (1996). Effects of microinjections of the neuropeptide substance P in the dorsal periaqueductal gray on the behaviour of rats in the plus-maze test. *Physiology and Behavior*, *60*, 1183–1186.
- Ahluwalia, A., De Felipe, C., O'Brien, J., Hunt, S. P., & Perretti, M. (1998). Impaired IL-1beta-induced neutrophil accumulation in tachykinin NK1 receptor knockout mice. *British Journal of Pharmacology*, *124*, 1013–1015.
- Albeck, D. S., McKittrick, C. R., Blanchard, D. C., Blanchard, R. J., Nikulina, J., McEwen, B. S., et al. (1997). Chronic social stress alters levels of corticotropin-releasing factor and arginine vasopressin mRNA in rat brain. *Journal of Neuroscience*, *17*, 4895–4903.
- Albuquerque, A. A. C., Leal-Cardoso, J. H., & Weinreich, D. (1997). Role of mast cell- and non-mast-cell-derived inflammatory mediators in immunologic induction of synaptic plasticity. *Brazilian Journal of Medical and Biological Research*, *30*, 909–912.
- Al-Chaer, E. D., Kawasaki, M., & Pasricha, P. J. (2000). A new model of chronic visceral hypersensitivity in adult rats induced by colon irritation during postnatal development. *Gastroenterology*, *119*, 1276–1285.
- Allen, B. J., Rogers, S. D., Ghilardi, J. R., Menning, P. M., Kuskowski, M. A., Basbaum, A. I., et al. (1997). Noxious cutaneous thermal stimuli induce a graded release of endogenous substance P in the spinal cord: Imaging peptide action in vivo. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *17*, 5921–5927.
- Anichini, M., Cesaretti, S., Lepori, M., Maddali Bongi, S., Maresca, M., & Zoppi, M. (1997). Substance P in the serum of patients with rheumatoid arthritis. *Revue du Rhumatisme English Edition*, *64*, 18–21.
- Anisman, H., Merali, Z., Poulter, M. O., & Hayley, S. (2005). Cytokines as a precipitant of depressive illness: Animal and human studies. *Current Pharmaceutical Designs*, *11*, 963–972.
- Bachert, C. (1998). Histamine—A major role in allergy? *Clinical and Experimental Allergy*, *28*, 15–19.
- Baker, K. G., Halliday, G. M., Hornung, J.-P., Geffen, L. B., Cotton, R. G. H., & Törk, I. (1991). Distribution, morphology and number of monoamine-synthesizing and substance P-containing neurons in the human dorsal raphe nucleus. *Neuroscience*, *42*, 757–775.
- Baker, S. J., Morris, J. L., & Gibbins, I. L. (2003). Cloning of a C-terminally truncated NK-1 receptor from guinea-pig nervous system. *Brain Research Molecular Brain Research*, *111*, 136–147.
- Baluk, P. (1997). Neurogenic inflammation in the skin and airways. *The Journal of Investigative Dermatology*, *2*, 76–81.
- Banik, R. K., Sato, J., Yajima, H., & Mizumura, K. (2001). Differences between the Lewis and Sprague-Dawley rats in chronic inflammation

- induced norepinephrine sensitivity of cutaneous C-fiber nociceptors. *Neuroscience Letters*, 299, 21–24.
- Banzett, R. B., Mulnier, H. E., Murphy, K., Rosen, S. D., Wise, R. J. S., & Adams, L. (2000). Breathlessness in humans activates insular cortex. *NeuroReport*, 11, 2117–2120.
- Baraniuk, J. N., Ali, M., Yuta, A., Fang, S.-Y., & Naranch, K. (1999). Hypertonic saline nasal provocation stimulates nociceptive nerves, substance P release, and glandular mucous exocytosis in normal humans. *American Journal of Respiratory and Critical Care Medicine*, 160, 655–662.
- Basso, A. S., Costa-Pinto, F. A., Britto, L. R. G., de Sá-Rocha, L. C., & Palermo-Neto, J. (2004). Neural pathways involved in food allergy signaling in the mouse brain: Role of capsaicin-sensitive afferents. *Brain Research*, 1009, 181–188.
- Basso, A. S., de Sá-Rocha, L. C., & Palermo-Neto, J. (2001). Immune-induced flavor aversion in mice: Modification by neonatal capsaicin treatment. *Neuroimmunomodulation*, 9, 88–94.
- Beaujouan, J.-C., Torrens, Y., Saffroy, M., Kemel, M.-L., & Glowinski, J. (2004). A 25 year adventure in the field of tachykinins. *Peptides*, 25, 339–357.
- Bellinger, D. L., Lorton, D., Romano, T. D., Olschowka, J. A., Felten, S. Y., & Felten, D. L. (1990). Neuropeptide innervation of lymphoid organs. *Annals of the New York Academy of Sciences*, 594, 17–33.
- Bensaid, M., Fauchoux, B. A., Hirsch, E., Agid, Y., Soubrie, P., & Oury-Donat, F. (2001). Expression of tachykinin NK2 receptor mRNA in human brain. *Neuroscience Letters*, 303, 25–28.
- Berman, A. S., Chancellor-Freeland, C., Zhu, G., & Black, P. H. (1996). Substance P primes murine peritoneal macrophages for an augmented proinflammatory cytokine response to lipopolysaccharide. *Neuroimmunomodulation*, 3, 141–149.
- Berrebi, D., Languépin, J., Ferkdadjji, L., Foussat, A., De Lagausie, P., Paris, R., et al. (2003). Cytokines, chemokine receptors, and homing molecule distribution in the rectum and stomach of pediatric patients with ulcerative colitis. *Journal of Pediatric Gastroenterology and Nutrition*, 37, 300–308.
- Berrettini, W. H., Rubinow, D. R., Nurnberger, J. I., Jr., Simmons-Alling, S., Post, R. M., & Gershon, E. S. (1985). Substance P immunoreactivity in affective disorders. *Biological Psychiatry*, 20, 965–970.
- Bertrand, C., Geppetti, P., Baker, J., Yamawaki, I., & Nadel, J. A. (1993). Role of neurogenic inflammation in antigen-induced vascular extravasation in guinea pig trachea. *Journal of Immunology*, 150, 1479–1485.
- Besedovsky, H. O., & del Rey, A. (2007). Physiology of psychoneuroimmunology: A personal view. *Brain, Behavior, and Immunity*, 21, 34–44.
- Black, P. H. (1994). Immune system–central nervous system interactions: Effect and immunomodulatory consequences of immune system mediators on the brain. *Antimicrobial Agents and Chemotherapy*, 38, 7–12.
- Black, P. H. (2002). Stress and the inflammatory response: A review of neurogenic inflammation. *Brain, Behavior, and Immunity*, 16, 622–653.
- Black, P. H. (2003). The inflammatory response is an integral part of the stress response: Implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. *Brain, Behavior, and Immunity*, 17, 350–364.
- Black, P. H., & Garbutt, L. D. (2002). Stress, inflammation, and cardiovascular disease. *Journal of Psychosomatic Research*, 52, 1–23.
- Blalock, J. E., & Smith, E. M. (2007). Conceptual development of the immune system as a sixth sense. *Brain, Behavior, and Immunity*, 21, 23–33.
- Bondy, B., Baghai, T. C., Minov, C., Schüle, C., Schwarz, M. J., Zwanzger, P., et al. (2003). Substance P serum levels are increased in major depression: Preliminary results. *Biological Psychiatry*, 53, 538–542.
- Bost, K. L., Breeding, S. A., & Pascual, D. W. (1992). Modulation of the mRNAs encoding substance P and its receptor in rat macrophages by LPS. *Regional Immunology*, 4, 105–112.
- Boyce, S., Smith, D., Carlson, E. J., Hewson, L., Rigby, M., & Harrison, T. (2001). Intra-amygdala injection of the substance P (NK₁ receptor) antagonist L-760735 inhibits neonatal vocalisation in guinea-pigs. *Neuropharmacology*, 41, 130–137.
- Bradesi, S., Eutamene, H., Garcia-Villar, R., Fioramonti, J., & Buéno, L. (2002). Acute and chronic stress differently affect visceral sensitivity to rectal distention in female rats. *Neurogastroenterology and Motility: The Official Journal of the European Gastrointestinal Motility Society*, 14, 75–82.
- Brodin, E., Rosen, A., Schott, E., & Brodin, K. (1994). Effects of sequential removal of rats from a group cage, and of individual housing of rats, on substance P, cholecystokinin and somatostatin levels in the periaqueductal grey and limbic regions. *Neuropeptides*, 26, 253–260.
- Brown, E. S., Vigil, L., Khan, D. A., Liggin, J. D. M., Carmody, T. J., & Rush, A. J. (2005). A randomized trial of Citalopram versus placebo in outpatients with asthma and major depressive disorder: A proof of concept study. *Biological Psychiatry*, 58, 865–870.
- Bruce, A. N. (1913). Vaso-dilator axon reflexes. *Quarterly Journal of Experimental Physiology*, 6, 339–354.
- Buckley, T. L., & Nijkamp, F. P. (1994). Airways hyperreactivity and cellular accumulation in a delayed-type hypersensitivity reaction in the mouse: Modulation by capsaicin-sensitive nerves. *American Journal of Respiratory and Critical Care Medicine*, 149, 400–407.
- Buske-Kirschbaum, A., Geiben, A., Hollig, H., Morschhauser, E., & Hellhammer, D. (2002). Altered responsiveness of the hypothalamus–pituitary–adrenal axis and the sympathetic adrenomedullary system to stress in patients with atopic dermatitis. *The Journal of Clinical Endocrinology and Metabolism*, 87, 4245–4251.
- Busse, W. W., & Sedgwick, J. B. (1992). Eosinophils in asthma. *Annals of Allergy*, 68, 286–290.
- Capuron, L., Raison, C. L., Musselman, D. L., Lawson, D. H., Nemeroff, C. B., & Miller, A. H. (2003). Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. *American Journal of Psychiatry*, 160, 1342–1345.
- Cardell, L. O., Uddman, R., & Edvinsson, L. (1994). Low plasma concentrations of VIP and elevated levels of other neuropeptides during exacerbations of asthma. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology*, 7, 2169–2173.
- Carr, M. J., & Udem, B. J. (2001). Inflammation-induced plasticity of the afferent innervation of the airways. *Environmental Health Perspectives*, 109, 567–571.
- Carter, M. S., & Krause, J. E. (1990). Structure, expression and some regulatory mechanisms of the rat preprotachykinin gene encoding substance P, neurokinin A, neuropeptide K and neuropeptide gamma. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 10, 2203–2214.
- Carvahlo, A. T. P., Elia, C. C. S., de Souza, H. S. P., Roberto, P., Elias, P., Pontes, E. L., et al. (2003). Immunohistochemical study of intestinal eosinophils in inflammatory bowel disease. *Journal of Clinical Gastroenterology*, 36, 120–125.
- Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003, July 18). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, 301, 386–389.
- Castairs, J. R., & Barnes, P. J. (1986). Autoradiographic mapping of substance P receptors in lung. *European Journal of Pharmacology*, 127, 295–296.
- Chang, L., Berman, S., Mayer, E. A., Suyenobu, B., Derbyshire, S., Naliboff, B., et al. (2003). Brain responses to visceral and somatic stimuli in patients with irritable bowel syndrome with and without fibromyalgia. *The American Journal of Gastroenterology*, 98, 1354–1361.
- Chappell, P. (2002, June). *Effects of CP-122, 721, a selective NK-1*

- receptor antagonist, in patients with major depression. Presented at the 42nd annual meeting of the New Clinical Drug Evaluation Unit (NCDEU), Boca Raton, FL.
- Chavolla-Calderón, M., Bayer, M. K., & Fontán, J. P. (2003). Bone marrow transplantation reveals an essential synergy between neuronal and hemopoietic cell neurokinin production in pulmonary inflammation. *Journal of Clinical Investigation*, *111*, 973–980.
- Chen, C.-Y., Bonham, A. C., Plopper, C. G., & Joad, J. P. (2003). Neuroplasticity in nucleus tractus solitarius neurons after episodic ozone exposure in infant primates. *Journal of Applied Physiology*, *94*, 819–827.
- Chen, C.-Y., Bonham, A. C., Schelegle, E. S., Gershwin, L. J., Plopper, C. G., & Joad, J. P. (2001). Extended allergen exposure in asthmatic monkeys induces neuroplasticity in nucleus tractus solitarius. *The Journal of Allergy and Clinical Immunology*, *108*, 557–562.
- Cheung, D., Van Der Veen, H., Den Hartig, J., Dijkman, J. H., & Sterk, P. J. (1994). Effects of inhaled substance P on airway hyperresponsiveness to methacholine in asthmatic subjects *in vivo*. *Journal of Applied Physiology*, *77*, 1325–1332.
- Chikanza, I. C., Petrou, P., & Chrousos, G. (2000). Perturbations of arginine vasopressin secretion during inflammatory stress. *Annals of the New York Academy of Sciences*, *917*, 825–834.
- Chowdrey, H. S., Jessop, D. S., & Lightman, S. L. (1990). Substance P stimulates arginine vasopressin and inhibits adrenocorticotropin release *in vivo* in the rat. *Neuroendocrinology*, *52*, 90–93.
- Chowdrey, H. S., Larsen, P. J., Harbuz, M. S., Jessop, D. S., Aguilera, G., Eckland, D. J. A., et al. (1995). Evidence for arginine vasopressin as the primary activator of the HPA axis during adjuvant-induced arthritis. *British Journal of Pharmacology*, *116*, 2417–2424.
- Chowdrey, H. S., Larsen, P. J., Harbuz, M. S., Lightman, S. L., & Jessop, D. S. (1995). Endogenous substance P inhibits the expression of corticotropin-releasing hormone during chronic inflammatory stress. *Life Sciences*, *57*, 2021–2029.
- Chrousos, G. P. (1998). Stressors, stress, and neuroendocrine integration of the adaptive response. *Annals of the New York Academy of Sciences*, *851*, 311–335.
- Chrousos, G. P. (2000). Stress, chronic inflammation, and emotional and physical well-being: Concurrent effects and chronic sequelae. *The Journal of Allergy and Clinical Immunology*, *106*, S275–291.
- Chu, H. W., Kraft, M., Krause, J. E., Rex, M. D., & Martin, R. J. (2000). Substance P and its receptor neurokinin 1 expression in asthmatic airways. *The Journal of Allergy and Clinical Immunology*, *106*, 713–722.
- Cieslewicz, G., Tomkinson, A., Adler, A., Duez, C., Schwarze, J., Takeda, K., et al. (1999). The late, but not early, asthmatic response is dependent on IL-5 and correlates with eosinophil infiltration. *The Journal of Clinical Investigation*, *104*, 301–308.
- Collins, S. M. (2001). Stress and the gastrointestinal tract: IV. Modulation of intestinal inflammation by stress: Basic mechanisms and clinical relevance. *American Journal of Physiology–Gastrointestinal and Liver Physiology*, *280*, 315–318.
- Conley, R. K., Cumberbatch, M. J., Mason, G. S., Williamson, D. J., Harrison, T., Locker, K., et al. (2002). Substance P (neurokinin 1) receptor antagonists enhance dorsal raphe neuronal activity. *The Journal of Neuroscience*, *22*, 7730–7736.
- Cooke, H. J., Sidhu, M., Fox, P., Wang, Y.-Z., & Zimmermann, E. M. (1997). Substance P as a mediator of colonic secretory reflexes. *American Journal of Physiology–Gastrointestinal and Liver Physiology*, *272*, 238–245.
- Cooper, P. E., Fernstrom, M. H., Rorstad, O. P., Leeman, S. E., & Martin, J. B. (1981). The regional distribution of somatostatin, substance P and neurotensin in the human brain. *Brain Research*, *218*, 219–232.
- Costa, M., Brookes, S. J. H., & Henning, G. W. (2000). Anatomy and physiology of the enteric nervous system. *Gut*, *47*, iv15–iv19.
- Cowan, A. R., Dean, C., Bago, M., & Seagard, J. L. (2000). Potentiation of non-N-methyl-D-aspartate receptor-induced changes in blood pressure by substance P in rats. *Neuroscience Letters*, *278*, 161–164.
- Creed, F., Guthrie, E., Ratcliffe, J., Fernandes, L., Rigby, C., Tomenson, B., et al. (2005). Does psychological treatment help only those patients with severe irritable bowel syndrome who also have a concurrent psychiatric disorder? *Australian and New Zealand Journal of Psychiatry*, *39*, 807–815.
- Crimi, N., Palermo, F., Oliveri, R., Palermo, B., Vancheri, C., Polosa, R., et al. (1990). Influence of antihistamine (astemizole) and anticholinergic drugs (ipratropium bromide) on bronchoconstriction induced by substance P. *Annals of Allergy*, *65*, 115–120.
- Crimi, N., Palermo, F., Oliveri, R., Vancheri, C., Palermo, R., Polosa, R., et al. (1988). Bronchospasm induced by inhalation of substance P: Effect of sodium cromoglycate. *Respiration*, *54*, 95–99.
- Cruwys, S. C., Garrett, N. E., & Kidd, B. L. (1995). Sensory denervation with capsaicin attenuates inflammation and nociception in arthritic rats. *Neuroscience Letters*, *193*, 205–207.
- Culman, J., Itoi, K., & Unger, T. (1995). Hypothalamic tachykinins: Mediators of stress responses? *Annals of the New York Academy of Sciences*, *771*, 204–218.
- Cutrufo, C., Evangelista, S., Cirillo, R., Ciucci, A., Conte, B., Lopez, G., et al. (1999). Effect of MEN 11467, a new tachykinin NK1 receptor antagonist, in acute rectocolitis induced by acetic acid in guinea-pigs. *European Journal of Pharmacology*, *374*, 277–283.
- Czeh, B., Fuchs, E., & Simon, M. (2006). NK₁ receptor antagonists under investigation for the treatment of affective disorders. *Expert Opinion on Investigational Drugs*, *15*, 479–486.
- Czeh, B., Simon, M., van der Hart, M. G. C., Schmelting, B., Hesselink, M. B., & Fuchs, E. (2005). Chronic stress decreases the number of parvalbumin-immunoreactive interneurons in the hippocampus: Prevention by treatment with a substance P receptor (NK₁) antagonist. *Neuropsychopharmacology*, *30*, 67–79.
- Dam, T. V., & Quirion, R. (1986). Pharmacological characterization and autoradiographic characterization of substance P receptors in guinea-pig brain. *Peptides*, *7*, 855–864.
- Dantzer, R., Bluthé, R.-M., Gheusi, G., Crimona, S., Layé, S., Parnet, P., & Kelley, K. W. (1998). Molecular basis of sickness behavior. *Annals of the New York Academy of Sciences*, *856*, 132–138.
- Dantzer, R., Bluthé, R.-M., Layé, S., Bret-Dibat, J.-L., Parnet, P., & Kelley, K. W. (1998). Cytokines and sickness behavior. *Annals of the New York Academy of Sciences*, *840*, 586–590.
- Dantzer, R., & Kelley, K. W. (2007). Twenty years of research on cytokine-induced sickness behavior. *Brain, Behavior, and Immunity*, *21*, 153–160.
- Davis, M., & Whalen, P. J. (2001). The amygdala: Vigilance and emotion. *Molecular Psychiatry*, *6*, 13–34.
- Days, C. V., Buller, K. M., & Day, T. A. (2004). Hypothalamic paraventricular nucleus neurons regulate medullary catecholamine cell responses to restraint stress. *The Journal of Comparative Neurology*, *478*, 22–34.
- De Araújo, J. E., Huston, J. P., & Brandão, M. L. (1998). Aversive effects of C-fragments of substance P in the dorsal periaqueductal gray matter. *Experimental Brain Research*, *123*, 84–89.
- De Araújo, J. E., Huston, J. P., & Brandão, M. L. (2001). Place aversion induced by microinjections of C-fragment of substance P into the dorsal periaqueductal gray of rats is mediated by tachykinin NK1 receptors. *Peptides*, *22*, 1447–1452.
- De Felipe, C., Herrero, J. F., O'Brien, J. A., Palmer, J. A., Doyle, C. A., Smith, A. J. H., et al. (1998, March 26). Altered nociception, analgesia and aggression in mice lacking the receptor for substance P. *Nature*, *392*, 394–397.
- De Giorgio, R., Tazzari, P. L., Barbara, G., Stanghellini, V., & Corinaldesi,

- R. (1998). Detection of substance P immunoreactivity in human peripheral leukocytes. *Journal of Neuroimmunology*, *82*, 175–181.
- DeRijk, R. H., Boelen, A., Tilders, F. J., & Berkenbosch, F. (1994). Induction of plasma interleukin-6 by circulating adrenaline in the rat. *Psychoneuroendocrinology*, *19*, 155–163.
- De Stefano, R., Selvi, E., Villanova, M., Frati, E., Manganelli, S., Franceschini, E., et al. (2000). Image analysis quantification of substance P immunoreactivity in the trapezius muscle of patients with fibromyalgia and myofascial pain syndrome. *Journal of Rheumatology*, *27*, 2906–2910.
- Deuschle, M., Sander, P., Herpfer, I., Fiebich, B. L., Heuser, I., & Lieb, K. (2005). Substance P in serum and cerebrospinal fluid of depressed patients: No effect of antidepressant treatment. *Psychiatry Research*, *136*, 1–6.
- Dewing, S. B. (1971). Remission of psoriasis associated with cutaneous nerve section. *Archives of Dermatology*, *104*, 220–221.
- de Wit, R., Herrstedt, J., Rapoport, B., Carides, A. D., Guo Guang-Ma, J., Elmer, M., et al. (2004). The oral NK1(1) antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: A combined analysis of two randomised, placebo-controlled phase III clinical trials. *European Journal of Cancer*, *40*, 403–410.
- Dey, R. D., Altemus, J. B., & Michalkiewicz, M. (1991). Distribution of vasoactive intestinal peptide- and substance P-containing nerves originating from neurons of airway ganglia in cat bronchi. *The Journal of Comparative Neurology*, *304*, 330–340.
- Dickerson, C., Udem, B., Bullock, B., & Winchurch, R. A. (1998). Neuropeptide regulation of proinflammatory cytokine responses. *Journal of Leukocyte Biology*, *63*, 602–605.
- Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and the cortisol response: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin*, *130*, 355–391.
- Di Maria, G. U., Bellofiore, S., & Geppetti, P. (1998). Regulation of airway neurogenic inflammation by neutral endopeptidase. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology*, *12*, 1454–1462.
- Di Sebastiano, P., Grossi, L., Di Mola, F. F., Angelucci, D., Friess, H., Marzio, L., et al. (1999). SR140333, a substance P receptor antagonist, influences morphological and motor changes in rat experimental colitis. *Digestive Diseases and Sciences*, *44*, 439–444.
- Donahue, R. R., LaGraize, S. C., & Fuchs, P. N. (2001). Electrolytic lesion of the anterior cingulate cortex decreases inflammatory, but not neuropathic nociceptive behavior in rats. *Brain Research*, *897*, 131–138.
- Dunn, A. J., Wang, J., & Ando, T. (1999). Effects of cytokines on cerebral neurotransmission: Comparison with the effects of stress. *Advances in Experimental Medicine and Biology*, *461*, 117–127.
- Ebner, K., Rupniak, N. M., Saria, A., & Singewald, N. (2004). Substance P in the medial amygdala: Emotional stress-sensitive release and modulation of anxiety-related behavior in rats. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 4280–4285.
- Ebner, K., & Singewald, N. (2005). Effects of NK1 receptor antagonist administration on basal and stress-induced substance P release in the amygdala. *Journal of Neurochemistry*, *94*, 183.
- Ebner, K., & Singewald, N. (2006). The role of substance P in stress and anxiety responses. *Amino Acids*, *31*, 251–272.
- Elenkov, I. J., Iezzoni, D. G., Daly, A., Harris, A. G., & Chrousos, G. P. (2005). Cytokine dysregulation, inflammation and well-being. *Neuroimmunomodulation*, *12*, 255–269.
- Elenkov, I. J., Papanicolaou, D. A., Wilder, R. L., & Chrousos, G. P. (1996). Modulatory effects of glucocorticoids and catecholamines on human interleukin-12 and interleukin-10 production: Clinical implications. *Proceedings of the Association of American Physicians*, *108*, 374–381.
- Elfvin, L. G., Lindh, B., & Hokfelt, T. (1993). The chemical neuroanatomy of sympathetic ganglia. *Annual Review of Neuroscience*, *16*, 471–507.
- Erin, N., Ersoy, Y., Ercan, F., Akici, A., & Oktay, S. (2004). NK-1 antagonist CP99994 inhibits stress-induced mast cell degranulation in rats. *Clinical and Experimental Dermatology*, *29*, 644–648.
- Eskandari, F., Webster, J. I., & Sternberg, E. M. (2003). Neural immune pathways and their connections to inflammatory diseases. *Arthritis Research & Therapy*, *5*, 251–265.
- Evangelista, S. (2001). Involvement of tachykinins in intestinal inflammation. *Current Pharmaceutical Design*, *7*, 19–30.
- Evangelista, S. (2005). Talnetant GlaxoSmithKline. *Current Opinions in Investigational Drugs*, *6*, 717–721.
- Fahy, J. V., Wong, H. H., Geppetti, P., Reis, J. M., Harris, S. C., Maclean, D. B., et al. (1995). Effect of an NK₁ receptor antagonist (CP-99,994) on hypertonic saline-induced bronchoconstriction and cough in male asthmatic subjects. *American Journal of Respiratory and Critical Care Medicine*, *152*, 879–884.
- Faria, M., Navarra, P., Tsagarakis, S., Besser, G. M., & Grossman, A. B. (1991). Inhibition of CRH-41 release by substance P, but not substance K, from rat hypothalamus in vitro. *Brain Research*, *538*, 76–78.
- Feistritzer, C., Clausen, J., Sturn, D. H., Djanani, A., Gunsilius, E., Wiedermann, C. J., et al. (2003). Natural killer cell functions mediated by the neuropeptide substance P. *Regulatory Peptides*, *116*, 119–126.
- Fischer, A., McGregor, G. P., Saria, A., Phillipin, B., & Kummer, W. (1996). Induction of tachykinin gene and peptide expression in guinea pig nodose primary afferent neurons by allergic airway inflammation. *The Journal of Clinical Investigation*, *98*, 2284–2291.
- Freed, A. L., Audus, K. L., & Lunte, S. M. (2002). Investigation of substance P transport across the blood-brain barrier. *Peptides*, *23*, 157–165.
- Fryer, A. D., & Wills-Karp, M. (1991). Dysfunction of M₂-muscarinic receptors in pulmonary parasympathetic nerves after antigen challenge. *Journal of Applied Physiology*, *71*, 2255–2261.
- Furmark, T., Appel, L., Michelgård, A., Wahlstedt, K., Åhs, F., Zancan, S., et al. (2005). Cerebral blood flow changes after treatment of social phobia with the neurokinin-1 antagonist GR205171, citalopram, or placebo. *Biological Psychiatry*, *58*, 132–142.
- Furness, J. B. (2000). Types of neurons in the enteric nervous system. *Journal of the Autonomic Nervous System*, *81*, 87–96.
- Fusayasu, E., Kowa, H., Takeshima, T., Nakaso, K., & Nakashima, K. (2007). Increased plasma substance P and CGRP levels, and high ACE activity in migraineurs during headache-free periods. *Pain*, *128*, 209–214.
- Gaffori, O., Stewart, J. M., & de Wied, D. (1984). Influence of substance P and fragments on passive avoidance behavior. *Experientia*, *40*, 89–91.
- Galeazza, M. T., Garry, M. G., Yost, H. J., Strait, K. A., Hargreaves, K. M., & Seybold, V. S. (1995). Plasticity in the synthesis and storage of substance P and calcitonin gene-related peptide in primary afferent neurons during peripheral inflammation. *Neuroscience*, *66*, 443–458.
- Garland, A., Necheles, J., White, S. R., Neeley, S. P., Leff, A. R., Carson, S. S., et al. (1997). Activated eosinophils elicit substance P release from cultured dorsal root ganglion neurons. *American Journal of Physiology—Lung Cellular and Molecular Physiology*, *273*, 1096–1102.
- Gavioli, E. C., Canteras, N. S., & De Lima, T. C. (1999). Anxiogenic-like effect induced by substance P injected into the lateral septal nucleus. *NeuroReport*, *10*, 3399–3403.
- Gavioli, E. C., Canteras, N. S., & De Lima, T. C. (2002). The role of lateral septal NK₁ receptors in mediating anxiogenic effects induced by intracerebroventricular injection of substance P. *Behavioural Brain Research*, *134*, 411–415.
- Geraciotti, T. D., Carpenter, L. L., Owens, M. J., Baker, D. G., Ekhaton, N. N., Horn, P. S., et al. (2006). Elevated cerebrospinal fluid substance P concentrations in posttraumatic stress disorder and major depression. *American Journal of Psychiatry*, *163*, 637–643.

- Gerard, N. P., Bao, L., Xiao-Ping, H., & Gerard, C. (1993). Molecular aspects of tachykinin receptors. *Regulatory Peptides*, *43*, 21–35.
- Germonpre, P. R., Bullock, G. R., Lambrecht, B. N., Van De Velde, V., Luyten, W. H. M. L., Joos, G. F., et al. (1999). Presence of substance P and neurokinin 1 receptors in human sputum macrophages and U-937 cells. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology*, *14*, 776–782.
- Giardina, G. A. M., Gagliardi, S., & Martinelli, M. (2003). Antagonists at the neurokinin receptors—Recent patent literature. *IDrugs*, *6*, 758–772.
- Glick, E. N. (1967). Asymmetrical rheumatoid arthritis after poliomyelitis. *British Medical Journal*, *3*, 26–29.
- Gold, P. W., & Chrousos, G. P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs. low CRH/NE states. *Molecular Psychiatry*, *7*, 254–275.
- Goldsby, R. A., Kindt, T. J., & Osborne, B. A. (2000). *Kuby immunology*. (4th ed.; pp. 384–386). New York: Freeman Press.
- Goode, T., O'Connell, J., Anton, P., Wong, H., Reeve, J., O'Sullivan, G. C., et al. (2000). Neurokinin-1 receptor expression in inflammatory bowel disease: Molecular quantitation and localisation. *Gut*, *47*, 387–396.
- Goode, T., O'Conner, T., Hopkins, A., Moriarty, D., O'Sullivan, G. C., Collins, K., et al. (2003). Neurokinin-1 receptor (NK-1r) expression is induced in human colonic epithelial cells by proinflammatory cytokines and mediates proliferation in response to substance P. *Journal of Cellular Physiology*, *197*, 30–41.
- Goto, T., & Tanaka, T. (2002). Tachykinins and tachykinin receptors in bone. *Microscopy Research and Technique*, *58*, 91–97.
- Gradin, K., Fatimunnisa, Q., Nomikos, G. G., Hillegaart, V., & Svensson, T. H. (1992). Substance P injection into the dorsal raphe increases blood pressure and serotonin release in the hippocampus of conscious rats. *European Journal of Pharmacology*, *218*, 363–367.
- Graham, R. M., Friedman, M., & Hoyle, G. W. (2001). Sensory nerves promote ozone-induced lung inflammation in mice. *American Journal of Respiratory and Critical Care Medicine*, *164*, 307–313.
- Greenwood, B., Doolittle, T., See, N. A., Koch, T. R., Dodds, W. J., & Davison, J. S. (1990). Effects of substance P and vasoactive intestinal polypeptide on contractile activity and epithelial transport in the ferret jejunum. *Gastroenterology*, *98*, 1509–1517.
- Gregg, T. R., & Siegel, A. (2001). Brain structures and neurotransmitters regulating aggression in cats: Implications for human aggression. *Progress in Neuro-Psychopharmacology*, *25*, 91–140.
- Guest, P. C., Knowles, M. R., Molon-Noblot, S., Salim, K., Smith, D., Murray, F., et al. (2004). Mechanisms of action of the antidepressants fluoxetine and the substance P antagonist L-000760735 are associated with altered neurofilaments and synaptic remodeling. *Brain Research*, *1002*, 1–10.
- Guiard, B. P., Froger, N., Hamon, M., Gardier, A. M., & Lanfumey, L. (2005). Sustained pharmacological blockade of NK1 substance P receptors causes functional desensitization of dorsal raphe 5-HT 1A autoreceptors in mice. *Journal of Neurochemistry*, *95*, 1713–1723.
- Guiard, B. P., Przybylski, C., Guilloux, J.-P., Seif, I., Froger, N., De Felipe, C., et al. (2004). Blockade of substance P (neurokinin 1) receptors enhances extracellular serotonin when combined with a selective serotonin reuptake inhibitor: An in vivo microdialysis study in mice. *Journal of Neurochemistry*, *89*, 54–63.
- Haddjeri, N., & Blier, P. (2001). Sustained blockade of neurokinin-1 receptors enhances serotonin neurotransmission. *Biological Psychiatry*, *50*, 191–199.
- Han, Y., Shaikh, M. B., & Siegel, A. (1996). Medial amygdaloid suppression of predatory attack behavior in the cat: I. Role of substance P pathway from the medial amygdala to the medial hypothalamus. *Brain Research*, *716*, 59–71.
- Harbuz, M. S., Chover-Gonzalez, A. J., & Jessop, D. S. (2003). Hypothalamic–pituitary–adrenal axis and chronic immune activation. *Annals of the New York Academy of Sciences*, *992*, 99–106.
- Harbuz, M. S., Jessop, D. S., Chowdrey, H. S., Blackwell, J. M., Larsen, P. J., & Lightman, S. L. (1995). Evidence for altered control of hypothalamic CRF in immune-mediated diseases. *Annals of the New York Academy of Sciences*, *771*, 449–458.
- Harbuz, M. S., Rees, R. G., Eckland, D., Jessop, D. S., Brewerton, D., & Lightman, S. L. (1992). Paradoxical responses of hypothalamic CRF mRNA and CRF-41 peptide and adenohipophyseal POMC mRNA during chronic inflammatory stress. *Endocrinology*, *130*, 1394–1400.
- Hargreaves, R. (2002). Imaging substance P receptors (NK₁) in the living human brain using positron emission tomography. *The Journal of Clinical Psychiatry*, *63*, 18–24.
- Harrison, S., & Geppetti, P. (2001). Substance P. *The International Journal of Biochemistry and Cell Biology*, *33*, 555–576.
- Hayashi, M., & Oshima, K. (1986). Neuropeptides in cerebral cortex of macaque monkey (*Macaca fuscata fuscata*): Regional distribution and ontogeny. *Brain Research*, *364*, 360–368.
- He, S.-H. (2004). Key role of mast cells and their major secretory products in inflammatory disease. *World Journal of Gastroenterology: WJG*, *10*, 309–318.
- Heijnen, C. J. (2007). Receptor regulation in neuroendocrine-immune communication: Current knowledge and future perspectives. *Brain, Behavior, and Immunity*, *21*, 1–8.
- Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: Hypothalamo–pituitary–adrenocortical axis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *29*, 1201–1213.
- Hermann, G. E., Holmes, G. M., & Rogers, R. C. (2005). TNF(alpha) modulation of visceral and spinal sensory processing. *Current Pharmaceutical Designs*, *11*, 1391–1409.
- Herpfer, I., Fiebich, B. L., Singewald, N., Hamke, M., & Lieb, K. (2005). Functional downregulation of the neurokinin 1 receptor by antidepressant, neuroleptics and mood stabilizers. *Pharmacopsychiatry*, *38*, A090.
- Herpfer, I., Hunt, S. P., & Stanford, S. C. (2005). A comparison of neurokinin 1 receptor knock-out (NK1^{-/-}) and wildtype mice: Exploratory behaviour and extracellular noradrenaline concentration in the cerebral cortex of anaesthetised subjects. *Neuropharmacology*, *48*, 706–719.
- Herpfer, I., & Lieb, K. (2003). Substance P and substance P receptor antagonists in the pathogenesis and treatment of affective disorders. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *4*, 56–63.
- Herpfer, I., & Lieb, K. (2005). Substance P receptor antagonists in psychiatry. *CNS Drugs*, *19*, 275–293.
- Heym, C., Braun, B., Shuyi, Y., Klimaschewski, L., & Colombo-Benkmann, M. (1995). Immunohistochemical correlation of human adrenal nerve fibres and thoracic dorsal root neurons with special reference to substance P. *Histochemistry and Cell Biology*, *104*, 233–243.
- Hökfelt, T., Pernow, B., & Wahren, J. (2001). Substance P: A pioneer amongst neuropeptides. *Journal of Internal Medicine*, *249*, 27–40.
- Holzer, P., & Holzer-Petsche, U. (1997a). Tachykinins in the gut: Part I. Expression, release and motor function. *Pharmacology and Therapeutics*, *73*, 173–217.
- Holzer, P., & Holzer-Petsche, U. (1997b). Tachykinins in the gut: Part II. Roles in neural excitation, secretion and inflammation. *Pharmacology and Therapeutics*, *73*, 219–263.
- Holzer, P., & Holzer-Petsche, U. (2001). Tachykinin receptors in the gut: Physiological and pathological implications. *Current Opinion in Pharmacology*, *1*, 583–590.
- Hoover, D. B., Chang, Y., Hancock, J. C., & Zhang, L. (2000). Actions of tachykinins with the heart and their relevance to cardiovascular disease. *Japanese Journal of Pharmacology*, *84*, 367–373.
- Howarth, P. H., Djukanovic, R., Wilson, J. W., Holgate, S. T., Springall,

- D. R., & Polak, J. M. (1995). Neuropeptide-containing nerves in endobronchial biopsies from asthmatic and non-asthmatic subjects. *American Journal of Respiratory Cell and Molecular Biology*, 3, 288–296.
- Hoyle, G. W., Graham, R. M., Finkelstein, J. B., Nguyen, K.-P. T., Gozal, D., & Friedman, M. (1998). Hyperinnervation of the airways in transgenic mice overexpressing nerve growth factor. *American Journal of Respiratory Cell and Molecular Biology*, 18, 149–157.
- Hunter, D. D., Myers, A. C., & Undem, B. J. (2000). Nerve growth factor-induced phenotypic switch in guinea pig airway sensory neurons. *American Journal of Respiratory and Critical Care Medicine*, 161, 1985–1990.
- Husum, H., Jiménez Vasquez, P. A., & Mathé, A. A. (2001). Changed concentrations of tachykinins and neuropeptide Y in brain of a rat model of depression: Lithium treatment normalizes tachykinins. *Neuropsychopharmacology*, 24, 183–191.
- Hwang, B. H., Katner, J., & Iyengar, S. (2005). Corticotropin-releasing factor mRNA and substance P receptor binding in the paraventricular hypothalamic nucleus, central nucleus of the amygdala, and locus coeruleus of Sprague-Dawley rats following restraint-induced stress. *Journal of Molecular Neuroscience*, 25, 239–250.
- Ichinose, M., Miura, M., Yamauchi, H., Kageyama, N., Tomaki, M., Oyake, T., et al. (1996). A neurokinin 1-receptor antagonist improves exercise-induced airway narrowing in asthmatic patients. *American Journal of Respiratory and Critical Care Medicine*, 153, 936–941.
- Imai, S., Tokunaga, Y., Maeda, T., Kikkawa, M., & Hukuda, S. (1997). Calcitonin gene-related peptide, substance P, and tyrosine hydroxylase-immunoreactive innervation of rat bone marrows: An immunohistochemical and ultrastructural investigation on possible efferent and afferent mechanisms. *Journal of Orthopaedic Research: Official Publication of the Orthopaedic Research Society*, 15, 133–140.
- Inoue, A., Ikoma, K., Morioka, N., Kumagai, K., Hashimoto, T., Hide, I., et al. (1999). Interleukin-1 β induces substance P release from primary afferent neurons through the cyclooxygenase-2 system. *Journal of Neurochemistry*, 73, 2206–2213.
- Iwamoto, I., Nakagawa, N., Yamazaki, H., Kimura, A., Tomioka, H., & Yoshida, S. (1993). Mechanism for substance P-induced activation of human neutrophils and eosinophils. *Regulatory Peptides*, 46, 228–230.
- Jacobs, B. L., Praag, H., & Gage, F. H. (2000). Adult brain neurogenesis and psychiatry: A novel theory of depression. *Molecular Psychiatry*, 5, 262–269.
- Jakab, R. L., Goldman-Rakic, P., & Leranth, C. (1997). Dual role of substance P/GABA axons in cortical neurotransmission: Synaptic triads on pyramidal cell spines and basket-like innervation of layer I-III calbindin interneurons in primate prefrontal neurons. *Cerebral Cortex*, 7, 359–373.
- Janiszewski, J., Bienenstock, J., & Blennerhassett, M. G. (2003). Picomolar doses of substance P trigger electrical responses in mast cells without degranulation. *American Journal of Physiology—Cell Physiology*, 267, 138.
- Järvikallio, A., Harvima, I. T., & Naukkarinen, A. (2003). Mast cells, nerves and neuropeptides in atopic dermatitis and nummular eczema. *Archives for Dermatological Research*, 295, 2–7.
- Jessell, T. M., Iversen, L. L., & Cuello, A. C. (1978). Capsaicin-induced depletion of substance P from primary sensory neurons. *Brain Research*, 152, 183–188.
- Jessop, D. S., Harbuz, M. S., & Lightman, S. L. (2001). CRH in chronic inflammatory stress. *Peptides*, 22, 803–807.
- Jessop, D. S., Renshaw, D., Larsen, P. J., Chowdrey, H. S., & Harbuz, M. S. (2000). Substance P is involved in terminating the hypothalamo-pituitary-adrenal axis response to acute stress through centrally located neurokinin-1 receptors. *Stress*, 3, 209–220.
- Joachim, R. A., Sagach, V., Quarcio, D., Dinh, Q. T., Arck, P. C., & Klapp, B. F. (2004). Neurokinin-1 receptor mediates stress-exacerbated allergic airway inflammation and airway hyperresponsiveness in mice. *Psychosomatic Medicine*, 66, 564–571.
- Joad, J. P., Munch, P. A., Bric, J. M., Evans, S. J., Pinkerton, K. E., Chen, C.-Y., et al. (2004). Passive smoke effects on cough and airways in young guinea pigs: Role of brainstem substance P. *American Journal of Respiratory and Critical Care Medicine*, 169, 499–504.
- Jones, R. S. G., & Olpe, H.-R. (1984a). Activation of the noradrenergic projection from locus coeruleus reduces the excitatory responses of anterior cingulate cortical neurones to substance P. *Neuroscience*, 13, 819–825.
- Jones, R. S. G., & Olpe, H.-R. (1984b). Monoaminergic modulation of the sensitivity of neurones in the cingulate cortex to iontophoretically applied substance P. *Brain Research*, 311, 297–305.
- Joos, G. F. (1989). The role of sensory neuropeptides in the pathogenesis of bronchial asthma. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology*, 19, 9–13.
- Joos, G., De Swert, K. O., Schelfhout, V., & Pauwels, R. A. (2003). The role of neural inflammation in asthma and chronic obstructive pulmonary disease. *Annals of the New York Academy of Sciences*, 992, 218–230.
- Jurjus, A. R., More, N., & Walsh, R. J. (1998). Distribution of substance P positive cells and nerve fibers in the rat thymus. *Journal of Neuroimmunology*, 90, 143–148.
- Juszczak, M. (2005). Vasopressin release from the rat hypothalamo-neurohypophysial system: Effects of tachykinin NK-1 and NK-2 receptors agonists and antagonists. *Neuroendocrinology Letters*, 26, 367–372.
- Kalin, N. H., Shelton, S. E., & Davidson, R. J. (2004). The role of the central nucleus of the amygdala in mediating fear and anxiety in the primate. *The Journal of Neuroscience: The Official Journal of the Society of Neuroscience*, 24, 5506–5515.
- Kalivas, P. W., & Miller, J. S. (1984). Substance P modulation of dopamine in the nucleus accumbens. *Neuroscience Letters*, 48, 55–59.
- Karalis, K. P., Kontopoulos, E., Muglia, L. J., & Majzoub, J. A. (1999). Corticotropin-releasing hormone deficiency unmasks the proinflammatory effect of epinephrine. *Proceedings of the National Academy of Sciences of the United States of America*, 96, 7093–7097.
- Katsuno, M., Aihara, M., Kojima, M., Osuna, H., Hosoi, J., Nakamura, M., et al. (2003). Neuropeptides concentrations in the skin of a murine (NC/Nga mice) model of atopic dermatitis. *Journal of Dermatological Science*, 33, 55–65.
- Kawashima, N., Fugate, J., & Kusnecov, A. W. (2002). Immunological challenge modulates brain orphanin Fq/nociception and nociceptive behavior. *Brain Research*, 949, 71–78.
- Keeble, J. E., & Brain, S. D. (2004). A role for substance P in arthritis? *Neuroscience Letters*, 361, 176–179.
- Keller, M., Montgomery, S., Ball, W., Morrison, M., Snavely, D., Liu, G., et al. (2006). Lack of efficacy of the substance P (neurokinin₁ receptor) antagonist aprepitant in the treatment of major depressive disorder. *Biological Psychiatry*, 59, 216–223.
- Kim, K. H., Park, K. C., Chung, J. H., & Choi, H. R. (2003). The effect of substance P on peripheral blood mononuclear cells in patients with atopic dermatitis. *Journal of Dermatological Science*, 32, 115–124.
- Kimura, M., Masuda, T., Hiwatashi, N., Toyota, T., & Nagura, H. (1994). Changes in neuropeptide-containing nerves in human colonic mucosa with inflammatory bowel disease. *Pathology International*, 44, 624–634.
- Koch, T. R., Carney, J. A., & Go, V. L. W. (1987). Distribution and quantitation of gut neuropeptides in normal intestine and inflammatory bowel diseases. *Digestive Diseases and Sciences*, 32, 369–376.
- Kodjo, M., K., Le Boulenger, F., Porcedda, P., Lamacz, M., Conlon, J. M., Pelletier, G., et al. (1995). Evidence for the involvement of chromaffin cells in the stimulatory effect of tachykinins on corticosteroid secretion by the frog adrenal gland. *Endocrinology*, 136, 3253–3259.
- Konsman, J. P., Luheshi, G. N., Bluthé, R.-M., & Dantzer, R. (2000). The

- vagus nerve mediates behavioural depression, but not fever, in response to peripheral immune signals; a functional anatomical analysis. *The European Journal of Neuroscience*, *12*, 4434–4446.
- Kramer, M. S. (2002, May). *Clinical update: Substance P antagonists in patients with major depression*. Paper presented at the 11th Association of European Psychiatrists Congress, Stockholm, Sweden.
- Kramer, M. S., Cutler, N., Feighner, J., Shrivastava, R., Carman, J., Sramek, J. J., et al. (1998, September 11). Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science*, *281*, 1640–1645.
- Kramer, M. S., Winokur, A., Kelsey, J., Preskorn, S. H., Rothschild, A. J., Snavely, D., et al. (2004). Demonstration of the efficacy and safety of a novel substance P (NK1) receptor antagonist in major depression. *Neuropsychopharmacology*, *29*, 385–392.
- Kraneveld, A. D., & Nijkamp, F. P. (2001). Tachykinins and neuro-immune interactions in asthma. *International Immunopharmacology*, *1*, 1629–1650.
- Kroegel, C., Gienbycz, M. A., & Barnes, P. J. (1990). Characterization of eosinophil cell activation by peptides. *Journal of Immunology*, *145*, 2581–2587.
- Krommydas, G. C., Gourgoulis, K. I., Angelopoulos, N. V., Kotrotsiou, E., Raftopoulos, V., & Paschalis-Adam, M. (2004). Depression and pulmonary function in outpatients with asthma. *Respiratory Medicine*, *98*, 220–224.
- Krommydas, G., Gourgoulis, K. I., Karamitsos, K., Krapis, K., Kotrotsiou, E., & Molyvdas, P. A. (2005). Therapeutic value of antidepressants in asthma. *Medical Hypotheses*, *64*, 938–940.
- Kuraishi, Y., Hirota, N., Sato, Y., Hanashima, N., Takagi, H., & Satoh, M. (1989). Stimulus specificity of peripherally evoked substance P release from the rabbit dorsal horn *in situ*. *Neuroscience*, *30*, 241–250.
- Kurina, L. M., Goldacre, M. J., Yeates, D., & Gill, L. E. (2001). Depression and anxiety in people with inflammatory bowel disease. *Journal of Epidemiology and Community Health*, *55*, 716–720.
- Ladenius, A. R. C., & Nijkamp, F. P. (1993). Capsaicin pretreatment of guinea pigs *in vivo* prevents ovalbumin-induced tracheal hyperreactivity *in vitro*. *European Journal of Pharmacology*, *235*, 127–131.
- Lai, J. P., Douglas, S. D., & Ho, W. Z. (1998). Human lymphocytes express SP and its receptor. *Journal of Neuroimmunology*, *86*, 80–86.
- Lambert, N., Lescoulié, P. L., Yassine-Diab, B., Enault, G., Mazières, B., De Préval, C., et al. (1998). Substance P enhances cytokine-induced vascular cell adhesion molecule-1 (VCAM-1) expression on cultured rheumatoid fibroblast-like astrocytes. *Clinical and Experimental Immunology*, *113*, 269–275.
- Langosch, J. M., Kupferschmid, S., Heinen, M., Walden, J., Herpfer, I., Fiebich, B. L., et al. (2005). Effects of substance P and its antagonist L-733060 on long term potentiation in guinea pig hippocampal slices. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *29*, 315–319.
- Larsen, P. J., Jessop, D. S., Patel, H., Lightman, S. L., & Chowdrey, H. S. (1993). Substance P inhibits the release of anterior pituitary adrenocorticotropic hormone via a central mechanism involving corticotrophin-releasing factor-containing neurons in the hypothalamic paraventricular nucleus. *Journal of Neuroendocrinology*, *5*, 99–105.
- Larsen, P. J., Mikkelsen, J. D., & Saermark, T. (1989). Binding of an iodinated substance P analog to a NK-1 receptor on isolated cell membranes from rat anterior pituitary. *Endocrinology*, *124*, 2548–2557.
- Lecci, A., Giuliani, M., Tramontana, M., Carini, F., & Maggi, C. A. (2000). Peripheral actions of tachykinins. *Neuropeptides*, *34*, 303–313.
- Lechin, F., van der Dijks, B., Orozco, B., Jara, H., Rada, I., Lechin, M. E., et al. (1998). Neuropharmacologic treatment of bronchial asthma with the antidepressant tianeptine: A double-blind, cross-over placebo-controlled study. *Clinical Pharmacology & Therapeutics*, *64*, 223–232.
- Lee, L. Y., Gu, Q., & Gleich, G. J. (2001). Effects of human eosinophil granule-derived cationic proteins on C-fiber afferents in the rat lung. *Journal of Applied Physiology*, *9*, 1318–1326.
- Lee, O. Y., Munakata, J., Naliboff, B. D., Chang, L., & Mayer, E. A. (2000). A double-blind parallel group pilot study of the effects of CJ-11,974 and placebo on perceptual and emotional responses to rectosigmoid distention in IBS patients. *Gastroenterology*, *118*, A846.
- Lehrer, P. M., Isenberg, S., & Hochron, S. M. (1993). Asthma and emotion: A review. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma*, *30*, 5–21.
- Levenstein, S., Prantera, C., Varvo, V., Scribano, M. L., Berto, E., Andreoli, A., et al. (1994). Psychological stress and disease activity in ulcerative colitis: A multidimensional cross-sectional study. *The American Journal of Gastroenterology*, *89*, 1219–1225.
- Lieb, K., Ahlvers, K., Dancker, K., Strohhusch, S., Reincke, M., Feige, B., et al. (2002). Effects of the neuropeptide substance P on sleep, mood, and neuroendocrine measures in healthy young men. *Neuropsychopharmacology*, *27*, 1041–1049.
- Lieb, K., Fiebich, B. L., Herpfer, I., Mantovani, M., Löffler, M., & Feuerstein, T. J. (2005). No modulatory effect of neurokinin-1 receptor antagonists on serotonin uptake in human and rat brain synaptosomes. *European Neuropsychopharmacology*, *15*, 641–646.
- Lieb, K., Walden, J., Grunze, H., Fiebich, B. L., Berger, M., & Normann, C. (2004). Serum levels of substance P and response to antidepressant pharmacotherapy. *Pharmacopsychiatry*, *37*, 238–239.
- Lightman, S. L., Windle, R. J., Ma, X.-M., Harbuz, M. S., Shanks, N. M., Julian, M. D., et al. (2002). Hypothalamic–pituitary–adrenal function. *Archives of Physiology and Biochemistry*, *110*, 90–93.
- Lilja, I., Gustafson-Svard, C., Franzen, L., & Sjødahl, R. (2000). Tumor necrosis factor-alpha in ileal mast cells in patients with Crohn's disease. *Digestion*, *61*, 68–76.
- Lilly, C. M., Bai, T. R., Shore, S. A., Hall, A. E., & Drazen, J. M. (1995). Neuropeptide content of lungs from asthmatic and nonasthmatic patients. *American Journal of Respiratory and Critical Care Medicine*, *151*, 548–553.
- Liotti, M., Brannan, S., Egan, G., Shade, R., Madden, L., Abplanalp, B., et al. (2001). Brain responses associated with consciousness of breathlessness (air hunger). *Proceedings of the National Academy of Sciences of the United States of America*, *98*, 2035–2040.
- Liu, L. Y., Coe, C. L., Swenson, C. A., Kelly, E. A., Kita, H., & Busse, W. W. (2002). School examinations enhance airway inflammation to antigen challenge. *American Journal of Respiratory and Critical Care Medicine*, *165*, 1062–1067.
- Liu, R., Ding, Y., & Aghajanian, G. K. (2002). Neurokinins activate local glutamatergic inputs to serotonergic neurons of the dorsal raphe nucleus. *Neuropsychopharmacology*, *27*, 329–340.
- Liu, S. (1995). Electron microscopic observation of substance P-like immunoreactive nerve fibres and innervation in the anterior pituitary of macaques. *The European Journal of Neuroscience*, *7*, 1664–1673.
- Lorenz, D., Wiesner, B., Zipper, J., Winkler, A., Krause, E., Beyermann, M., et al. (1998). Mechanism of peptide-induced mast cell degranulation: Translocation and patch-clamp studies. *The Journal of General Physiology*, *112*, 577–591.
- Lorton, D., Bellinger, D. L., Felten, S. Y., & Felten, D. (1990). Substance P innervation of the rat thymus. *Peptides*, *11*, 1269–1275.
- Lorton, D., Lubahn, C., & Bellinger, D. L. (2003). Potential use of drugs that target neural-immune pathways in the treatment of rheumatoid arthritis and other autoimmune disorders. *Current Drug Targets—Inflammation and Allergy*, *2*, 1–30.
- Lorton, D., Lubahn, C., Engan, C., Shcaller, J., Felten, D. L., & Bellinger, D. L. (2000). Local application of capsaicin into the draining lymph nodes attenuates expression of adjuvant-induced arthritis. *Neuroimmunomodulation*, *7*, 115–125.
- Lotz, M., Vaughan, J. H., & Carson, D. A. (1988, September 2). Effect of

- neuropeptides on production of inflammatory cytokines by human monocytes. *Science*, 241, 1218–1221.
- Lu, B., Figini, M., Emanuelli, C., Geppetti, P., Grady, E. F., Gerard, N. P., et al. (1997). The control of microvasculature permeability and blood pressure by neutral endopeptidase. *Nature Medicine*, 3, 904–907.
- Lucas, H. J., Brauch, C. M., Settas, L., & Theoharides, T. C. (2006). Fibromyalgia—new concepts of pathogenesis and treatment. *International Journal of Immunopathology and Pharmacology*, 19, 5–10.
- Lunde, H., Hedner, J., & Svedmyr, N. (1994). Lack of efficacy of 4 weeks treatment with the neurokinin receptor antagonist FK224 in mild to moderate asthma [Abstract]. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology*, 7, 151S.
- Lydiard, R. B. (2001). Irritable bowel syndrome, anxiety and depression: What are the links? *The Journal of Clinical Psychiatry*, 62, 38–45.
- Maccari, S., Mormède, P., Piazza, P. V., Simon, H., Angelucci, L., & Le Moal, M. (1992). Hippocampal type I and type II corticosteroid receptors are modulated by central noradrenergic systems. *Psychoneuroendocrinology*, 17, 103–112.
- MacQueen, G., Marshall, J., Perdue, M., Siegel, S., & Bienenstock, J. (1989, January 6). Pavlovian conditioning of rat mucosal mast cells to secrete rat mast cell protease II. *Science*, 243, 83–85.
- Maeno, H., Kiyama, H., & Tohyama, M. (1993). Distribution of the substance P (NK₁) receptor in the central nervous system. *Molecular Brain Research*, 18, 43–58.
- Maggi, C. A. (1995). The mammalian tachykinin receptors. *General Pharmacology*, 26, 911–944.
- Maggi, C. A. (1997). The effects of tachykinins on inflammatory and immune cells. *Regulatory Peptides*, 70, 75–90.
- Maier, S. F. (2003). Bi-directional immune-brain communication: Implications for understanding stress, pain, and cognition. *Brain, Behavior, and Immunity*, 17, 69–85.
- Maier, S. F., & Watkins, L. R. (1998). Cytokines for psychologists: Implications of bi-directional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychological Review*, 105, 83–107.
- Malberg, J. E., Eisch, A. J., Nestler, E. J., & Duman, R. S. (2000). Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *Journal of Neuroscience*, 20, 9104–9110.
- Malendowicz, L. K., Andreis, P. G., Nussdorfer, G. G., & Markowska, A. (1996). The possible role of endogenous substance P in the modulation of the response of rat pituitary–adrenal axis to stresses. *Endocrine Research*, 22, 311–318.
- Mantyh, C. R., Vigna, S. R., Bollinger, R., Mantyh, P. W., Maggio, J. E., & Pappas, T. N. (1995). Differential expression of substance P receptors in patients with Crohn's disease and ulcerative colitis. *Gastroenterology*, 109, 850–860.
- Mapp, C. E., Miotto, D., Braccioni, F., Saetta, M., Turato, G., Maestrelli, P., et al. (2000). The distribution of neurokinin-1 and neurokinin-2 receptors in human central airways. *American Journal of Respiratory and Critical Care Medicine*, 161, 207–215.
- Margariños, A. M., Deslandes, A., & McEwen, B. S. (1999). Effects of antidepressants and benzodiazepine treatments on the dendritic structure of CA3 pyramidal neurons after chronic stress. *European Journal of Pharmacology*, 371, 113–122.
- Margariños, A. M., McEwen, B. S., Flugge, G., & Fuchs, E. (1996). Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 16, 3534–3540.
- Marriott, I., & Bost, K. L. (2001). Substance P receptor mediated macrophage responses. *Advances in Experimental Medicine and Biology*, 493, 247–254.
- Marshall, J. S., & Waserman, S. (1995). Mast cells and the nerves—Potential interactions in the context of chronic disease. *Clinical and Experimental Allergy*, 25, 102–110.
- Martensson, B., Nyberg, S., Toresson, G., Brodin, E., & Bertilsson, L. (1989). Fluoxetine treatment of depression: Clinical effects, drug concentrations and monoamine metabolites and N-terminally extended substance P in cerebrospinal fluid. *Acta Psychiatrica Scandinavica*, 79, 586–596.
- Martling, C. R., Matran, R., Alving, K., Hökfelt, T., & Lundberg, J. M. (1990). Innervation of lower airways and neuropeptide effects on bronchial and vascular tone in the pig. *Cell and Tissue Research*, 260, 223–233.
- Mason, D., MacPhee, I., & Antoni, F. (1990). The role of the neuroendocrine system in determining genetic susceptibility to experimental allergic encephalomyelitis in the rat. *Immunology*, 70, 1–5.
- Massi, M., Panocka, I., & de Caro, G. (2000). The psychopharmacology of tachykinin NK-3 receptors in laboratory animals. *Peptides*, 21, 1597–1609.
- Matalka, K. Z. (2003). Neuroendocrine and cytokine-induced responses to minutes, hours, and days of mental stress. *Neuroendocrinology Letters*, 24, 283–292.
- Maubach, K. A., Martin, K., Chicchi, G., Harrison, T., Wheeldon, A., Swain, C. J., et al. (2002). Chronic substance P (NK₁) receptor antagonist and conventional antidepressant treatment increases burst firing of monoamine neurones in the locus coeruleus. *Neuroscience*, 109, 609–617.
- Maunder, R. (2000). Mediators of stress effects in inflammatory bowel disease: Not the usual suspects. *Journal of Psychosomatic Research*, 48, 569–577.
- Mayberg, H. S., Liotti, M., Brannan, S. K., McGinnis, S., Mahurin, R. K., Jerabek, P. A., et al. (1999). Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. *American Journal of Psychiatry*, 156, 675–682.
- Mazumdar, S., & Das, K. M. (1992). Immunocytochemical localization of vasoactive intestinal peptide and substance P in the colon from normal subjects and patients with inflammatory bowel disease. *The American Journal of Gastroenterology*, 87, 176–181.
- Mazzone, S. B. (2004). Tachykinins and obstructive airway disease. *Treatments in Respiratory Medicine*, 3, 201–216.
- Mazzone, S. B., & Geraghty, D. P. (2000). Respiratory actions of tachykinins in the nucleus of the solitary tract: Characterization of receptors using selective agonists and antagonists. *British Journal of Pharmacology*, 129, 1121–1131.
- McDougall, S. J., Widdop, R. E., & Lawrence, A. J. (2005). Central autonomic integration of psychological stressors: Focus on cardiovascular modulation. *Autonomic Neuroscience: Basic & Clinical*, 123, 1–11.
- McEwen, B. S., & Magariños, A. M. (1997). Stress effects on morphology and function of the hippocampus. *Annals of the New York Academy of Sciences*, 821, 271–284.
- McKay, D. M., & Bienenstock, J. (1994). The interaction between mast cells and nerves in the gastrointestinal tract. *Immunology Today*, 15, 533–538.
- McLean, S. (2005). Do substance P and the NK₁ receptor have a role in depression and anxiety? *Current Pharmaceutical Design*, 11, 1529–1547.
- Mertz, H., Morgan, V., Tanner, G., Pickens, D., Price, R., Shyr, Y., et al. (2000). Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology*, 118, 842–848.
- Messenger, J. P., Anderson, R. L., & Gibbins, I. L. (1999). Neurokinin-1 receptor localisation in guinea pig autonomic ganglia. *The Journal of Comparative Neurology*, 412, 693–704.
- Miao, F. J., Janig, W., & Levine, J. D. (2000). Nociceptive neuroendocrine negative feedback control of neurogenic inflammation activated by

- capsaicin in the rat paw: Role of the adrenal medulla. *The Journal of Physiology*, 527, 601–610.
- Millan, M. J., Lejeune, F., De Nanteuil, G., & Gobert, A. (2001). Selective blockade of neurokinin (NK)(1) receptors facilitates the activity of adrenergic pathways projecting to the frontal cortex and dorsal hippocampus in rats. *Journal of Neurochemistry*, 76, 1949–1954.
- Miller, M. J. S., Sadowska-Krowicka, H., Jeng, A. Y., Chotinaruemol, S., Wong, M., Clark, D. A., et al. (1993). Substance P levels in experimental ileitis in guinea pigs: Effects of misoprostol. *American Journal of Physiology—Gastrointestinal and Liver Physiology*, 265, 321–330.
- Mimoda, T., Kitamura, N., Hondo, E., & Yamada, J. (1998). Immunohistochemical colocalization of serotonin, substance P and Met-enkephalin-Arg6-Gly7-Leu8 in the endocrine cells of the ruminant duodenum. *Anatomia, Histologia, Embryologia*, 27, 65–69.
- Mönnikes, H., Rüter, J., König, M., Grote, C., Kobelt, P., Klapp, B. F., et al. (2003). Differential induction of *c-fos* expression in brain nuclei by noxious and non-noxious colonic distention: Role of afferent C-fibers and 5-HT₃ receptors. *Brain Research*, 966, 253–264.
- Morcuede, S., Gadd, C. A., Peters, M., Moss, A., Harris, E. A., Sheasby, A., et al. (2003). Increased neurogenesis and brain-derived neurotrophic factor in neurokinin-1 receptor gene knockout mice. *European Journal of Neuroscience*, 18, 1828–1836.
- Moriarty, D., Goldhill, J., Selve, N., O'Donoghue, D. P., & Baird, A. W. (2001). Human colonic anti-secretory activity of the potent NK1 antagonist SR140333: Assessment of potential anti-diarrhoeal activity in food allergy and inflammatory bowel disease. *British Journal of Pharmacology*, 133, 1346–1354.
- Morrow, L. E., McClellan, J. L., Conn, C. A., & Kluger, M. J. (1993). Glucocorticoids alter fever and IL-6 responses to psychological stress and to lipopolysaccharide. *American Journal of Physiology—Regulatory, Integrative and Comparative Physiology*, 264, 1010–1016.
- Mrazek, D. A. (2003). Psychiatric symptoms in patients with asthma causality, comorbidity, or shared genetic etiology. *Child and Adolescent Psychiatric Clinics of North America*, 12, 459–471.
- Mukaiyama, O., Morimoto, K., Nosaka, E., Takahashi, S., & Yamashita, M. (2004). Greater involvement of neurokinins found in guinea pig models of severe asthma compared with mild asthma. *International Archives of Allergy and Immunology*, 134, 263–272.
- Mulak, A., & Bonaz, B. (2004). Irritable bowel syndrome: A model of the brain–gut interactions. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, 10, RA55–62.
- Musselman, D. L., Evans, D. L., & Nemeroff, C. B. (1998). The relationship of depression to cardiovascular disease: Epidemiology, biology, and treatment. *Archives of General Psychiatry*, 55, 580–592.
- Mutoh, T., Bonham, A. C., & Joad, J. P. (2000). Substance P in the nucleus of the solitary tract augments bronchopulmonary C fiber reflex output. *American Journal of Physiology—Regulatory, Integrative and Comparative Physiology*, 279, 1215–1223.
- Myers, A. C. (2001). Transmission in autonomic ganglia. *Respiration Physiology*, 125, 99–111.
- Myers, A. C., Kajekar, R., & Udem, B. J. (2002). Allergic inflammation-induced neuropeptide production in rapidly adapting afferent nerves in guinea pig airways. *American Journal of Physiology—Lung Cellular and Molecular Physiology*, 282, 775–781.
- Nagano, M., Saitow, F., Haneda, E., Konishi, S., Hayashi, M., & Suzuki, H. (2005). Distribution and pharmacological characterization of primate NK-1 and NK-3 tachykinin receptors in the central nervous system of the rhesus monkey. *British Journal of Pharmacology*, 147, 1–8.
- Nakaya, Y., Kaneko, T., Shigemoto, R., Nakanishi, S., & Mizuno, N. (1994). Immunohistochemical localization of substance P receptor in the central nervous system of the adult rat. *The Journal of Comparative Neurology*, 347, 249–274.
- Naliboff, B. D., Derbyshire, S. W. G., Munakata, J., Berman, S., Mandelkern, M., Chang, L., et al. (2001). Cerebral activation in patients with irritable bowel syndrome and control subjects during rectosigmoidal stimulation. *Psychosomatic Medicine*, 63, 365–375.
- Neumann, S., Doubell, T. P., Leslie, T., & Woolf, C. J. (1996, November 28). Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. *Nature*, 384, 360–364.
- Nieber, K., Baumgarten, C. R., Rathack, R., Furkert, J., Oehme, P., & Kunkel, G. (1992). Substance P and β -endorphin-like immunoreactivity in lavage fluids of subjects with and without allergic asthma. *The Journal of Allergy and Clinical Immunology*, 90, 646–652.
- Nolan, Y., Conner, T. J., Kelly, J. P., & Leonard, B. E. (2000). Lipopolysaccharide administration produces time-dependent and region-specific alterations in tryptophan and tyrosine hydroxylase activities in rat brain. *Journal of Neural Transmission*, 107, 1393–1401.
- Nussdorfer, G. G., & Malendowicz, L. K. (1998). Role of tachykinins in the regulation of the hypothalamo–pituitary–adrenal axis. *Peptides*, 19, 949–968.
- O'Byrne, P. M. (1988). Allergen-induced airway hyperresponsiveness. *The Journal of Allergy and Clinical Immunology*, 81, 119–127.
- O'Conner, T. M., O'Connell, J., O'Brien, D. I., Goode, T., Bredin, C. P., & Shanahan, F. (2004). The role of substance P in inflammatory disease. *Journal of Cellular Physiology*, 201, 167–180.
- Ollerenshaw, S. L., Jarvis, D., Sullivan, C. E., & Woolcock, A. J. (1991). Substance P immunoreactive nerves in airways from asthmatics and non-asthmatics. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology*, 4, 673–682.
- Olsson, A., Regnéll, G., Träskman-Bendz, L., Ekman, R., & Westrin, A. (2004). Cerebrospinal neuropeptide Y and substance P in suicide attempters during long-term antidepressant treatment. *European Neuropsychopharmacology*, 14, 479–485.
- Ortega, A. N., McQuaid, E. L., Canino, G., Goodwin, R. D., & Fritz, G. K. (2004). Comorbidity of asthma and anxiety and depression in Puerto Rican children. *Psychosomatics*, 45, 93–99.
- Otsuka, M., & Yoshioka, K. (1993). Neurotransmitter function of mammalian tachykinins. *Physiology Reviews*, 73, 229–307.
- Patachini, R., & Maggi, C. A. (2001). Peripheral tachykinin receptors as targets for new drugs. *European Journal of Pharmacology*, 429, 13–21.
- Pennefather, J. N., Lecci, A., Cadenas, M. L., Patak, E., Pinto, F. M., & Maggi, C. A. (2004). Tachykinins and tachykinin receptors: A growing family. *Life Sciences*, 74, 1445–1463.
- Pérez Fontán, J. J., Cortright, D. N., Krause, J. E., Velloff, C. R., Karpitskiy, V. V., Carver, T. W., et al. (2000). Substance P and neurokinin-1 receptor expression by intrinsic airway neurons in the rat. *American Journal of Physiology—Lung Cellular and Molecular Physiology*, 278, L344–L355.
- Pernow, B. (1981). Substance P: Its distribution, pharmacological actions and possible physiological role in sensory neurons. *Clinical Physiology*, 1, 235–251.
- Perretti, M., Ahluwalia, A., Flower, R. J., & Manzini, S. (1993). Endogenous tachykinins play a role in IL-1-induced neutrophil accumulation: Involvement of NK-1 receptors. *Immunology*, 80, 73–77.
- Phillips, J. E., Hey, J. A., & Corboz, M. R. (2003). Tachykinin NK₃ and NK₁ receptor activation elicits secretion from porcine airway submucosal glands. *British Journal of Pharmacology*, 138, 254–260.
- Pickering, A. E., Boscan, P., & Paton, J. F. R. (2003). Nociception attenuates parasympathetic but not sympathetic baroreflex via NK₁ receptors in the rat nucleus tractus solitarii. *The Journal of Physiology*, 551, 589–599.
- Pothoulakis, C., Castagliuolo, I., LaMont, T., Jaffer, A., O'Keane, J. C., Snider, R. M., et al. (1994). CP-96,345, a substance P antagonist, inhibits rat intestinal responses to *Clostridium difficile* toxin A but not cholera toxin. *Proceedings of the National Academy of Sciences of the United States of America*, 91, 947–951.
- Quartara, L., & Altamura, M. (2006). Tachykinin receptors antagonists: From research to clinic. *Current Drug Targets*, 7, 975–992.

- Quartara, L., & Maggi, C. A. (1997). The tachykinin NK1 receptor: Part I. Ligands and mechanisms of cellular activation. *Neuropeptides*, *6*, 537–563.
- Quartara, L., & Maggi, C. A. (1998). The tachykinin NK₁ receptor: Part II. Distribution and pathophysiological roles. *Neuropeptides*, *32*, 1–49.
- Raithel, M., Schneider, H. T., & Hahn, E. G. (1999). Effect of substance P on histamine secretion from gut mucosa in inflammatory bowel disease. *Scandinavian Journal of Gastroenterology*, *5*, 496–503.
- Rameshwar, P., & Gascón, P. (1995). Substance P (SP) mediates production of stem cell factor and interleukin-1 in bone marrow stroma: Potential autoregulatory role for these cytokines in SP receptor expression and induction. *Blood*, *86*, 482–490.
- Ray, A., & Cohn, L. (1999). Th2 cells and GATA-3 in asthma: New insights into the regulation of airway inflammation. *The Journal of Clinical Investigation*, *104*, 985–993.
- Reiss, A. B., & Glass, A. D. (2006). Atherosclerosis: Immune and inflammatory aspects. *Journal of Investigative Medicine*, *54*, 123–131.
- Renzi, D., Pellegrini, B., Tonelli, F., Surrenti, C., & Calabro, A. (2000). Substance P (neurokinin-1) and neurokinin A (neurokinin-2) receptor gene and protein expression in the healthy and inflamed human intestine. *American Journal of Pathology*, *157*, 1511–1522.
- Rettenbacher, M., & Reubi, J. C. (2001). Localization and characterization of neuropeptide receptors in human colon. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *364*, 291–304.
- Ribeiro, S. J., Teixeira, R. M., Calixto, J. B., & De Lima, T. C. (1999). Tachykinin NK(3) receptor involvement in anxiety. *Neuropeptides*, *33*, 181–188.
- Ribeiro-da-Silva, A., & Hökfelt, T. (2000). Neuroanatomical localisation of substance P in the CNS and sensory neurons. *Neuropeptides*, *34*, 256–271.
- Rimón, R., Le Grevés, P., Nyberg, F., Heikkilä, L., Salmela, L., & Terenius, L. (1984). Elevation of substance P-like peptides in the CSF of psychiatric patients. *Biological Psychiatry*, *19*, 509–516.
- Ritz, T., Steptoe, A., DeWilde, S., & Costa, M. (2000). Emotions and stress increase respiratory resistance in asthma. *Psychosomatic Medicine*, *62*, 401–412.
- Rohleder, N., Wolf, J. M., Herpfer, I., Fiebich, B. L., Kirschbaum, C., & Lieb, K. (2006). No response of plasma substance P, but delayed increase of interleukin-1 receptor antagonist to acute psychosocial stress. *Life Science*, *22*, 3082–3089.
- Romagnani, S. (2000). T-cell subsets (Th1 versus Th2). *Annals of Allergy, Asthma, and Immunology*, *85*, 9–18.
- Rosén, A., Zhang, Y.-X., Lund, I., Lundberg, T., & Yu, L.-C. (2004). Substance P microinjected into the periaqueductal gray matter induces antinociception and is released following morphine administration. *Brain Research*, *1001*, 87–94.
- Rosenkranz, M. A., Busse, W. W., Johnstone, T., Swenson, C. A., Crisafi, G. M., Jackson, M. M., et al. (2005). Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 13319–13324.
- Rupniak, N. M., Carlson, E. J., Shephard, S., Bentley, G., Williams, A. R., Hill, A., et al. (2003). Comparison of the functional blockade of the rat substance P (NK₁) receptors by GR205171, RP67580, SR140333 and NKP-608. *Neuropharmacology*, *45*, 231–241.
- Rupniak, N. M., & Kramer, M. S. (1999). Discovery of antidepressant and anti-emetic efficacy of substance P receptor (NK₁) antagonists. *Trends in Pharmacological Sciences*, *20*, 485–490.
- Rupniak, N. M., Webb, J. K., Fisher, A., Smith, D., & Boyce, S. (2003). The substance P (NK1) receptor antagonist L-770735 inhibits fear conditioning in gerbils. *Neuropharmacology*, *44*, 516–523.
- Russell, I. J., Orr, M. D., Littman, B., Vipraio, G. A., Alboukrek, D., Michalek, J. E., Lopez, Y., & MacKillip, F. (1994). Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. *Arthritis and Rheumatism*, *37*, 1593–1601.
- Russell, L. C., & Burchiel, K. J. (1984). Neurophysiological effects of capsaicin. *Brain Research*, *320*, 165–176.
- Ryckmans, T., Berton, O., Grimée, R., Kogej, T., Lambert, Y., Pasau, P., Talaga, P., & Genicot, C. (2002). Dual NK1-antagonists—Serotonin reuptake inhibitors as potential antidepressants: Part 2. SAR and activity of benzyloxyphenethyl piperazine derivatives. *Bioorganic & Medicinal Chemistry Letters*, *12*, 3195–3198.
- Santarelli, L., Gobbi, G., Blier, P., & Hen, R. (2002). Behavioral and physiologic effects of genetic or pharmacologic inactivation of the substance P receptor (NK1). *The Journal of Clinical Psychiatry*, *63*, 11–17.
- Santarelli, L., Gobbi, G., Debs, P. C., Sibille, E. T., Blier, P., Hen, R., & Heath, M. J. (2001). Genetic and pharmacological disruption of neurokinin 1 receptor function decreases anxiety-related behaviors and increases serotonergic function. *Proceedings of the National Academy of Sciences of the United States of America*, *98*, 1912–1917.
- Sapolsky, R. M., Rivier, C., Yamamoto, G., Plotsky, P., & Vale, W. (1987, October 23). Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. *Science*, *238*, 522–524.
- Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews*, *21*, 55–89.
- Saria, A. (1999). The tachykinin NK-1 receptor in the brain: Pharmacology and putative functions. *European Journal of Pharmacology*, *375*, 51–60.
- Saunders, P. R., Kosecka, U., McKay, D. M., & Perdue, M. H. (1994). Acute stressors stimulate ion secretion and increase epithelial permeability in rat intestine. *American Journal of Physiology—Gastrointestinal and Liver Physiology*, *267*, 794–799.
- Schedlowski, M., Fluge, T., Richter, S., Tewes, U., Schmidt, R. E., & Wagner, T. O. (1995). Beta-endorphin, but not substance-P, is increased by acute stress in humans. *Psychoneuroendocrinology*, *20*, 103–110.
- Scheerens, H., Buckley, T. L., Muis, T., Van Loveren, H., & Nijkamp, F. P. (1996). The involvement of sensory neuropeptides in toluene diisocyanate-induced tracheal hyperreactivity in the mouse airways. *British Journal of Pharmacology*, *119*, 1665–1671.
- Schiepers, O. J., Wichers, M. C., & Maes, M. (2005). Cytokines and major depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *29*, 201–217.
- Scholzen, T. E., Steinhoff, M., Bonaccorsi, P., Klein, R., Amadesi, S., Geppetti, P., et al. (2001). Neutral endopeptidase terminates substance P-induced inflammation in allergic contact dermatitis. *Journal of Immunology*, *166*, 1285–1291.
- Schuiling, M., Zuidhof, A. B., Zaagsma, J., & Meurs, H. (1999a). Involvement of tachykinin NK₁ receptor in the development of allergen-induced airway hyperreactivity and airway inflammation in conscious, unrestrained guinea pigs. *American Journal of Respiratory and Critical Care Medicine*, *159*, 423–430.
- Schuiling, M., Zuidhof, A. B., Zaagsma, J., & Meurs, H. (1999b). Role of tachykinin NK₁ and NK₂ receptors in allergen-induced early and late asthmatic reactions, airway hyperresponsiveness, and airway inflammation in conscious, unrestrained guinea pigs. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology*, *29*, 48–52.
- Schwetz, I., Bradesi, S., McRoberts, J. A., Sablad, M., Miller, J. C., Zhou, H., et al. (2004). Delayed stress-induced colonic hypersensitivity in male Wistar rats: Role of neurokinin-1 and corticotropin-releasing factor-1 receptors. *American Journal of Physiology—Gastrointestinal and Liver Physiology*, *286*, 683–691.
- Sergeyev, V., Fetisov, S., Mathé, A. A., Jimenez, P. A., Bartfai, T., Mortas, P., et al. (2005). Neuropeptide expression in rats exposed to chronic mild stresses. *Psychopharmacology*, *178*, 115–124.

- Sertl, K., Wiedermann, C. J., Kowalski, M. L., Hurtado, S., Plutchok, J., Linnoila, I., et al. (1988). Substance P: The relationship between receptor distribution in rat lung and the capacity of substance P to stimulate vascular permeability. *The American Review of Respiratory Disease*, *138*, 151–159.
- Severini, C., Improta, G., Falconieri-Erspamer, F., Salvadori, S., & Erspamer, V. (2002). The tachykinin peptide family. *Pharmacological Reviews*, *54*, 285–322.
- Shaikh, M. B., Steinberg, A., & Siegel, A. (1993). Evidence that substance P is utilized in medial amygdaloid facilitation of defensive rage behavior in the cat. *Brain Research*, *625*, 283–294.
- Shanks, N., Harbuz, M. S., Jessop, D. S., Perks, P., Moore, P. M., & Lightman, S. L. (1998). Inflammatory disease as chronic stress. *Annals of the New York Academy of Sciences*, *840*, 599–607.
- Sharkey, K. A. (1992). Substance P and calcitonin gene-related peptide (CGRP) in gastrointestinal inflammation. *Annals of the New York Academy of Sciences*, *664*, 425–442.
- Sharkey, K. A., & Kroese, A. B. A. (2001). Consequences of intestinal inflammation on the enteric nervous system: Neuronal activation induced by inflammatory mediators. *The Anatomical Record*, *262*, 79–90.
- Shelton, R. C. (2004). The dual-action hypothesis: Does pharmacology matter? *Journal of Clinical Psychiatry*, *65*, 5–10.
- Shigemoto, R., Nakaya, Y., Nomura, S., Ogawa-Meguro, R., Ohishi, H., Kaneko, T., et al. (1993). Immunocytochemical localization of rat substance P receptor in the striatum. *Neuroscience Letters*, *153*, 157–160.
- Shirasaki, H., Asakura, K., Narita, S.-I., & Kataura, A. (1998). Expression of substance P (NK₁) in human nose. *Acta Otolaryngologica*, *118*, 717–722.
- Shirayama, Y., Mitsushio, H., Takashima, M., Ichikawa, H., & Takahashi, K. (1996). Reduction of substance P after chronic antidepressants treatment in the striatum, substantia nigra and amygdala of the rat. *Brain Research*, *739*, 70–78.
- Shults, C. W., Quirion, R., Chronwall, B., Chase, T. N., & O'Donohue, T. L. (1984). A comparison of the anatomical distribution of substance P and substance P receptors in the rat central nervous system. *Peptides*, *5*, 1097–1128.
- Siegel, R. A., Düker, E.-M., Pahnke, U., & Wuttke, W. (1987). Stress-induced changes in cholecystokinin and substance P concentrations in discrete brain regions of the rat hypothalamus. *Neuroendocrinology*, *46*, 75–81.
- Simon, C., Portailier, P., Chamoin, M. C., & Ternaux, J. P. (1992). Substance P like-immunoreactivity release from enterochromaffin cells of rat caecum mucosa: Inhibition by serotonin and calcium-free medium. *Neurochemistry International*, *20*, 529–536.
- Smith, D. W., Hewson, L., Fuller, P., Williams, A. R., Wheeldon, A., & Rupniak, N. M. J. (1999). The substance P antagonist L-760, 735 inhibits stress-induced NK₁ receptor internalisation in the basolateral amygdala. *Brain Research*, *848*, 90–95.
- Smith, V. C., Sagot, M. A., Wong, H., & Buchan, A. M. (2000). Cellular expression of the neurokinin 1 receptor in the human antrum. *Journal of the Autonomic Nervous System*, *79*, 165–172.
- Solin, O., Eskola, O., Hamill, T. G., Bergman, J., Lehtikoinen, P., Grönroos, T., et al. (2004). Synthesis and characterization of a potent, selective, radiolabeled substance-P antagonist for NK₁ receptor quantitation: ([¹⁸F]SPA-RQ). *Molecular and Imaging Biology: MIB: The Official Publication of the Academy of Molecular Imaging*, *6*, 373–384.
- Solmaz, M., Kavuk, I., & Sayar, K. (2003). Psychological factors in the irritable bowel syndrome. *European Journal of Medical Research*, *8*, 549–556.
- Solway, J., & Leff, A. R. (1991). Sensory neuropeptides and airway function. *Journal of Applied Physiology*, *71*, 2077–2087.
- Sommer, C., & Kress, M. (2004). Recent findings on how proinflammatory cytokines cause pain: Peripheral mechanisms in inflammatory and neuropathic hyperalgesia. *Neuroscience Letters*, *361*, 184–187.
- Souery, D., Papakostas, G. I., & Trivedi, M. H. (2006). Treatment-resistant depression. *Journal of Clinical Psychiatry*, *67*, 16–22.
- Southwell, B. R., Woodman, H. L., Murphy, R., Royal, S. J., & Furness, J. B. (1996). Characterisation of substance P-induced endocytosis of NK1 receptors on enteric neurons. *Histochemistry and Cell Biology*, *106*, 563–571.
- Stacey, A. E., Woodhall, G. L., & Jones, R. S. (2002). Activation of neurokinin-1 receptors promotes GABA release at synapses in the rat entorhinal cortex. *Neuroscience*, *115*, 575–586.
- Stam, R., Akkermans, L. M. A., & Wiegant, V. M. (1997). Trauma and the gut: Interactions between stressful experience and intestinal function. *Gut*, *40*, 704–709.
- Stead, R. H., Tomioka, M., Quinonez, G., Simon, G. T., Felten, S. Y., & Bienenstock, J. (1987). Intestinal mucosal mast cells in normal and nematode-infected rat intestines are in intimate contact with peptidergic nerves. *Proceedings of the National Academy of Sciences of the United States of America*, *84*, 2975–2979.
- Steinberg, R., Alonso, R., Rouquier, L., Desvignes, C., Michaud, J.-C., Cudennec, A., et al. (2002). SSR240600 [(R)-2-(1-[2-[4-{2-[3,5-Bis-(trifluoromethyl)phenyl]acetyl]-2-(3,4-dichlorophenyl)-2-morpholinyl]-ethyl]-4-piperidinyl)-2-methylpropanamide], a centrally active nonpeptide antagonist of the tachykinin neurokinin 1 receptor: II. Neurochemical and behavioral characterization. *The Journal of Pharmacology and Experimental Therapeutics*, *303*, 1180–1188.
- Stoyanova, I. I., & Gulubova, M. V. (2002). Mast cells and inflammatory mediators in chronic ulcerative colitis. *Acta Histochemica*, *104*, 185–192.
- Straub, R. H., & Cutolo, M. (2001). Involvement of the hypothalamus-pituitary-adrenal/gonadal axis and the peripheral nervous system in rheumatoid arthritis. *Arthritis and Rheumatism*, *44*, 493–507.
- Sturiale, S., Barbara, G., Qiu, B., Figini, M., Geppetti, P., Gerard, N., et al. (1999). Neutral endopeptidase (EC 3.4.24.11) terminates colitis by degrading substance P. *Proceedings of the National Academy of Sciences of the United States of America*, *96*, 11653–11658.
- Sun, G., Stacey, M. A., Vittori, E., Marini, M., Bellini, A., Kleimberg, J., et al. (1998). Cellular and molecular characteristics of inflammation in chronic bronchitis. *European Journal of Clinical Investigation*, *28*, 364–372.
- Tack, J., Broekaert, D., Fischler, B., Oudenhove, L. V., Gevers, A. M., & Janssens, J. (2006). A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. *Gut*, *55*, 1095–1103.
- Teixeira, R. M., & De Lima, T. C. M. (2003). Involvement of tachykinin NK₁ receptor in the behavioral and immunological responses to swimming stress in mice. *Neuropeptides*, *37*, 307–315.
- Teixeira, R. M., Santos, A. R. S., Ribeiro, S. J., Calixto, J. B., Rae, G. A., & De Lima, T. C. M. (1996). Effects of central administration of tachykinin receptor agonists and antagonists on plus-maze behavior in mice. *European Journal of Pharmacology*, *311*, 7–14.
- Tibério, I. F. L. C., Leick-Maldonado, E. A., Miyahara, L., Kasahara, D. I., Spilborghs, G. M. G. T., Martins, M. A., & Saldiva, P. H. N. (2003). Effects of neurokinins on airway and alveolar eosinophil recruitment. *Experimental Lung Research*, *29*, 165–177.
- Tkacs, N. C., & Li, J. (1999). Immune stimulation induces Fos expression in brainstem amygdala afferents. *Brain Research Bulletin*, *48*, 223–231.
- Tomaki, M., Ichinose, M., Miura, M., Hirayama, Y., Yamauchi, H., Nakajima, N., et al. (1995). Elevated substance P content in induced sputum from patients with asthma and patients with chronic bronchitis. *American Journal of Respiratory and Critical Care Medicine*, *151*, 613–617.
- Torebjörk, H. E., Lundberg, L. E. R., & LaMotte, R. H. (1992). Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *Journal of Physiology*, *448*, 765–780.

- Tough, I. R., Lewis, C. A., Fozard, J., & Cox, H. M. (2003). Dual and selective antagonism of neurokinin NK₁ and NK₂ receptor-mediated responses in human colon mucosa. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *367*, 104–108.
- Tseng, W.-Y., Tsao, C.-F., Ko, C.-C., & Huang, H.-T. (2001). Local capsaicin application to the stellate ganglion and stellatectomy attenuate neurogenic inflammation in rat bronchi. *Autonomic Neuroscience: Basic & Clinical*, *94*, 25–33.
- Tudoric, N., Zhang, M., Kljajic-Turkalj, M., Niehus, J., Cvoricsec, B., Jurgovsky, K., et al. (2000). Allergen challenge induces decrease of serum neutral endopeptidase (NEP) in asthmatics. *Peptides*, *21*, 359–364.
- Ueda, H. (1999). In vivo molecular signal transduction of peripheral mechanisms of pain. *Japanese Journal of Pharmacology*, *79*, 263–268.
- Umeno, E. J. A., Nadel, J. A., Huang, H. T., & McDonald, D. M. (1989). Inhibition of neutral endopeptidase potentiates neurogenic inflammation in the rat trachea. *Journal of Applied Physiology*, *66*, 2647–2652.
- Undem, B. J., Hunter, D. D., Liu, M., Haak-Frendscho, M., Oakragly, A., & Fischer, A. (1999). Allergen-induced sensory neuroplasticity in airways. *International Archives of Allergy and Immunology*, *118*, 150–153.
- Undem, B. J., Kajekar, R., Hunter, D. D., & Myers, A. C. (2000). Neural integration and allergic disease. *The Journal of Allergy and Clinical Immunology*, *106*(Suppl.), S213–S220.
- Urry, H. L., van Reekum, C. M., Johnstone, T., Kalin, N. H., Thurow, M. E., Schaefer, H. S., et al. (2006). Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. *Journal of Neuroscience*, *26*, 4415–4425.
- van der Kleij, H. P. M., Kraneveld, A. D., Redegeld, F. A. M., Gerard, N. P., Morteau, O., & Nijkamp, F. P. (2003). The tachykinin NK₁ receptor is crucial for the development of non-atopic airway inflammation and hyperresponsiveness. *European Journal of Pharmacology*, *476*, 249–255.
- van der Velden, V. H. J., Naber, B. A. E., Van Hal, P. T. W., Overbeek, S. E., Hoogsteden, H. C., & Versnel, M. A. (1999). Peptidase activities in serum and bronchoalveolar lavage fluid from allergic asthmatics—comparison with healthy non-smokers and smokers and effects of inhaled glucocorticoids. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology*, *29*, 813–823.
- van Hagen, P. M., Hofland, L. J., ten Bokum, A. M. C., Lichtenauer-Kaligis, E. G. R., Kwekkeboom, D. J., Ferone, D., et al. (1999). Neuropeptides and their receptors in the immune system. *Annals of Medicine*, *31*, 15–22.
- Vanhatalo, S., & Soinila, S. (2001). Evidence for nodose ganglion as the source of innervation to the anterior lobe of the pituitary. *Neuroscience*, *107*, 491–497.
- Vaupel, R., Jarry, H., Schlömer, H.-T., & Wuttke, W. (1988). Differential response of substance P-containing subtypes of adrenomedullary cells to different stressors. *Endocrinology*, *123*, 2140–2145.
- Veale, D., Farrell, M., & Fitzgerald, O. (1993). Mechanism of joint sparing in a patient with unilateral psoriatic arthritis and a longstanding hemiplegia. *British Journal of Rheumatology*, *32*, 413–416.
- Venkova, K., Sutkowski-Markmann, D. M., & Greenwood-Van Meerveld, B. (2002). Peripheral activity of a new NK-1 receptor antagonist TAK-637 in the gastrointestinal tract. *The Journal of Pharmacology and Experimental Therapeutics*, *300*, 1046–1052.
- Wallace, J. L., McCafferty, D. M., & Sharkey, K. A. (1998). Lack of beneficial effect of a tachykinin receptor antagonist in experimental colitis. *Regulatory Peptides*, *73*, 95–101.
- Walsh, D. A., Salmon, M., Featherstone, R., Wharton, J., Church, M. K., & Polak, J. M. (1994). Differences in the distribution and characteristics of tachykinin NK₁ binding sites between human and guinea pig lung. *British Journal of Pharmacology*, *113*, 1407–1415.
- Weinreich, D., & Undem, B. J. (1987). Immunological regulation of synaptic transmission in isolated guinea pig autonomic ganglia. *The Journal of Clinical Investigations*, *79*, 1529–1532.
- Weinreich, D., Undem, B. J., Taylor, G., & Barry, M. F. (1995). Antigen-induced long-term potentiation of nicotinic synaptic transmission in the superior cervical ganglion of the guinea pig. *Journal of Neurophysiology*, *73*, 2004–2016.
- Weiss, D. W., Hirt, R., Tarcic, N., Berzon, Y., Ben-Zur, H., Breznitz, S., et al. (1996). Studies in psychoneuroimmunology: Psychological, immunological, and neuroendocrinological parameters in Israeli civilians during and after a period of Scud missile attacks. *Behavioral Medicine*, *22*, 5–14.
- Westermark, T., Rantapää-Dahlqvist, S., Wällberg-Jonsson, S., Kjörrell, U., & Forsgren, S. (2001). Increased content of bombesin/GRP in human synovial fluid in early arthritis: Different pattern compared with substance P. *Clinical and Experimental Rheumatology*, *19*, 715–720.
- Wieggers, G. J., & Reul, J. M. (1998). Induction of cytokine receptors by glucocorticoids: Functional and pathological significance. *Trends in Pharmacological Sciences*, *19*, 317–332.
- Windle, R. J., Wood, S. A., Kershaw, Y. M., Lightman, S. L., Ingram, C. D., & Harbuz, M. S. (2001). Increased corticosterone pulse frequency during adjuvant-induced arthritis and its relationship to alterations in stress responsiveness. *Journal of Neuroendocrinology*, *13*, 905–911.
- Wolf, S. S., Moody, T. W., Quirion, R., & O'Donahue, T. L. (1985). Biochemical characterization and autoradiographic localization of central SP receptors using [¹²⁵I]physalaemin. *Brain Research*, *332*, 299–307.
- Woolf, C. J., & Salter, M. W. (2000, June 9). Neuronal plasticity: Increasing the gain in pain. *Science*, *288*, 1765–1768.
- Woolley, D. E., & Tetlow, L. C. (2000). Mast cell activation and its relation to proinflammatory cytokine production in the rheumatoid lesion. *Arthritis Research*, *2*, 65–74.
- Xu, G., & Zhao, Z. (2001). Change in excitability and phenotype of substance P and its receptor in cat A β sensory neurons following peripheral inflammation. *Brain Research*, *923*, 112–119.
- Yamano, M. S., Hillyard, C. J., Girgis, S., MacIntyre, I., Emson, P. C., & Tohyama, M. (1988). Presence of a substance P-like immunoreactive neuron system from the parabrachial area to the central amygdaloid nucleus of the rat with reference to coexistence with calcitonin-gene related peptide. *Brain Research*, *451*, 179–188.
- Yeager, M. P., Guyre, P. M., & Munck, A. U. (2004). Glucocorticoid regulation of the inflammatory response to injury. *Acta Anaesthesiologica Scandinavica*, *48*, 799–813.
- Zhao, Z. Q., Yang, H. Q., Zhang, K. M., & Zhuang, X. X. (1992). Release and depletion of substance P by capsaicin in substantia gelatinosa studied with the antibody microprobe technique and immunohistochemistry. *Neuropeptides*, *23*, 161–167.
- Zocchi, A., Varnier, G., Arban, R., Griffante, C., Zanetti, L., Bettelini, L., et al. (2003). Effects of antidepressant drugs and GR 205171, a neurokinin-1 (NK1) receptor antagonist, on the response in the forced swim test and on monoamine extracellular levels in the frontal cortex of the mouse. *Neuroscience Letters*, *345*, 73–76.

Received June 10, 2006

Revision received February 2, 2007

Accepted May 14, 2007 ■