Lithium treatment alters cellular metabolism, glutamate, and GABA.

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ABSTRACT

In recent years, metabolomic and protein expression studies have identified significant differences in cellular energy metabolism in patients with bipolar disorder compared to healthy control subjects. In bipolar subjects, metabolite and gene expression patterns suggest cells are increasingly reliant on glycolysis rather than oxidative phosphorylation for ATP production. Such a glycolytic shift would likely reduce the efficiency of ATP production and could alter rates of neuronal firing due to energy depletion. In addition, synthesis and consumption of glutamate and GABA are tied into energy metabolism through interconversion with α-ketoglutarate, a component of the TCA cycle. We thus questioned whether modulating cellular metabolism could prove therapeutic in bipolar disorder. As a first step toward testing this hypothesis, we performed metabolomic analyses on 293T cells treated with lithium to assess whether the most effective known treatment for bipolar disorder affects metabolism. 293T cells were selected as a preliminary model due to their clean, robust performance in metabolomics assays, as well as their overall metabolic similarity to neurons. Here, we show that lithium treatment of 293T cells significantly raises glutamate and GABA levels and significantly reduces fructose 2,6-bisphosphate, a key activator of glycolysis. These results suggest that at least some of lithium's therapeutic activity may arise from its ability to modulate metabolism in a way that shifts it to more closely resemble that of healthy controls. If bipolar disorder is at least in part a metabolic disorder, it is possible that metabolism-modulating drugs, such as metformin, may have therapeutic potential in bipolar disorder.

METHODS

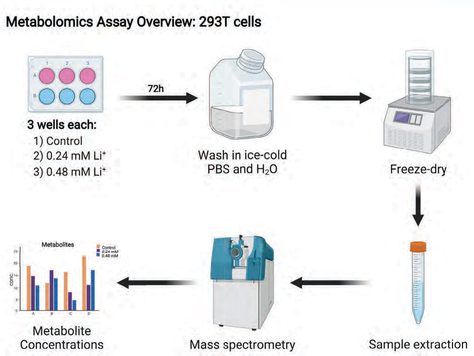


Fig. 1. Experiment design. HEK 293T cells were treated with vehicle (water), low-dose Li^+ (0.24 mM), or high-dose lithium (0.48 mM) for 72h. Metabolomics were then performed to identify changes in metabolic pathways. Li^+ concentrations were selected based on measured concentrations in CSF of patients on Li^+ treatment.

RESULTS

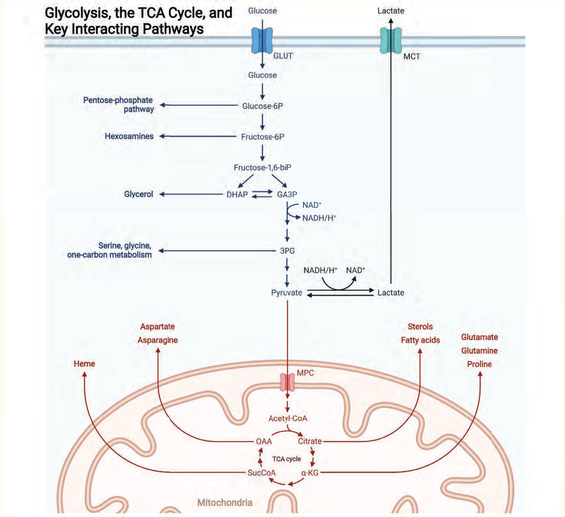


Fig. 2. Overview of key metabolic pathways of interest. We hypothesize oxidative glycolysis is elevated in bipolar disorder.

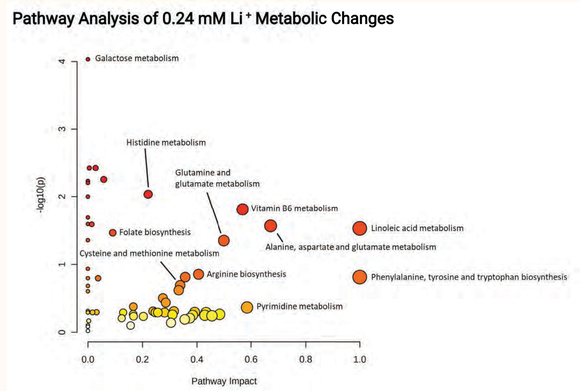
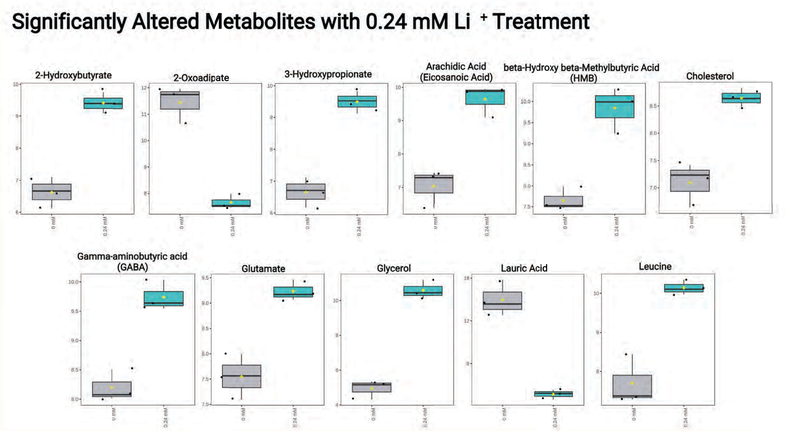


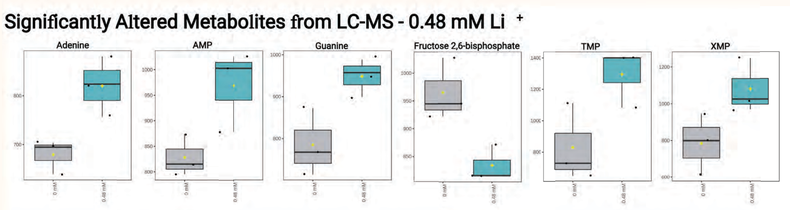
Fig. 3. MetaboAnalyst pathway analysis indicating which metabolic pathways are most affected by low-dose lithium treatment. The x-axis represents the statistical significance of metabolite changes, whereas the y-axis represents how large an impact metabolite changes have on that particular pathway. The size of the circle represents the number of metabolites included in the pathway. A number of hits are highly significant with low impact, generally a result of testing only one or two metabolites within the pathway.

Table 1. Top hits from 0.24 mM Li^+ treatment. Metabolites highlighted in yellow are increased, those highlighted in blue are decreased.

Compound	Raw p-value	FDR-adjusted
Glycerol	0.0002152	0.023888
Lauric acid	0.00089978	0.027344
2-Oxoadipate	0.00099735	0.027344
3-Hydroxypropionate	0.0012035	0.027344
2-Hydroxybutyrate	0.0012317	0.027344
Gamma-aminobutyric acid	0.0020305	0.037565
Leucine	0.003183	0.03967
HMB	0.0034922	0.03967
Cholesterol	0.0037351	0.03967
Arachidic acid	0.0037373	0.03967
Glutamate	0.0039313	0.03967
Methionine	0.0073897	0.068355
Glycine	0.0090198	0.077015
Isoleucine	0.010979	0.087048
Glucose	0.012781	0.089906
Ornithine	0.013502	0.089906
Aspartate	0.013769	0.089906
Mannose	0.017996	0.1032
Tryptophan	0.018492	0.1032
Pyridoxal	0.018595	0.1032
Adenine	0.022541	0.11373
Cytosine	0.023936	0.11373
Heptadecanoic acid	0.02497	0.11373
Lysine	0.025357	0.11373
O-Phosphoethanolamine	0.025614	0.11373
Linoleate	0.029419	0.11832
Inosine	0.030063	0.11832
Myristic acid	0.031496	0.11832
Threonine	0.031774	0.11832
glyceryl laurate	0.031979	0.11832
Serine	0.034297	0.1228
Glutamine	0.037519	0.12608
Palmitate	0.037735	0.12608
Heptanoic acid	0.038756	0.12608
Malonate	0.040584	0.12608
Oleic acid	0.041235	0.12608
Kynurenine	0.042026	0.12608
Alpha-monopropionin	0.04387	0.12815
Monocaprin	0.046828	0.13328



(Above) Fig. 4. Significantly altered metabolites with 0.24 mM Li^+ treatment. Glutamate, GABA, and 2-hydroxybutyrate, a ketone body, are elevated. **(Below) Fig. 5. Significantly altered metabolites from 0.48 mM Li^+ LC-MS data only**. Purines appear to be consistently elevated. Most notably, however, is the decrease in fructose 2,3-bisphosphate, which is a key activator of glycolysis.



RESULTS

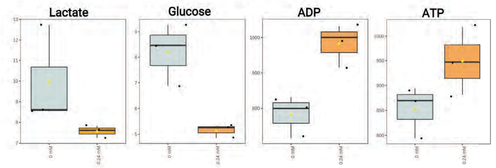


Fig. 6. A number of metabolite levels changed in a manner consistent with a decrease in glycolysis. However, they did not achieve FDR-corrected significance.

DISCUSSION

- Results support hypothesis that lithium may slow glycolysis.
- Next experiment: repeat assay with iPSC-derived neurons from bipolar and control subjects.

Future goals:

- Real-time measurements of glycolysis and oxidative phosphorylation with or without different fuel sources, drugs, or mitochondrial stressors (Seahorse).
- Investigate how metabolism may lead to changes in neuronal morphology/function.
- Identify metabolism-modifying supplements or drugs that may be potential treatments for bipolar disorder.

ACKNOWLEDGEMENTS

Univ. of Iowa Dept. of Psychiatry INSPIRE NIH T32

Iowa Neuroscience Institute RPOE Program

Univ. of Iowa Metabolomics Core Facility

All figures created with BioRender.com and MetaboAnalyst.ca

Roy J. Carver Charitable Trust