Are lithium effects dependent on genetic/epigenetic architecture?

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Although lithium (Li) is considered the gold-standard for treatment of bipolar disorder (BD), the mechanisms by which it exerts its mood stabilizing effects remain unclear. Studies have long suggested that, acting via inhibition of glycogen synthase kinase-3 (GSK3 β), Li induces the transcription and expression of neurotrophic proteins linked to the activation of cell survival signaling cascades. This activation is thought to occur, at least in part, through the phosphatidylinositol 3-kinase (PI3K) pathway, as Li exposure increases PI3K/Akt1 anti-apoptotic activity and inhibition of PI3K blocks the neurotrophic effects of Li. Our recent study evaluating Li-induced gene expression alterations in lymphoblastoid cell lines (LCL) from BD patients and controls supports a role for PI3K/Akt and anti-apoptotic pathways in Li mechanisms of action [1]. While treatment in LCLs from controls did not lead to any significant differences, Li altered the expression of 236 genes in cells from patients. As hypothesized, those genes, which included some related to the PI3K pathway, were significantly enriched for signaling pathways related to inhibition of apoptosis and promotion of resilience mechanisms.

Such apparent beneficial effects of Li have raised important discussions regarding its potential widespread use in the population. However, while associations have been reported between Li content in drinking water and psychiatric outcomes, its prophylactic use in preventing BD has not been confirmed [2]. Accordingly, our findings on the more pronounced changes in patients compared to controls suggest that the effects of Li are highly dependent on the disease genetic architecture, and cell survival mechanisms may not be induced in all subjects. This is supported by evidence of a genetic and epigenetic basis for Li responsiveness, as suggested by studies showing that particular genetic variants and/or methylation patterns may interfere with treatment outcome in patients [3, 4].

Accordingly, SNPs in or near the *AKT* gene have been associated with Akt differential activity [5], which strongly supports the hypothesis that genomic variability may underlie PI3K/Akt pathway-mediated responses. Moreover, inhibition of Gsk3 by direct activation of Akt or by Li has been shown to reduce DNA methylation. In this same vein, decreased global methylation has been observed in BD patients who respond to Li, strongly suggesting that Li responsiveness goes beyond the effects of genetic variants alone. Considering that polymorphisms and methylation status can work together to control gene expression,

these studies point toward possible genetic/epigenetic regulation of the PI3K/Akt pathway and perhaps of Li mechanisms of action.

Stratification of BD patients according to their response to Li treatment has been considered an important strategy to define more homogeneous phenotypes for genetic studies. In fact, cellular features of induced pluripotent stem cell-derived neurons from BD patients, such as neuronal excitability and spiking activity, have been recently shown to discriminate between Li responders and non-responders [6], suggesting that further investigation of findings in regard to specific effects of Li based on a person's genetic and epigenetic architecture is warranted.

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