Increased gene expression of diacylglycerol kinase eta in bipolar disorder

Bipolar disorder (BD) is a highly heritable neuropsychiatric illness characterized by recurrent episodes of depression and mania or hypomania. Recent genome-wide association studies of BD have proposed novel candidates, including the gene encoding the η isoform of diacylglycerol kinase (DGKH; Baum et al. 2008a). The association of this gene with BD was replicated at the haplotype level in a Sardinian sample (Squassina et al. 2009), but not for individual SNPs or as a predictor of lithium response (Manchia et al. 2009). Diacylglycerol kinase (DGK) regulates the intracellular concentration of diacylglycerol, which is a main component of inositol signalling systems targeted by the major anti-BD agent, lithium (reviewed in van Blitterswijk et al. 2000; see also Harwood, 2005, for discussion of the inositol-depletion hypothesis and lithium and BD). DGKH is highly expressed in brain and is also glucocorticoid-inducible and stress-responsive (Klauck et al. 1996; Murakami et al. 2003). Here, we present evidence that gene expression of DGKH is increased in BD.

We quantified DGKH mRNA by real-time quantitative polymerase chain reaction in a collection of 100 post-mortem brain-tissue samples donated by The Stanley Medical Research Institute. All samples were derived from the dorsolateral prefrontal cortex and originated from three diagnostic groups: BD (n = 31), schizophrenia (n = 35) and unaffected controls (n = 34). We used intron-spanning primers TGA CAG CAC AGA AAC AGA TGA AT and GGA GAC CGA GGT GCA GTT T as well as a fluorescent probe (Universal Probe Library no. 69, Roche Applied Science, USA) under amplification conditions described previously (Wendland et al. 2009). Experiments were done after the specimen code was broken and they were thus unblinded. Using G*Power version 3.1.2 (Faul et al. 2007), we determined our sample had some power (56%) to detect medium effect sizes (f = 0.25) and excellent power (94%) for large effect sizes (f = 0.4) in a fixed-effects omnibus analysis of variance test. The entire dataset has been uploaded to The Stanley Medical Research Institute databank (http://www.stanleyresearch.org/brain). We did not apply multiple testing correction for all comparable expression genetics studies uploaded to this databank. All experiments were conducted under protocols approved by the Institutional Review Board of the National Institute of Mental Health Division of Intramural Research Programs in Bethesda, MD.

One-way analysis of variance showed that the three diagnostic groups differed significantly in their DGKH mRNA expression levels (F_{2,97} = 4.44, p = 0.01). As shown in Fig. 1, BD samples displayed significantly increased DGKH levels (Tukey's post-hoc analysis, p < 0.05), with the mean expression level being about 25% higher in BD than in controls. We also quantified two known DGKH transcript variants (Murakami et al. 2003) with transcript-specific probes but did not observe significant differences; moreover, we did not observe significant sex or age effects (data not shown).

We genotyped all samples for two SNPs within the genomic DGKH locus, rs1170191 and rs1012053, that remained associated with BD in a meta-analysis (Baum et al. 2008b). Allelic and genotypic frequencies did not significantly differ between the three diagnostic groups for both SNPs. There was no association of either SNP with DGKH mRNA levels, even after inclusion of diagnosis as covariate (data not shown).

Our data suggest that increased gene expression of DGKH is involved in the pathogenesis of BD. Interestingly, the BD disorder group did not differ significantly from the schizophrenia group (although the latter was also not significantly different from normal controls, Fig. 1), raising the possibility that the observed increase is not specific for BD. The average expression level was 20% higher in schizophrenia donors compared to controls, but this did not reach statistical significance in the post-hoc test. Larger post-mortem and other functional studies with greater power might clarify the role of DGKH in other psychiatric disorders. The DGKH over-expression hypothesis described above can be tested in future genetics studies once expression quantitative trait loci have been identified.
for DGKH. Further, model organisms over-expressing Dgkh may allow further insight into pathogenetic mechanisms of BD. The lack of correlation of SNPs that first implicated DGKH in BD with expression levels suggests that other variants conferring allele-specific expression may result in stronger association signals with the disorder. It thus seems warranted to identify variants correlating with high levels of DGKH mRNA or gain-of-function coding polymorphisms as carriers of these alleles can be postulated to be increased risk for BD. It is our hope that this study might contribute to the elucidation of the pathogenesis of this debilitating disorder.

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Statement of Interest

None.

References


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