OP 8

Can genetic alterations in inositol biosynthesis affect patients responsiveness to valproic acid?

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Objective: Bipolar disorder (BD) affects approximately 1% of the world's population. Valproic acid (VPA) is widely prescribed to treat BD. Patients with BD exhibit different responsiveness to VPA. The molecular mechanisms underlying the responsiveness to VPA are not known. VPA interferes with inositol biosynthesis and depletes inositol levels. VPA depletes inositol by inhibiting 1D-myo-inositol-3 phosphate synthase encoded by *INO1*. This study was carried out to identify molecular mechanisms that alter the VPA sensitivity.
Methods: Yeast was utilized as it has been exploited to study the effect of VPA on inositol metabolism. Deletion mutants that carried a deletion of a specific gene in the inositol metabolism were utilized. These deletion mutants were screened for inositol auxotrophy. Their growth and VPA sensitivity were compared to WT. The *INO1* gene expression was quantified in the presence and absence of VPA using real time PCR.
Results: Deletion mutants of genes encode for inositol hexakisphosphate kinases (IP6Ks) showed inositol auxotrophy and decreased growth in the absence of inositol. Their growths were hypersensitive to VPA compared to WT. They showed decreased *INO1* expression. VPA does not increase the *INO1* expression of these deletion mutants as in WT.
Conclusion: The results of the study suggested that perturbation of IP6Ks in the inositol biosynthesis pathway exacerbates VPA induced inositol depletion altering the therapeutic action of VPA. These findings have implications for understanding the genetic factors that contribute to patients responsiveness to VPA and to improve treatment efficacy for BD.