

Abstract

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Valproate decreases inositol biosynthesis.

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BACKGROUND: Lithium and valproate (VPA) are used for treating bipolar disorder. The mechanism of mood stabilization has not been elucidated, but the role of inositol has gained substantial support. Lithium inhibition of inositol monophosphatase, an enzyme required for inositol recycling and de novo synthesis, suggested the hypothesis that lithium depletes brain inositol and attenuates phosphoinositide signaling. Valproate also depletes inositol in yeast, *Dictyostelium*, and rat neurons. This raised the possibility that the effect is the result of myo-inositol-1-phosphate (MIP) synthase inhibition.

METHODS: Inositol was measured by gas chromatography. Human prefrontal cortex MIP synthase activity was assayed in crude homogenate. INO1 was assessed by Northern blotting. Growth cones morphology was evaluated in cultured rat neurons.

RESULTS: We found a 20% in vivo reduction of inositol in mouse frontal cortex after acute VPA administration. As hypothesized, inositol reduction resulted from decreased MIP synthase activity: .21-.28 mmol/LVPA reduced the activity by 50%. Among psychotropic drugs, the effect is specific to VPA. Accordingly, only VPA upregulates the yeast INO1 gene coding for MIP synthase. The VPA derivative N-methyl-2,2,3,3-tetramethyl-cyclopropane carboxamide reduces MIP synthase activity and has an affect similar to that of VPA on rat neurons, whereas another VPA derivative, valpromide, poorly affects the activity and has no affect on neurons.

CONCLUSIONS: The rate-limiting step of inositol biosynthesis, catalyzed by MIP synthase, is inhibited by VPA; inositol depletion is a first event shown to be common to lithium and VPA.

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