Effect of valproate derivatives on human brain myo-inositol-1-phosphate (MIP) synthase activity and amphetamine-induced rearing

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Abstract:
We have recently shown that valproate (VPA) decreases intracellular concentrations of inositol, like lithium but via a different mechanism, namely by inhibiting myo-inositol-1-phosphate (MIP) synthase. Valnoctamide (VCD) and valrocemide (VGD) are VPA derivatives which are anticonvulsants and have been shown in animal models to be significantly less teratogenic than VPA. We now show that 1 mM of either VCD or VGD drastically inhibits human brain crude homogenate MIP synthase activity. We studied the mechanism of the effect of VCD and found that it reduced the enzyme activity by an apparent competitive mode of inhibition at concentrations within the therapeutic range of VPA (K_i = 0.18 mM). We studied the behavioral effect of VGD and found that both lithium and VGD attenuated amphetamine-induced increase in rearing. These data support clinical study of these VPA-derivatives in bipolar disorder.

Key words:
bipolar disorder, valnoctamide, valrocemide, myo-inositol-1-phosphate (MIP) synthase, teratogenicity, amphetamine