Novel targets for valproic acid: up-regulation of melatonin receptors and neurotrophic factors in C6 glioma cells.

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Abstract
Valproic acid (VPA) is a potent anti-epileptic and effective mood stabilizer. It is known that VPA enhances central GABAergic activity and activates the mitogen-activated protein kinase-extracellular signal-regulated kinase (MAPK-ERK) pathway. It can also inhibit various isoforms of the enzyme, histone deacetylase (HDAC), which is associated with modulation of gene transcription. Recent in vivo studies indicate a neuroprotective role for VPA, which has been found to up-regulate the expression of brain-derived neurotrophic factor (BDNF) in the rat brain. Given the interaction between the pineal hormone, melatonin, and GABAergic systems in the central nervous system, the effects of VPA on the expression of the mammalian melatonin receptor subtypes, MT1 and MT2, were examined in rat C6 glioma cells. The effects of VPA on the expression of glial cell line-derived neurotrophic factor (GDNF) and BDNF were also examined. RT-PCR studies revealed a significant induction of melatonin MT1 receptor mRNA in C6 cells following treatment with 3 or 5 mm VPA for 24 h or 5 mm VPA for 48 h. Western analysis and immunocytochemical detection confirmed that the VPA-induced increase in MT1 mRNA results in up-regulation of MT1 protein expression. Blockade of the MAPK-ERK pathway by PD98059 enhanced the effect of VPA on MT1 expression, suggesting a negative role for this pathway in MT1 receptor regulation. In addition, significant increases in BDNF, GDNF and HDAC mRNA expression were observed after treatment with VPA for 24 or 48 h. Taken together, the present findings suggest that the neuroprotective properties of VPA involve modulation of neurotrophic factors and receptors for melatonin, which is also thought to play a role in neuroprotection. Moreover, the foregoing suggests that combinations of VPA and melatonin could provide novel therapeutic strategies in neurological and psychiatric disorders.

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