Valproic acid induces the glutamate transporter excitatory amino acid transporter-3 in human oligodendroglioma cells.

Bianchi MG, Franchi U, Gazzola R, Reia L, Allegri M, Uggeri J, Chiu M, Sala R, Bussolati O.

Unit of General Pathology, Department of Biomedical, Biotechnological and Translational Sciences (SBiBiT), University of Parma, 43125 Parma, Italy.

Abstract

Glutamate transport in early, undifferentiated oligodendrocytic precursors has not been characterized thus far. Here we show that human oligodendroglioma Hs683 cells are not endowed with EAAT-dependent anionic amino acid transport. However, in these cells, but not in U373 human glioblastoma cells, valproic acid (VPA), an inhibitor of histone deacetylases, markedly induces SLC1A1 mRNA, which encodes for the glutamate transporter EAAT3. The effect is detectable after 8h and persists up to 120h of treatment. EAAT3 protein increase becomes detectable after 24h of treatment and reaches its maximum after 72-96h, when it is eightfold more abundant than control. The initial influx of d-aspartate increases in parallel, exhibiting the typical features of an EAAT3-mediated process. SLC1A1 mRNA induction is associated with the increased expression of PDGFRA mRNA (+150%), a marker of early oligodendrocyte precursor cells, while the expression of GFAP, CNP and TUBB3 remains unchanged. Short term experiments have indicated that the VPA effect is shared by trichostatin A, another inhibitor of histone deacetylases. On the contrary, EAAT3 induction is neither prevented by inhibitors of mitogen-activated protein kinases nor triggered by a prolonged incubation with lithium, thus excluding a role for the GSK3β/β-catenin pathway. Thus, the VPA-dependent induction of the glutamate transporter EAAT3 in human oligodendroglioma cells likely occurs through an epigenetic mechanism and may represent an early indicator of commitment to oligodendrocytic differentiation.

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