EFFECTS OF HISTONE DEACETYLASE INHIBITORS ON THE DEVELOPMENT OF EPILEPSY AND PSYCHIATRIC COMORBIDITY IN WAG/RIJ RATS

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Histone deacetylases (HDACs) are a family of proteins involved in both physiological and pathological conditions by regulating the status of chromatin histone acetylation (1,2). Alterations in histone acetylation and related HDACs have been correlated with many diseases, especially complex brain disorders such as epilepsy (3,4). Recently the modulation of chromatin structure through histone modifications has emerged as an important regulator of gene transcription in the brain and altered histone acetylation seems to contribute to changes in gene expression associated with epilepsy and the epileptogenic process (5). Inhibitors of HDACs (HDACis) have been tested in different experimental models of epilepsy with some success (6,7).

Here, we investigated the effects of two HDACi, valproate (VPA; 200mg/kg/day o.s.) and Butyrate (BUT; 30mg/kg/day o.s.), on the development of absence seizures and related psychiatric/neurologic comorbidities in WAG/Rij rats, a genetic model of absence epilepsy, epileptogenesis and mild-depression comorbidity according to our previously validated protocol (8). The potential antiepileptogenic effect of these HDACi was tested by analysis of EEG recordings, whereas the effects in epilepsy comorbidity were evaluated in the following behavioral tests: elevated plus maze (EPM), forced swimming test (FST) and passive avoidance. Our results have shown that, early-chronic HDACi treatment, started before absence seizure onset, significantly reduced the development of absence epilepsy (VPA 75%, BUT 51%) and ameliorated depressive like-behavior in WAG/Rij rats. Furthermore, early-chronic HDACi treatment improved the cognitive performance in this rat strain. WAG/Rij rats showed reduced acetylation of histones analyzed by Western Blotting of homogenized brain in comparison to WAG/Rij before the onset of seizure. Early-chronic HDACi treatment triggered acetylation of histones and α-tubulin suggesting that HDAC-dependent mechanisms are involved in the antiepileptogenic and psychiatric comorbidity of these drugs.

In conclusion, our results suggest that histone modifications may have a crucial role in the development of epilepsy and early treatment with HDACi might be a possible strategy for preventing epileptogenesis also affecting animal behaviour and comorbidity. HDACi might find therapeutic applicability for epilepsy and HDAC as a new molecular target to develop potential therapeutic agents for epilepsy.

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