

The Sodium Valproate: Doctor Jekyll and Mister Hyde



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Opinion

The sodium valproate (VPA) is a very simple structural compound derived from the valeric acid produced by a plant "*Valeriana officinalis*". Extracts of this plant were used by the doctors of Ancient Greece to cure insomnia and by the Romans to treat palpitations and arrhythmia. VPA was used for the first time as an anticonvulsant in 1963 [1] and in 1974 Jevson and Clark [2] after their clinical study on 63 patients whom 40 of them had failed to respond to other anticonvulsants concluded that in 43% of patients, epilepsy stopped completely, and in 22% of patients, the attacks were reduced by 50%. An unusual side effect was temporary hair loss. Since then VPA is widely used to treat almost all types of seizures and epilepsy syndromes, and is used successfully, for patients displaying epilepsy resistant to other medications [3]. Behind its anticonvulsant effect, VPA targets also a wide range of neurological diseases including some neurodegenerative pathologies, addiction, bipolar and obsessive-compulsive disorders and migraine [4]. Face to its broad therapeutic spectrum, this simple molecule has complex mode of actions. As an anticonvulsant agent VPA potentiates the GABAergic transmission, but also inhibits Glutamatergic transmission, blocked some voltage-gated channels and modulates serotonergic and dopaminergic neurotransmission [5]. One unexpected and fundamental effect of VPA is to inhibit histone deacetylase (HDAC) and by this way VPA impairs gene transcription. As epigenetic drugs can modulate global gene expression in tumors, VPA was showed to target signaling pathways in cancer cells and then became a good candidate in new clinical trial [4].

Nevertheless, effects of prenatal VPA exposure has been reported since the early 1980s [6]. Indeed, exposure to VPA in the first trimester of pregnancy is associated with an increase in the rate of several birth defects, clinically defined as the fetal valproate syndrome (FVS), including spina bifida, cardiac and craniofacial, skeletal anomalies associated with behavioral delays

[7] Furthermore maternal use of VPA during pregnancy increases the risk of autism by a factor 4 [8]. Consequently, in the epilepsy community valproate should be used judiciously in women of childbearing age. But some authors still discussed the balance risks versus benefits of the use of VPA in epileptic women. One argument in favor of VPA is the fact that uncontrolled seizures can lead to injury both for the pregnant woman and the fetus and can be occasionally be fatal [5]. An unambiguous dialogue between doctors and women under VPA treatment is fundamental. One major challenge for pharmaceutical company is to be developed new drugs with a VPA like antiepileptic activity but devoid of birth defects. Based on humans' cases of autism following prenatal exposure to VPA, since 2000 several groups have demonstrated that a prenatal exposure to VPA in rodents reproduced the core signs of human autism that are deficits in social interactions and communication associated with repetitive behaviors. Consequently, VPA rodents have been adopted as environmental models to study several aspects of autistic neurodevelopmental diseases [9]. Several brain regions were impacted by VPA exposure such as the cerebellum, neocortical structures and the limbic system. Those brain structures are implicated in the perception of the environment, in motor coordination, processing of emotions, sensory integration... [10]. Based on observations in VPA rodents' theories on the origins of the autistic spectrum disorders have been proposed such as the intense world corresponding to a hyperactivity and plasticity of local neuronal circuitry [11], and the excitation/inhibition imbalance in key neuronal circuitry [12]. Interestingly, the rodent VPA model of autism is actually used as a platform for preclinical studies and some compounds (NMDA receptor antagonists, oxytocin, anti-oxidant, neuroprotective agents) are shown to ameliorate their behavioral disorders. Consequently, those compounds are may be effective candidates for pharmacological treatments of autism [9]. The prevalence of autism increases worthwhile and prenatal exposures to various

environmental factors such as pesticides, heavy metal, endocrine disruptors, are suspected to be responsible of numerous cases of autism [13]. The VPA is one of the most documented environmental cause of autism and clearly demonstrate the importance epigenetic processes in a such neurodevelopmental pathology. I think VPA acting as doctor Jekyll (as an anti-epileptic) and as Mister Hyde (as a risk factor for autism) is not an isolated case. Consequently, it is important in the context of autism, that a detail epidemiologic study should be performed in all countries including a questionnaire about the life and its environment for women during their pregnancy. By this way, new risk factors (including compounds pod with clear beneficial effects on the quality of life) may be detected and the used of rodent may serve to confirm their potential implications in autism.

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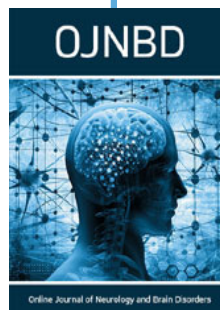


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