Key Words: valproate, autism, risk, folic acid, translational model, irritability

Valproate-Autism Labyrinth

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ABSTRACT *~ Valproate and Autism complexity is manifold. From an established environmental risk factor for autism, to a translational animal model, valproate's composite mode of action might unfold to address core autistic domains transcending mere aggressive behavioural control.* Psychopharmacology Bulletin. *2024;54(4):131–133.*

Prenatal maternal valproate (VAL) exposure has been consistently tied to a three-to-five-fold higher risk of autism spectrum disorder (ASD) in the offsprings.[1] Risk (circa 40%) appears to be higher among children born to mothers without epilepsy (e.g. bipolar).[2] This risk appears to be dose-dependent and linked to higher doses. Interestingly, children born to fathers on valproate around time of conception remain at heightened risk (albeit less than maternal risk). Several teratogenic mechanisms of VAL are proposed including, inter alia, its effects on the metabolism of folate (antagonism), SAMe and histones (histone deacetylase inhibition), thus affecting DNA methylation. VAL crosses the human placenta and was found at higher concentrations in fetal blood.[3] Aberrant excitation/inhibition transmission, neuroinflammation, diminished neurogenesis, and oxidative stress are also involved in valproate-induced neurotoxicity in ASD.[4] Moreover, a likely contributory mechanism could be valproate disrupting fasciculation of the mesoteloencephalic tract with a selective reduction of DA output from VTA.[5] Importantly, maternal folic acid supplementation prevents autistic behaviors in a rat model induced by prenatal exposure to valproic acid[6] and periconceptional folate (vitamin B9) has been associated with a reduced risk of autism and also mitigated the severity of autism traits.[7]

Of related interest, prenatal VAL exposure in rodents has been well established as a reliable translational model to study the pathophysiology of ASD, which has helped demonstrate neurobiological changes in rodents, non-human primates, and brain organoids from human pluripotent stem cells.[8] It is one of the most widely used animal models in the field. The gestational exposure of 400–600 mg/kg (i.p. or s.c.) of VAL in rodents at around GD 11.5–12.5 has consistently

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TABLE 1

Mechanisms of Action of Valproate

- VGS/KC blockade
- GABA potentiator
- Signal transduction downstreaming
- PK-C inhibition
- DA blockade
- 5HT modulation
- ↓ GHB
- Histone deacetylase inhibition
- Anti-glutamate
- ↑ Bcl-2 (anti-apoptotic)

demonstrated substantial disruptive effects on rodent-equivalent measures of the 3 core behavioural traits characteristic of ASD. These models represent a scaffold to test potential psychopharmacological agents targeting core domains of ASD-a big void in current pharmacopeia. FDA-approved risperidone and aripiprazole are indicated for severe irritability associated with ASD only.[9] In the same vein, a 12-week, DBPC trial of VAL was completed in 27 youth ages 5–15 years with ASD and irritability.[10] Authors reported 62.5% of VAL group had a response vs. 9% placebo. Mean blood level for responders was 89.8 μg/mL. Irritability, insomnia, headache and weight gain were among the adverse effects reported. Use of VAL in ASD can be advantageous to address comorbidities as well (e.g. seizures, tics, bipolarity … etc). A notable exception here is the related behavioural phenotype seen in Rett's syndrome (no longer included in a DSM-5-TR under umbrella of ASD). Use of valproate (VAL), to control seizures in Rett's syndrome, has been linked to 3-fold increase of fracture risk. Moreover, it is postulated that VAL by virtue of hailstone deacetylase inhibition might exacerbate the effects of MECP2 mutations in Rett's syndrome.[11]

Beyond behavioural control in ASD by VAL, this author (A.N.) has come across a number of cases on clinical grounds that demonstrated prosocial and verbal gains as well after commencing VAL. Majority of these cases had EDs (but not manifestly epileptic). Some posited these EDs might account for deficits in attention, language and behaviour. Accordingly, VAL by virtue of antiepileptic actions might explain these interesting outcomes. Larger well conducted studies are needed to replicate these findings. Another possible contributory mechanism is VAL allosteric enhancement of GABA inhibition. Dysfunction in the GABAergic system is considered an emerging signature of ASD.[12] Other mechanisms relate to VAL composite modes of action and pluripotent pharmacological portfolio (Table 1) including neuroprotection. ✤

Disclosures

Authors have nothing to declare.

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