Prenatal exposure to valproic acid induces a dose dependent impairment in sensorimotor gating in a mouse model of autism

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Neonatal exposure to MK-801, an N-methyl-D-aspartate receptor antagonist, affects prepulse inhibition and methamphetamine-induced locomotor activity in young adult rats

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Objective: Blockade of N-methyl-D-aspartate (NMDA) receptors has been shown to produce some of the abnormal behaviors related to schizophrenia in rodents and humans. Specifically, we previously found rats treated neonatally with the non-competitive NMDA antagonist MK-801 show behavioral abnormalities in a later period (Uehara et al., 2009). The aim of this study was to determine whether brief disruption of NMDA receptor function at the neonatal stage is sufficient to produce dopamine supersensitivity and sensorimotor gating deficits in the late adolescence or early adulthood in the rat.

Methods: Male pups received MK-801 (0.20 mg/kg), or an equal volume of saline on postnatal day (PD) 7 through 10. Methamphetamine (MAP) administration was in pre- (PD 36–38) or post- (PD 64–66) puberty in rats. We also tested prepulse inhibition at these periods in these animals.

Results: Neonatal MK-801 treatment augmented MAP-induced hyperlocomotion in both pre- and post-puberty, whereas spontaneous locomotor activity and rearing were not changed. MK-801 also disrupted PPI without affecting startle amplitudes.

Conclusion: These results suggest that transient blockade of NMDA receptors during a critical stage of development cause exaggerated dopamine transmission and sensorimotor gating deficits in the adolescence and early adulthood stages. Our findings indicate also that rats transiently exposed to NMDA blockers in neonatal periods are useful for the study of pathophysiology and treatment of schizophrenia.

Policy of full disclosure: None.

Prenatal exposure to valproic acid induces a dose dependent impairment in sensorimotor gating in a mouse model of autism

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Objective: Prepulse inhibition (PPI) is a measure of sensorimotor gating and is altered in many neuropsychiatric conditions. In autism spectrum (AS), restrictive and repetitive behaviors may be related to differences in sensorimotor gating. Although etiology of AS remains unclear, exposure in utero to valproic acid (VPA, anti-epilepsy drug), may be a risk factor. Prenatal exposure to VPA in the mouse is a potentially useful model of autism. However previous studies have involved multiple treatments with relatively large doses. In this pilot experiment, we examined whether postnatal sequelae occur at single exposure to VPA at low and moderate doses.

Methods: Pregnant mice were given a subcutaneous injection of 100 mg/kg or 200 mg/kg on gestation day (GD) 17. As this was a pilot, to minimize animal numbers, controls used received an intravenous saline injection on either GD9 or GD17 for a parallel experiment. The adult offspring (n = 6 VPA 100 mg; n = 11 VPA 200 mg; n = 10 saline control) were tested for PPI using standard acoustic startle paradigm of 2-min habituation, 6 pulse alone trials, 10 prepulse-plus-pulse trials, and finally 6 pulse alone trials. Three PPI Parameters were analysed: startle reactivity to pulse alone, startle habituation, comparing startle reaction in the first and last blocks. PPI in the prepulse-plus-pulse trials relative to startle in pulse-alone trials.

Results: Both VPA groups had stronger startle reactivity than controls. There was no significant group difference in startle habituation. There was a significant prepulse x group interaction reflecting a dose-dependent change in PPI; at prepulse 77/pulse 110 dB and prepulse 83/pulse 120 dB, PPI was greatest in controls > VPA 100 mg > VPA 200 mg.

Conclusion: The present results provide direct experimental evidence that a single prenatal exposure to VPA causes PPI changes analogous to those found in autism, and the lowering of PPI is dose-dependent.

Policy of full disclosure: None.