Title	Prenatal exposure to valproic acid induces a dose dependent impairment in sensorimotor gating in a mouse model of autism
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Citation	The 27th World Congress of the International College of Neuro-Psychopahrmacology (CINP), Hong Kong, 6–10 June 2010. In International Journal of Neuropsychopharmacology, 2010, v. 13, suppl. S1, p. 68, abstract no. P-02.039
Issued Date	2010
URL	http://hdl.handle.net/10722/137092
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dexamethasone (DEX)/corticotrophin releasing hormone (CRH) test. Some papers reported the activity of HPA axis is negatively regulated by hippocampus. However, it is not known whether newborn cells in the adult hippocampus are involved in it. The present study has examined the effect of early maternal separation (MS) stress and irradiation (IRR), which make hippocampal neurogenesis decreased, on the HPA axis.

Methods: In MS groups Sprague-Dawley rat pups were exposed to 180 min of maternal separation during postnatal day 2–14. The activity of HPA axis was estimated by the method of the DEX/CRH test when the rats reached 90 days old. 7 days after bromo-deoxyuridine (BrdU) administration they were sacrificed and the number of BrdU-labeled cells in bilateral dentate gyrus was counted as newborn cells with immu-nohistochemistry. In the IRR groups rats were subjected to repeated 5 Gy dose irradia-tion (5 Gy on Days 1, 4 and 8) directed at the whole cranium. After 3 weeks and 7 weeks of IRR DEX/CRH test was performed.

Results: The maximal rise of the plasma corticosterone concentration after CRH injection was significantly greater in the MS group than in the control group. However the number of BrdU-labeled cells was not significantly different between both groups. The study with IRR is under analysis.

Conclusion: These findings provide the first evidence that the DEX/CRH test revealed HPA system alterations in MS stress. However, the activity of HPA axis was not correlated with the number of newborn cells in maternal separation stress. The investigation with IRR will add new information of the relationship between HPA axis and adult neurogenesis.

Policy of full disclosure: None.

P-02.037 Neonatal exposure to MK-801, an N-methyl-D-asparate receptor antagonist, affects prepulse inhibition and methamphetamine-induced locomotor activity in young adult rats

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Objective: Blockade of N-methyl-D-asparate (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; 1.0 mg/kg, i.p.)-induced locomotor activity was in pre- (postnatal day; 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.

P-02.038 Studying the 'two-hit' hypothesis of schizophrenia in rats and mice: role of Brain-Derived Neurotrophic Factor (BDNF)

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Objective: Epidemiological studies suggest that schizophrenia is caused by an early developmental disruption, such as a genetic deficit or environmental stress, which increases vulnerability to later factors, such as drug abuse or social stress, i.e. the 'two-hit' hypothesis. In rats, we demonstrated persistent effects of two developmental disruptions on cognitive function and brain-derived neurotrophic factor (BDNF) expression (Choy et al., Hippocampus, 2008).

Methods: To further assess the relationship between reduced BDNF levels and neurodevelopmental stress, we used male and female BDNF heterozygous (Het) mice. As a second neurodevelopmental stress, these mice received corticosterone (CORT) in the drinking water from 6–9 weeks of age. Behavioural testing commenced from 11 weeks of age (n = 14–20 per group).

Results: Wild-type mice, wild-type mice receiving CORT, or BDNF Het mice, showed intact Y-maze spatial memory in adulthood, as evidenced by a significant preference to spend time in the novel arm one- or two hours after the 2-arm pre-exposure. In contrast, male, but not female CORT-treated BDNF Het mice showed disrupted short-term spatial memory. As expected, BDNF levels, assessed by Western Blot, were reduced by approximately 50 % in BDNF Het mice but were not further decreased by CORT treatment.

Conclusion: These results demonstrate an interaction of reduced BDNF levels in the brain, neurodevelopmental stress and cognition. In rats we observed persistent effects of two developmental disruptions on cognitive function and BDNF expression in the hippocampus. In mice with reduced BDNF levels, CORT treatment induced cognitive deficits which were not observed in the single 'hit' controls. This effect appeared to be specific for male mice. These results may help to explain the development of cognitive deficits in patients with mental illnesses with a neurodevelopmental origin, such as schizophrenia.

Policy of full disclosure: None.

P-02.039 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-dependant.

Policy of full disclosure: None.