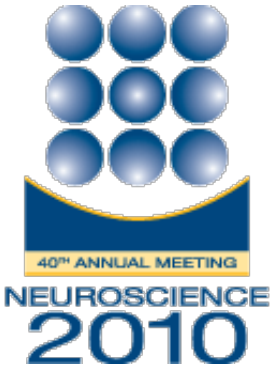

Presentation Abstract

Program#/Poster#:	363.21/BB14
Title:	Neonatal exposure to NMDA receptor antagonists halts the maturation of parvalbumin-positive fast-spiking interneurons, leading to altered network activity in adulthood
Location:	Halls B-H
Presentation Time:	Monday, Nov 15, 2010, 8:00 AM - 9:00 AM
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Abstract:

Repetitive exposure of adult mice to ketamine, a NMDA-R antagonist, increases the levels of the proinflammatory cytokine interleukin-6 in the brain which, through activation of the superoxide-producing enzyme NADPH-oxidase (Nox2), leads to the loss of the GABAergic phenotype of parvalbumin-positive (PV) fast-spiking interneurons and to a decreased inhibitory activity in the prefrontal cortex. The effects of activation of the IL-6/Nox2 pathway on the PV-interneuronal system are reversible in the adult brain, but permanent if they occur during a critical period in the developing cortex. This period corresponds to the second postnatal week in mice, when the exposure to NMDA-R antagonists on postnatal days 7, 9 and 11 leads to a permanent loss of parvalbumin immunoreactive neurons, as well as to schizophrenia-like behaviors when animals reach adulthood. This effect is absent in Nox2-deficient animals, suggesting that activation of the IL-6/Nox2 pathway is involved in the permanent loss of PV-interneurons in this neurodevelopmental model.

To understand the fate of the PV-interneurons in ketamine-treated mice, we tested the hypothesis that the blockade of NMDA receptors during this critical period does not lead to the death of the interneurons, but to an arrest of their normal postnatal maturational program. Using the G42 mouse line, which expresses EGFP in 50 % of the PV-interneuronal population in cortex, we analyzed the effects of perinatal ketamine exposure on parvalbumin immunoreactivity and on the excitatory inputs to these cells when the animals were 3 and 5 weeks old.

Treatment with ketamine on postnatal days 7, 9, and 11 led to the loss of parvalbumin expression in frontal regions but not to the death of the neurons. Whole-cell patch clamp recordings revealed that the amplitude of spontaneous excitatory postsynaptic currents was decreased in PV-interneurons of ketamine-treated mice as compared to age-matched controls. These physiological alterations were correlated with disruptions in network activity, as demonstrated by results showing alterations in auditory evoked related potentials and decreased evoked gamma oscillatory activity when animals were tested in adulthood.

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