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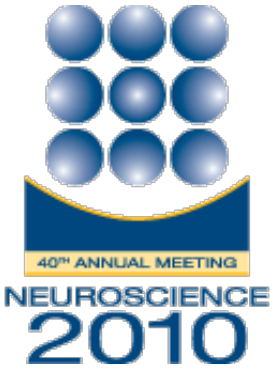

Presentation Abstract

Program#/Poster#:	363.27/CC2
Title:	A role for DNA methylation in the NMDA receptor antagonist-mediated loss of phenotype of parvalbumin-positive fast-spiking interneurons
Location:	Halls B-H
Presentation Time:	Monday, Nov 15, 2010, 10:00 AM -11:00 AM
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Abstract:

Exposure to N-methyl-D-aspartate receptor antagonists produces psychosis in humans, and exacerbates symptoms in schizophrenia patients. We have recently shown that these antagonists induce the activation of the IL-6/Nox2 pathway, which leads to a widespread increase in superoxide production in brain. This increased oxidative stress, in turn, is responsible for the loss of GABAergic phenotype of the fast-spiking inhibitory neurons expressing the calcium binding protein parvalbumin (PV). The effects of the NMDA-R antagonists are reversible in the adult brain, but produce permanent effects when treatments are performed during critical periods of postnatal brain development, specifically during the period when the PV-interneuronal network begins to mature.

This period corresponds to the second postnatal week in mice, where a plethora of gene transcription changes take place that lead to mature fast-spiking interneurons when animals reach their fifth week of age.

Mutual information analyses of the transcriptional changes occurring during the period of PV-interneuronal maturation yielded changes in a cluster of genes involved in chromatin remodeling, with most of them being downregulated during this transition. This led us to test the hypothesis that activation of the IL-6/Nox2 pathway during NMDA-R antagonist exposures could be producing changes in DNA methylation and in this way alter the phenotype of PV-interneurons. We have found that the DNA methylation inhibitors 5-Azacytidine and Zebularine prevent the loss of phenotype of PV-interneurons caused by prolonged exposure to ketamine. Furthermore, we have shown that inhibition of DNA methylases also

prevents an increase in superoxide production and the effects of IL-6 in these interneurons. Epigenetic modification of chromatin, which through DNA methylation can regulate and dysregulate gene transcription, has been suggested to play an important role in neuronal differentiation and could be involved in the environmental origins of schizophrenia. Epigenetic dysregulation of specific promoters have been shown in schizophrenia postmortem samples, and several schizophrenia-linked genes are subject to epigenetic regulation. Our results suggest that alterations in DNA methylation during the critical period of PV-interneuronal maturation may lead to a permanent disruption of this inhibitory circuitry as observed in schizophrenia.

Disclosures: **M. Behrens:** None. **A. Hasenstaub:** None. **T.J. Sejnowski:** None.

Keyword(s): PARVALBUMIN

NMDA RECEPTOR

GABAERGIC

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