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Commentary

Gestational Methylazoxymethanol Acetate Administration Alters Proteomic and Metabolomic Markers of Hippocampal Glutamatergic Transmission

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Gestational methylazoxymethanol acetate (MAM) administration produces deficits consistent with those observed in schizophrenia patients, including anatomical changes, behavioral deficits, and altered neuronal information processing (for review see Lodge and Grace (2009b)). Behaviorally, MAM-treated rats display deficits in prepulse inhibition of startle, latent inhibition, working memory, social interaction, and an enhanced response to psychomotor stimulants. The mechanisms underlying these deficits have not been conclusively demonstrated; however, neurophysiological studies have confirmed that MAM-treated rats display an augmented dopamine system function, consistent with the enhanced dopamine signaling proposed to underlie the positive symptoms of schizophrenia in humans. These deficits in dopamine system regulation can be attributed to a lack of interneuron function within the ventral hippocampus (Lodge *et al*, 2009a), a finding consistent with postmortem (Konradi *et al*, 2011) and imaging studies (Lahti *et al*, 2006) in human schizophrenia patients. Although gestational MAM administration recapitulates a pathodevelopmental process leading to a schizophrenia-like phenotype, the molecular changes underlying these neurophysiological and behavioral alterations have not previously been examined.

In the current issue, Bahn and colleagues (Hradetzky *et al*, 2011) describe important and relevant molecular effects of gestational MAM administration that further validate the MAM-treated rat as a model relevant to human disease. Using proteomic and metabolomic analyses, the authors report that gestational MAM administration induces molecular alterations that are largely localized to the hippocampus. Specifically, LC–MS analysis of hippocampal tissue demonstrated 38 (out of 673) proteins that were altered by MAM-treatment. Interestingly these alterations were restricted to the hippocampus with no significant differences observed for the 743 proteins identified from the frontal cortex. The candidate proteins with the greatest statistical significance were verified by immunoblot analysis, and three proteins demonstrated a significant correlation with LC–MS analysis, namely AMPA1, PMCA1, and HPCA. In addition, the AMPA1 immunoblots identified two distinct bands, corresponding to phosphorylated and non-phosphorylated forms of the receptor. These bands were differentially altered by MAM treatment, indicating a potential reduction in phosphorylation of the AMPA1 subunit of the receptor.

To characterize the pathways associated with the proteomic changes, analyses using *in silico* modeling were performed on the proteins identified by LC–MS. Thus, pathway analysis of the 38 differentially expressed hippocampal proteins demonstrated a significant association with glutamatergic signaling. Of particular relevance to glutamatergic transmission were changes in AMPA-receptor subunit expression and phosphorylation that suggest MAM-treated rats may display alterations in hippocampal synaptic transmission and synaptic plasticity. Indeed, electrophysiological studies in hippocampal slices confirmed that MAM-treated rats display a decrease in AMPA receptor-mediated field potentials, reflective of altered EPSPs. A further association with aberrant glutamatergic signaling was demonstrated by metabolomic analysis using ^{1}H-NMR. Consistent with the proteomic data, pathway analysis of the hippocampal metabolites demonstrated that the most significant canonical pathway affected by prenatal MAM administration was the glutamatergic system. Specifically, changes in glutamate, N-acetyl aspartyl glutamate and overlapping spectra of glutamate/glutamine were observed.

Taken together, the study by Bahn and colleagues (Hradetzky *et al*, 2011) further validates the MAM-treated rat as a model relevant to human disease, and extends this work to demonstrate that gestational MAM administration significantly alters glutamatergic markers throughout the hippocampus, in accord with human studies demonstrating alterations in hippocampal function (Konradi *et al*, 2011;

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Lahti *et al*, 2006) and glutamatergic signaling (Tsai and Coyle, 2002). Given similar deficits in anatomical, behavioral, neurophysiological, and now molecular markers, the MAM model is an exceptionally well-validated model with the potential to aid in preclinical drug discovery and development. Indeed, the MAM model has provided insight into therapeutic approaches such as the rapid onset of antipsychotic drug action (Valenti *et al*, 2011) and identification of novel targets, such as positive allosteric modulators selective for the α5-subunit of the $GABA_A$ receptor (Gill *et al*, 2011).

DISCLOSURE

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REFERENCES

Gill KM, Lodge DJ, Cook JM, Aras S, Grace AA (2011). A novel α5$GABA_A$R-positive allosteric modulator reverses hyperactivation of the dopamine system in the MAM model of schizophrenia. *Neuropsychopharmacology* **36**: 1903–1911.

Hradetzky E, Sanderson TM, Tsang TM, Sherwood JL, Fitzjohn SM, Lakics V *et al* (2011). The methylazoxymethanol acetate (MAM-E17) rat model: molecular and functional effects in the hippocampus. *Neuropsychopharmacology* **37**: 364–377.

Konradi C, Yang CK, Zimmerman EI, Lohmann KM, Gresch P, Pantazopoulos H *et al* (2011). Hippocampal interneurons are abnormal in schizophrenia. *Schizophr Res* **131**: 165–173.

Lahti AC, Weiler MA, Holcomb HH, Tamminga CA, Carpenter WT, McMahon R (2006). Correlations between rCBF and symptoms in two independent cohorts of drug-free patients with schizophrenia. *Neuropsychopharmacology* **31**: 221–230.

Lodge DJ, Behrens MM, Grace AA (2009a). A loss of parvalbumin-containing interneurons is associated with diminished oscillatory activity in an animal model of schizophrenia. *J Neurosci* **29**: 2344–2354.

Lodge DJ, Grace AA (2009b). Gestational methylazoxymethanol acetate administration: a developmental disruption model of schizophrenia. *Behav Brain Res* **204**: 306–312.

Tsai G, Coyle JT (2002). Glutamatergic mechanisms in schizophrenia. In *Annual Review of Pharmacology and Toxicology*. pp 165–179.

Valenti O, Cifelli P, Gill KM, Grace AA (2011). Antipsychotic Drugs Rapidly Induce Dopamine Neuron Depolarization Block in a Developmental Rat Model of Schizophrenia. *J Neurosci* **31**: 12330–12338.