AMPHETAMINE ALTERS GROUP I mGluR EXPRESSION IN THE RAT STRIATUM AND MEDIAL PREFRONTAL CORTEX

C.B. Shaffer[1], M.D., L.M. Mao[2], M.D., E.E. Fibuch[1], M.D., J.Q. Wang[1,2], Ph.D., M.D.

[1]Department of Anesthesiology, University of Missouri-Kansas City School of Medicine, Saint Luke's Hospital, Kansas City, Missouri. [2]Department of Basic Medical Science, University of Missouri-Kansas City, School of Medicine, Kansas City, Missouri.

Introduction: Group I metabotropic glutamate receptors (mGluR1/mGluR5 subtypes) and their key scaffolding protein Homer1b/c are densely expressed in the striatum. These receptors are believed to play important roles in the regulation of psychostimulant action[1]. The psychostimulant amphetamine increases extracellular glutamate levels, which in turn activates postsynaptic mGluR1/5 in striatal neurons. It is, however, unclear whether amphetamine has any impact on striatal mGluR1/5 expression. In this study, we hypothesized that alterations in mGluR1/5 and Homer 1b/c expression in the rat striatum and medial prefrontal cortex (mPFC) would occur in response to an acute injection of amphetamine *in vivo*.

Methods: Following IACUC approval, adult male Wistar rats received an intraperitoneal injection of saline (n = 4) or amphetamine (5 mg/kg, n = 5). Motor responses to amphetamine were monitored continuously following drug administration. For detecting gene expression, rats were anesthetized and sacrificed 1 h after saline or amphetamine injection. Brains were removed, and the striatum, including the dorsal (caudate putamen) and ventral (nucleus accumbens) striatum, and mPFC were dissected. Synaptic proteins were extracted for Western blot analysis of changes in mGluR1, mGluR5, and Homer1b/c protein levels with specific antibodies. The density of immunoblots was measured using optical scanning. Data were statistically analyzed using Student's t-test ($p<0.05$).

Results: A single injection of amphetamine induced a typical increase in motor activity, confirming that a behaviorally active dose of the drug was used. At this dose, amphetamine markedly reduced mGluR5 protein levels in the striatum, while increasing mGluR5 protein levels in the mPFC. Unlike mGluR5, mGluR1 protein expression in both the striatum and mPFC was not significantly altered in amphetamine-treated rats relative to saline-treated rats. Homer1b/c protein levels in the two regions also remained stable in response to amphetamine administration. Actin protein levels showed no difference between amphetamine- and saline-treated groups.

Conclusion: These data identify mGluR5 as a sensitive target of amphetamine. Acute amphetamine exposure is able to alter striatal mGluR5 expression in a subtype- and region-specific manner.

Discussion: Amphetamine increases glutamate release in the striatum[1] which can activate mGluRs in striatal neurons to produce drug effects. Group I mGluRs have been demonstrated to undergo rapid desensitization following ligand stimulation of the receptor[1]. Thus, our finding of a loss of synaptic mGluR5 after amphetamine suggests a previously unrecognized mechanism for such desensitization. Of note, amphetamine has no effect on glutamate release in the mPFC[1]. Future studies are needed to define the role of amphetamine-stimulated mGluR5 expression in this region.

References:

1. *Wang JQ, Mao L, Parelkar NK, Tang Q, Liu Z, Sarwar S and Choe ES. (2003). Glutamate-regulated behavior, transmitter release, gene expression and addictive plasticity in the striatum: roles of metabotropic glutamate receptors. Current Neuropharmacology 1: 1-20.*