AMPHETAMINE ALTERS ACID-SENSING ION CHANNEL EXPRESSION IN THE RAT STRIATUM

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Introduction: The acid-sensing ion channel (ASIC) is specifically activated by a drop in the extracellular pH level. These channels are widely expressed in mammalian brains and actively modulate synaptic transmission and a variety of neuronal activities. In the striatum, two ASIC subtypes (ASIC1 and ASIC2) are densely expressed. Given the fact that the striatum is a central site for processing biological actions of drugs of abuse, expression of abundant ASICs in this structure implies a potential involvement of the channel in drug effects. In this study, we examined the expression of ASIC1 and ASIC2 in the rat striatum in response to chronic exposure to the psychostimulant amphetamine *in vivo*.

Methods: Following IACUC approval, adult male Wistar rats (2 groups, n = 6 per group) received intraperitoneal injections of saline or amphetamine (once daily for 7 days, 1.25 mg/kg for day 1 and day 7, 4 mg/kg for days 2-6). At 14 days after the termination of drug injection, rats were sacrificed after anesthesia. Brains were removed and sliced into coronal sections (400 μm). The dorsal (caudate putamen, CPu) and ventral (nucleus accumbens, NAc) striatum were dissected in artificial cerebrospinal fluid. A membrane-impermeable cross-linking reagent bis(sulfosuccinimidyl)suberate (BS^3) was added. BS^3 only cross-links ASICs on the surface of live cells to form high-molecular weight aggregates which can be readily separated from normal intracellular monomer ASIC proteins. Densities of immunoblots were measured using optical scanning and the data were analyzed (t-test ($p < 0.05$)).
Results: BS^3-treated striatal tissue showed a high-molecular weight band of ASIC1 and ASIC2 (surface channels) and a monomeric molecular weight band of ASIC1 and ASIC2 (intracellular channels). Quantification analysis revealed that 70-80% of ASIC1 and ASIC2 are expressed in the surface membrane of normal striatal neurons. Chronic amphetamine administration induced parallel increases in ASIC1 protein levels in both surface and intracellular pools in the CPu at a 14-day withdrawal period. Similar results were also observed in the NAc. In contrast to ASIC1, ASIC2 and α-actinin in their protein levels remained unchanged in the CPu and NAc of amphetamine-treated rats.

Conclusion: These data identified the central ASIC as a sensitive target to repeated stimulant exposure.

Discussion: Various synaptic proteins have been screened for their responses to repeated drug exposure. Plastic changes in the expression and function of all responsive proteins are thought to operate in concert to control drug effects. In this study, a new responsive gene is identified. Following repeated amphetamine administration, ASIC expression was regulated in striatal regions. This identifies the

channel as an important element of molecular adaptations to drug exposure. Indeed, ASICs have been implicated in various mental disorders[1]. This study represents an initial effort toward elucidating the precise role of ASICs in processing the addictive action of drugs of abuse.

References:

1. Wemmie JA, Price MP, and Welsh MJ (2006) Acid-sensing ion channels: advances, questions and therapeutic opportunities. Trends Neurosci 29: 578-586.