

Acid-sensing ion channels as a novel target for drug addiction

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Improving the treatment and prevention of drug addiction is an important goal for modern medicine. Ion channels have recently become very attractive targets in the search of new pharmacotherapies. Extracellular proton concentrations in the brain may be an important signal for neuronal function. Proton concentrations change both acutely when synaptic vesicles release their acidic contents into the synaptic cleft and chronically during ischemia and seizures. Acid-sensing ion channels (ASICs) are proton-gated cationic channels activated by a drop in extracellular pH. They are enriched in the mammalian brain with a high synaptic density. Accumulating evidence suggests that ASIC1a contributes to synaptic activity related to learning/memory and fear conditioning, and also plays a critical role in neurodegenerative diseases. In this study, we explored the functional role of ASICs in response to cocaine in the striatum using electrophysiology, molecular biology and behavioral testing. A rapid drop in extracellular pH induced transient inward currents in all medium spiny neurons (MSNs). The pH value for half maximal activation (pH_{50}) was 6.25, close to that obtained in homomeric ASIC1a channels. Based on PcTX1 and zinc sensitivity, ASIC1a (70.5% of neurons) and heteromeric ASIC1a-2 channels (29.5% of neurons) appeared responsible for the acid-induced currents in MSNs. ASIC currents were diminished in MSNs from ASIC1, but not ASIC2, null mice. Furthermore, a drop in pH induced calcium influx by activating homomeric ASIC1a channels and activation of ASICs increased the membrane excitability of MSNs. Chronic systemic injection of cocaine (20 mg/kg, once daily for 5 consecutive days; 14 days of withdrawal) increased ASIC1a, but not ASIC2, protein levels in the striatum, including the dorsal (caudate putamen) and the ventral (nucleus

accumbens) striatum. No significant changes in ASIC1a or 2 protein levels in the median prefrontal cortex and the hippocampus were observed following the chronic cocaine administration. Amiloride (6 mg/kg; i.p.), a non-selective ASIC blocker, did not alter spontaneous motor activities of mice including total distance, horizontal activity, stereotypy time and counts, vertical activity and time. In contrast, amiloride at the same concentration did decrease the locomotor responses (total distance) to challenge treatment with cocaine in repeated cocaine-, but not saline-pretreated mice. These data demonstrate that functional ASIC1a is the dominant component in the striatum; chronic cocaine administration markedly increases ASIC1a expression in the striatum and antagonism of ASICs decrease behavioral sensitization to cocaine. Together, ASIC1a might be a novel target for drug addiction therapy.