STRESS-INDUCED INCREASES IN EXTRACELLULAR SEROTONIN IN THE VENTRAL HIPPOCAMPUS IS ATENUATED IN RATS DURING AMPHETAMINE WITHDRAWAL

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ABSTRACT

Amphetamine withdrawal is characterized by heightened anxiety states, and serotonin (5-HT) in the ventral hippocampus (vH) is associated reduced anxiety. Therefore, we tested the hypothesis that rats subjected to amphetamine withdrawal would exhibit attenuated stress-induced 5-HT overflow in the vH using in vivo microdialysis. Male Sprague-Dawley rats were treated with 2.5 mg/kg amphetamine or saline for 14 consecutive days. Within two weeks of the last amphetamine treatment, a microdialysis probe was inserted into the vH and perfused with artificial cerebral spinal fluid overnight. The following day, a 5-HT baseline was established and the rats were subjected to 20 min of restraint stress. Preliminary results suggest that the stress-induced release of 5HT in the amphetamine-treated group was attenuated in response to the stressor. This result is consistent with our earlier studies in anesthetized rats which showed that chronic amphetamine (2.5 mg/kg; 14 days) decreased KCl- and corticosterone-induced 5-HT increases in vH. Interestingly, the blockade of the corticosterone-sensitive organic cation transporter 3 using intra-vH decynium-22 dose-dependently increased extracellular 5-HT in saline pretreated rats but had no effect in rats chronically pretreated with amphetamine. Furthermore, western immunoblot analysis indicated that OCT3 expression in the vH increased in rats treated with chronic amphetamine. These results suggest that chronic amphetamine alters both the release of 5-HT in response to stress and decreases the availability of extracellular 5-HT in the vH through increased OCT3-mediated 5-HT clearance. The persistence of attenuated serotonergic responses to stress in the vH during amphetamine withdrawal may contribute to drug relapse. Supported by NIH RO2 DA019921 (GLF) and NSF 0921874 (KJR).