

Effects of Methamphetamine and Related Substances on Egocentric Learning in Adult Rats

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Introduction: Methamphetamine (MA) causes marked neurotoxicity and cognitive deficits in humans after chronic use. Neurotoxic effects as well as deficits in egocentric route-based learning have been demonstrated in rats following MA exposure. MA reduces the levels of dopamine (DA), serotonin (5-HT), and their associated transporters in the brain. The relationship of cognitive deficits to the depleted monoamines is unknown. Therefore, the aim of this study was to compare stimulant drugs with selective effects on DA, 5-HT, or both to those of MA. Amphetamine (AMPH) is known to target the DA system, whereas fenfluramine (FEN) targets the 5-HT system. We used doses of these drugs that are known to deplete the associated monoamine. We hypothesized that decreased levels of 5-HT would produce greater deficits in egocentric route-based learning in the rat model of chronic MA abuse.

Methods: Five groups of adult Sprague-Dawley rats (n=21) were injected (4 doses at 2 h intervals) with saline, 10 mg/kg MA, 12.5 mg/kg MA, 16 mg/kg FEN, or 25 mg/kg AMPH subcutaneously. The higher dose of AMPH was given to mimic the elevation in body temperature observed with MA, whereas the dose of FEN was set to be equimolar to the higher doses of MA. Body temperatures were monitored every 15 min following the first injection for the duration of the treatment. Two weeks after treatment, animals were assessed for 18 days in a test of egocentric route-based learning, the Cincinnati water maze (CWM). Errors and latencies to find the platform at the end of the maze were recorded.

Results: Rats treated with either dose of MA showed deficits in route-based learning as compared to the saline controls. Similarly, rats in the AMPH treatment group exhibited the largest deficits in the CWM. The rats in the FEN treatment group did not differ from the saline controls.

Conclusions: These data, while correlative, suggest that dopamine depletions are more involved in egocentric route-based learning deficits in this model of chronic MA use 5-HT.