Serotonin release by drugs of abuse may contribute to addiction through antidepressant properties. Extracellular 5HT increased in the hypothalamus with local fluoxetine[12], an antidepressant, and amphetamine-induced release of hypothalamic 5HT increased with chronic systemic LiCl[13], both antidepressants. Inhibiting the serotonin systems with 8-OHDA eliminated conditioned suppression of saccharin intake[14]. This suggests that one function of some 5HT system is some aspect of conditioned negative reinforcement (learned avoidance). Microdialysis suggests that AMPH, COC, fluoxetine and LiCl may have 5HT effects in common, so it is possible that these drugs enable systems for escape or avoidance of aversive consequences. It is not inconceivable that serotonergic properties of some drugs of abuse could help explain addiction in terms of facilitating the escape from aversive aftereffects. In conclusion, the results support the working hypothesis that DA plays a role in drug positive reinforcement (learned approach) and suggests that serotonin plays a role in drug negative reinforcement (learned escape or avoidance). (Supported by USPHS grant DA-03597).

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Psychostimulant Properties of MDMA

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The debate over the therapeutic usefulness of methylenedioxymethamphetamine (MDMA) versus its neurotoxic and abuse potentials has resulted in a renewed interest in the basic pharmacological effects of this amphetamine analog. Based on human reports of mild sympathomimetic side effects and biochemical studies indicating that MDMA activates both the serotonin and dopamine systems, the neuropharmacological basis for the psychostimulant effects of MDMA were investigated.

BEHAVIORAL PROFILE OF MDMA-INDUCED LOCOMOTION

MDMA (2.5-10.0 mg/kg, SC) dose dependently increased locomotor activity measured in photocell activity cages for at least 2 hours [1]. Characterization of the qualitative aspects of the behavioral effects produced by MDMA was conducted using the Behavior Pattern Monitor (BPM) System. Each BPM chamber consists of a black Plexiglas holeboard with three floor holes and seven wall holes, a 4 x 8 array of infrared photobeams and a rearing touch plate. A similar range of doses (1.25-10.0 mg/kg, SC) were also found to increase horizontal locomotion for at least 2 hours measured in this apparatus [2]. In addition this hyperactivity was accompanied by an initial decrease in investigatory holepokes and rearings followed by subsequent increase at the highest doses tested. Rats injected with 5.0 and 10.0 mg/kg exhibited thigmotaxis and a tendency to avoid the center of the experimental chamber, a behavioral profile similar to hallucinogen-like drugs.

Various psychostimulant drugs can produce a conditioned locomotion when tested in the presence of environmental cues that were repeatedly associated with the drug experience. MDMA (5mg/kg, SC) paired for 5 days to a distinct environment paired with the presence of an olfactory stimulus, produced enhanced locomotion during a test probe with the odor alone [3]. The observation that the stimulus properties of MDMA can also become associated with environmental cues indicates a behavioral effect which MDMA has in common with other classical psychostimulants such as amphetamine and cocaine.

NEUROCHEMICAL PROFILE OF MDMA-INDUCED LOCOMOTION

The neurochemical substrates for the psychostimulant properties of MDMA have also been investigated. The role of the mesolimbic dopamine system in the locomotor stimulation produced by MDMA was examined following 6-OHDA

lesions of the nucleus accumbens. As with amphetamine and cocaine, destruction of dopamine terminals in the region of the nucleus accumbens attenuated the MDMA-induced hyperactivity. Interestingly, rats treated with amphetamine (0.5 mg/kg, SC) after a previous injection of MDMA (5 mg/kg, SC) seem to exhibit an enhanced locomotor response or sensitization. This may reflect the behavioral effects caused by serotonin neurotoxicity associated with exposure to MDMA, as has been reported by others [4]. Thus, a loss of serotonergic inhibition of a dopamine-mediated component of locomotor hyperactivity results in an increased locomotor response. The importance of this serotonergic modulation of dopamine neurotransmission was demonstrated further by showing that a serotonin antagonist, methysergide (2.5-10.0 mg/kg, SC), markedly potentiated the increase in locomotion produced by MDMA (10.0 mg/kg, SC) [5].

CONCLUSIONS

In summary, the stimulation of locomotor activity by MDMA and the importance of mesolimbic dopamine in this response reflects similarities with the prototype stimulant, amphetamine. It is important to note that these parameters are frequently associated with rewarding aspects of drugs and drug abuse. Additionally, the behavioral profile of MDMA shares certain characteristics with hallucinogen-like agents. This mixture of stimulus properties and neurochemical actions suggests a unique pharmacology for MDMA which may be associated with potential behavioral toxicity in addition to the previously revealed neurotoxicity.

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Comparison of the Behavioral and Neurochemical Effects of 5, 7-DHT, MDMA and D, L-Fenfluramine

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Three experiments were performed. In the first, separate groups (n=9-10) of male Sprague-Dawley rats (250 g) were injected with different doses of 5,7-dihydroxytryptamine (5,7-DHT; 0, 50, 100 and 150 ug/kg, i.c.v.; 30-45 min following nomifensine and desipramine, 15 mg/kg, i.p.) or 3,4-methylenedioxymethamphetamine (MDMA; 0, 10, 20, and 40 mg/kg, s.c., b.i.d x 4 d) then subjected to a series of behavioral tests beginning 2-3 weeks post-injection. The rats were sacrificed 10 weeks post-injection and regional CNS monoamines and metabolites determined by HPLC. 5,7-DHT produced selective and dose-dependent but non-uniform reductions (46-95%) in regional 5-HT and 5-HIAA concentrations. The hippocampus and hypothalamus were the most and least sensitive, respectively. In contrast, MDMA produced uniform falls in CNS 5-HT and 5-HIAA levels which did not exceed 39%. The lowest dose (50 ug) of 5,7-DHT reduced open field exploration. All 5,7-DHT doses impaired swimming ability. 5,7-DHT failed to affect the acquisition of one- and two-way conditioned avoidance responses. MDMA did not affect any of the behaviors studied.

In the second experiment, rats (n=6-12/group) were treated with 5,7-DHT (0, 50 or 200 ug, i.c.v.), MDMA (0, 10 or 40 mg/kg, s.c., b.i.d. x 4 d), or d,l-fenfluramine (FEN; 0, 5 or 20 mg/kg, s.c., b.i.d x 4 d). Open field behavior (12 min), morphine analgesia (5.0 mg/kg, s.c.), and swimming ability (14 min) were examined on the 3 days immediately preceding sacrifice either 2 or 8 weeks later. The effects of 5,7-DHT on CNS 5-HT and 5-HIAA levels were substantially greater than those produced by the substituted amphetamines. The neurochemical effects of the treatments, furthermore, were greater 2 weeks than 8 weeks post-injection. The 5,7-DHT 200 ug dose potentiated morphine analgesia 8 but not 2 weeks post-injection. No other behavioral effects were observed.

In the third, rats (n=8-12/group) were treated with either saline (1.0 ml/kg, s.c., b.i.d. x 4 d), MDMA (40 mg/kg, s.c., b.i.d. x 4 d) or FEN (12 mg/kg, s.c., b.i.d. x 4 d). The animals were food deprived and trained for 5 weeks in a 8-arm radial maze for food reinforcement. The performance of the MDMA, FEN and saline treated animals did not differ.

Repeated high doses of MDMA and FEN do not lead to dysfunctions in exploratory behavior, motor coordination or stamina, thermal pain sensitivity, morphine analgesia, avoidance conditioning, or short-term spatial memory. 5-HT neurons, furthermore, recover from the depleting effects of MDMA and FEN. The behavioral effects of 5,7-DHT appear to be test, dose and time dependent. The functional consequences of substantial reductions in CNS 5-HT levels, however, are subtle and difficult to discern.

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