169.5 FURTHER STUDIES ON THE NEUROCHEMICAL EFFECTS OF 4,5-METHYLENEDIOXYMETHAMPHETAMINE AND RELATED ANALOGUES. C.J. Schmidt* and W. Lovenberg* (SPON: F. Miller). Biochem. Sci., Merrell Dow Research Institute, Cincinnati, OH 45215

3,4-Methylenedioxymethamphetamine (MDMA) is a psychedelic amphetamine derivative with unique behavioral and neurochemical characteristics. These behavioral effects have made MDMA a popular drug of abuse amoung college students and young professionals. We have previously presented data indicating that MDMA produces neurochemical alterations in serotonergic neurons reminiscent of the selective neurotoxin, p-chloroamphetamine. Acute administration of MDMA produces distinct acute and long-term depletions of rat brain serotonin and 5-hydroxyindoleacetic acid with little or no persistent effect on dopaminergic parameters. We have further characterized the effects of MDMA on serotonergic neurochemistry and have made comparisons with the N-desmethyl- and N-ethyl-analogues of MDMA.

Both stereoisomers of MDMA (10 or 20 mg/kg) were found to produce the acute (3 h) depletion of cortical and striatal serotonin reported for the racemic drug. However, after one week the depletion of brain serotonin was significantly greater in animals administered (+)-MDMA compared to those given the (-)-stereoisomer. When [$^3$H]serotonin uptake was measured into whole brain synaptosomes one week after MDMA administration (20 mg/kg), a significant reduction (56 percent) in uptake was found only for animals treated with (+)-MDMA.

Acute administration of racemic methylenedioxyamphetamine (MDA), MDMA, or N-ethyl-methylenedioxyamphetamine (MDE) at 10 or 20 mg/kg produced a similar depletion of cortical serotonin at 3 h. However, this effect of the N-ethyl derivative was reversed by one week. Furthermore, the decrease in high affinity serotonin uptake measured at one week following MDA or MDMA (20 mg/kg) was not observed with MDE at the same dose.

The results indicate that MDMA has both immediate and long-term effects on serotonergic neurons in the rat brain. Acutely, MDMA produces a reversible depletion of serotonin by a mechanism which is not stereospecific. Both MDA and MDE have a similar acute effects. The more persistent effects of MDMA on serotonin concentrations are associated with a decrease in the uptake of [$^3$H]serotonin suggesting a loss in serotonin uptake sites due to the degeneration of serotonergic terminals. The latter effect does appear to be stereoselective and to be a property of the (+)-stereoisomer of MDMA. In contrast to the ability of all three analogues to cause an acute decrease in serotonin concentrations only MDA and MDMA produced the long-term depletion of serotonin and the reduction in [$^3$H]serotonin uptake at the 20 mg/kg dose administered.

169.6 METHLENEDIOXYMETHAMPHETAMINE (MDMA)-INDUCED EFFLUX OF DOPAMINE AND SEROTONIN IN RAT NUCLEUS ACCUMBENS. L.J. SPANOS AND B.K. YAMAMOTO. Department of Pharmacology, Northeastern Ohio Universities College of Medicine, Rootstown, Ohio 44272

Methylenedioxymethamphetamine (MDMA) is an amphetamine-like stimulant that has been used as a psychotherapeutic agent. It is known on the street as "Ecstasy" possessing hallucinogenic properties with potential abuse liability. Little is known about the pharmacology of MDMA and its action on brain transmitter systems. Due to its behavioral action and its proposed psychotherapeutic effect, MDMA-induced dopamine and serotonin efflux using in vivo voltammetry was studied in the nucleus accumbens, a mesolimbic structure shown to be affected by amphetamine-like compounds.

Male Sprague-Dawley rats were anesthetized with urethane and implanted with stearate-modified carbon paste electrodes into the nucleus accumbens. The coordinates were AP +0.26mm from bregma, LAT +0.12, and VERT -0.62 from dura. In vivo voltammetric recordings using linear sweep scans from -0.2 to +0.4V and semidifferential signal processing were made at five minute intervals. Peak currents were measured at +0.15 (DA) and +0.30V (5HT). MDMA (5 mg/kg) was injected after a stable baseline was established. Electrode placement was verified by expelling the carbon paste with a 5V potential. Data are expressed as percent of the baseline electrochemical signal ± SEM.

| MINUTES | DOPAMINE | SEROTONIN |
|---|---|---|
| 0 | 100.0 ± 0.1 | 100.0 ± 0.1 |
| 30 | 95.4 ± 3.8 | 102.1 ± 4.1 |
| 60 | 78.1 ± 5.1* | 96.9 ± 7.0 |
| 90 | 80.4 ± 8.8* | 89.4 ± 7.7* |
| 120 | 83.6 ± 11.7* | 88.5 ± 8.6* |
| 150 | 92.5 ± 15.0 | 86.0 ± 5.7* |

*Significantly different from baseline, $p<0.05$, N=8.

These results show that dopamine efflux is significantly reduced within 60 minutes following MDMA and returns within 93% of baseline after 2.5 hours. Serotonin release is also decreased but in contrast to dopamine, remains depressed at the end of the 2.5 hour period. These data suggest that MDMA affects mesolimbic neurotransmission by an acute effect on dopamine efflux and a possible neurotoxic action on serotonin neurons.

169.7 MDMA-INDUCED SEROTONIN DEPLETION POTENTIATES THE PSYCHOMOTOR STIMULANT EFFECTS OF MDMA ON RATS PERFORMING ON THE DIFFERENTIAL-REINFORCEMENT-OF-LOW-RATE (DRL) SCHEDULE. A. Li*, G. Marek*, G. Vosmer, L. Seiden. Department of Pharmacol. & Physiol. Sci., The University of Chicago, Chicago, IL 60637.

(+)3,4-methylenedioxymethamphetamine(MDMA), an analogue of amphetamine, was administered to rats trained on the DRL 72-sec schedule at doses of 0.5, 1,2,4, and 6 mg/kg. Acute administration of MDMA at 2,4, and 6 mg/kg increased the response rate and decreased the reinforcement rate of rats performing under a DRL 72-sec schedule as is seen for amphetamine and other psychomotor stimulants. Acute administration of MDMA also shifted the interresponse time (IRT) distribution to the left toward shorter IRT's, characteristic of other psychomotor stimulants. After repeated administration of MDMA for 4 days (6 mg/kg s.c., twice daily at 8:00 a.m. and 8:00 p.m.), MDMA was again administered at 0.5, 1,2,4, and 6 mg/kg and it was found that the acute psychomotor stimulant effects of MDMA were enhanced. The decrease in reinforcements was significantly greater in magnitude at 0.5, 1, 2, and 6 mg/kg of MDMA, and the increase in response rate was enhanced at 2,4, and 6 mg/kg of MDMA after repeated MDMA administration. Additionally, the MDMA-induced shift to shorter IRT's was clearly enhanced at the 1 and 2 mg/kg dosages after repeated administration of MDMA. Repeated administration of MDMA not only shifted the MDMA dose-response curve to the left, but also increased the maximal response to MDMA at all dosages.

Repeated administration of MDMA for 4 days resulted in generalized long-term depletion of serotonin (5-HT) throughout the brain ranging from approximately 20% in midbrain and pons-medulla to about 45% in the hippocampus and frontal cortex. This suggests that serotonergic neurons normally exert an inhibitory action upon the rate-increasing and reinforcement-decreasing effects of MDMA. Since dopamine mediates the psychomotor stimulatory effects of amphetamine on the DRL schedule, our results suggest that the potentiation of MDMA on DRL 72-s behavior following loss of 5-HT innervation resulted from the removal of an inhibitory influence of 5-HT on the dopaminergic system. This research supported by PHS MH 11191; MH-10562 RSA (L. Seiden) and NIDA DA-00250; MSTP Grant GM-07281 (Marek).

169.8 REGIONAL DIFFERENCES IN THE EFFECT OF METHYL-PHENYL-6-TETRAHYDROPYRIDINE ON TYROSINE HYDROXYLASE ACTIVITY IN MICE. I. Sziraki*, M. Juhasz*, Gy. Kobor*, A. Lajtha and Cs. Vadasz*. Neurochemistry Division, Nathan S. Kline Institute, Orangeburg, NY 10962.

Alterations in the brain of mice after MPTP administration similarly to those in primates include nigral cell loss, reduction of striatal dopamine (DA) and homovanilic acid (HVA) content, and decreased DA uptake (Heikkila et al., Science, 224, 145, 1984, Hallman et al., Eur. J. Pharm. 97, 133, 1984, Sershen et al., Eur. J. Pharm. 102, 175, 1984). MPTP exerts differential neurotoxic effect on dopaminergic pathways as it destroys DA neurons in A-8, A-9 but not in A-10 regions, induces DA depletion in nigrostriatal and mesolimbic terminal fields without pronounced effect on levels in DA and its metabolites in dopaminergic neurons in hypothalamus, retina, and frontal cortex (Heikkila et al., Hallman et al., Melamed et al., Eur. J. Pharm. 102, 175, 1984).

To further characterize the effect of MPTP administration on central dopaminergic systems of mice we studied its effect on tyrosine hydroxylase (TH) activity. Mice were injected i.p. either with MPTP (30 mg/kg) or with saline on three consecutive days. One day after the last injection their locomotor activity was measured by a video-image-analyzer system for ten 1-min observation sessions. Statistical analysis of the data indicate that there are differences in the time pattern of the locomotor activity by analyzing the consecutive discrete observation sessions between the treated and control animals, without any effect on the total distance covered by the animals or on speed of their locomotion. The animals were killed immediately after the locomotor activity test, and their brain was rapidly removed and measured by radioenzymatic method. The right striatal halves were analyzed by HPLC-EC for DA and HVA. Marked depletion in both DA (83%; $p < 0.001$) and HVA (45%; $p < 0.05$) levels and a shift in DA to HVA ratio was observed verifying the effectiveness of the treatment.

MPTP administration alters TH activity in the brain regions examined, in a selective manner. TH activity in SN-A10 region was unchanged. Significant decrements in TH activities were observed both in CS (48%; $p < 0.02$) and TO (41%; $p < 0.05$). We did not find significant correlation ($r = 0.64$, $p > 0.05$) between the decrease in TH activity in the nigrostriatal (CS) and mesolimbic (TO) terminal fields. In hypothalamus a 20% statistically non significant increase of TH activity was found. Preliminary kinetic experiments of this study suggest that MPTP treatment slightly increases the apparent $K_m$ of striatal TH for tyrosine and induces marked decrease in $V_{max}$, no change was found either in $K_m$ or $V_{max}$ of TH in SN-A10.

Regional differences in the effect of MPTP on TH activity reported here are consistent with the regional differences in DA depletion observed under similar experimental conditions.