251.7 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA) SUPPRESSES SEROTONERGIC DORSAL RAPHE NEURONAL ACTIVITY IN FREELY MOVING CATS AND IN MIDBRAIN SLICES IN VITRO. T.J. Trulson and M.E. Trulson. Dept. Anat., Coll. Med., Texas A&M Univ., College Station, TX 77843.

The synthetic amphetamine analog, 3,4-methylene-dioxymethamphetamine (MDMA) has attracted a great deal of attention recently due to its widespread abuse. This substituted phenylethylamine is structurally related to a large variety of other synthetic and naturally occurring compounds including amphetamine, mescaline, and DOM. Although a close structural analog of certain hallucinogenic drugs, MDMA is neither a true hallucinogen nor a potent stimulant. Rather, MDMA produces a unique state of enhanced emotional and sensory awareness. Since previous studies have shown that certain substituted phenylethylamines have potent actions on serotonin (5HT)-containing neurons, we investigated the effects of MDMA on the activity of 5HT-containing dorsal raphe (RD) neurons in freely moving cats and in midbrain slices in vitro. Cats were implanted for macro- and micro-electrodes as previously described (Brain Res. 163, 1979, 135). After recovery from surgery the cats were placed in recording chambers and allowed to adapt to the novel setting. They then received i.p. doses of dl-MDMA (0.25 - 5.0 mg/kg) and unit activity which was monitored for several hours. MDMA produced a dose-dependent decrease in RD unit activity from approximately 10% at the lowest dose tested to a nearly total inhibition of unit activity at the highest dose ($P<0.01$, ANOVA). An additional group of cats was pretreated with P-chlorolphenylalanine (PCPA), 150 mg/kg/day for 3 consecutive days) and then administered a high dose of MDMA (5 mg/kg). Pretreatment with PCPA greatly attenuated the suppressant action of MDMA on RD neurons. In order to ascertain whether the effects of MDMA on RD neurons are mediated by a local effect on RD cells or due to an indirect action, we examined the effects of MDMA on the activity of 5HT-containing RD neurons recorded from mouse brain slices in vitro. Brain slices were prepared using a standard procedure as previously described (Brain Res. Bull., 18, 1987, 179). MDMA was administered to the incubation bath using a nonpulsating exchange pump. MDMA produced a dose-dependent decrease in the activity of 5HT-containing RD neurons recorded in vitro. An additional group of mice was pretreated with PCPA (400 mg/kg/day for 3 consecutive days) prior to recording. The suppressant effects of the MDMA on RD unit activity was greatly attenuated by prior depletion of 5HT with PCPA. The effects of MDMA on RD neurons appear to be due to the release of 5HT onto autoreceptors since the suppression of unit activity is blocked by depletion of 5HT with PCPA. Thus, the effects of MDMA on the central 5HT system seem to be very similar to those of P-chloroamphetamine.

251.8 (±)METHYLENEDIOXYMETHAMPHETAMINE (MDMA) EXERTS TOXIC EFFECTS ON CENTRAL SEROTONERGIC NEURONS IN PRIMATES. G.A. Ricaurte*, L.S. Forno, M.A. Wilson* L.E. DeLanney, I. Irwin, M.E. Molliver and J.W. Langston (SPON: J. Hotson) Dept. of Neurology, Stanford Univ. Sch. of Med., Stanford, CA 94305; Dept. of Pathology, Veterans Adm. Med. Ctr., Palo Alto, CA 94304; Depts. of Neuroscience and Neurology, Johns Hopkins Univ. Sch. of Med., Baltimore, MD 21205; Inst. for Med. Res., San Jose, CA 95128.

MDMA is a popular recreational drug that has been proposed as a useful adjunct to psychotherapy. Recent reports indicate that MDMA is toxic to central serotonergic nerve terminals in rats. Since studies in rodents do not necessarily predict the toxicity of a drug in primates, this study was undertaken to evaluate the toxic potential of MDMA on serotonergic neurons in the brain of non-human primates.

Eleven squirrel monkeys (Saimiri sciureus) and six cynomolgus monkeys (Macaca fascicularis) were used. MDMA was administered subcutaneously twice daily at approximately 0800 and 1700 hours for 4 days. The following doses were tested: 2.5, 3.75 and 5 mg/kg. Two weeks later, monkeys were killed under deep ether anesthesia and the brain was removed for combined chemical and anatomical analysis.

MDMA produced a selective, long-lasting, dose-related depletion of serotonin and 5-hydroxyindoleacetic acid (5HIAA) in all of the brain regions analyzed (cerebral cortex, caudate nucleus, hippocampus and hypothalamus). The most severely affected area was the cerebral cortex where serotonin was reduced by 90%. Since long-term depletions of serotonin and 5HIAA appear to be reliable predictors of serotonergic nerve fiber degeneration, these results suggest that MDMA damages serotonergic fibers in the primate brain. This was confirmed morphologically by means of immunohistochemical studies which showed that MDMA produced a marked reduction in the number and density of serotonin-immunoreactive axons throughout the cerebral cortex.

The effect of MDMA on serotonergic cell bodies was also examined. MDMA produced no obvious cell loss in either the dorsal or median raphe nuclei. However, in the dorsal raphe nucleus striking cytological changes were found. Numerous shrunken nerve cells were observed which contained brownish-red spherical cytoplasmic inclusions. These inclusions often displaced the nucleus to the periphery of the cell. Whether these changes reflect direct damage to cell bodies or reaction to extensive axonal injury remains to be determined. The eventual fate of these cell bodies needs to be ascertained.

The present results indicate that central serotonergic neurons in non-human primates are very sensitive to the toxic effect of MDMA. Given the increasingly widespread use of MDMA, these findings may have important public health implications.

251.9 A COMPARISON OF THE EFFECTS OF REPEATED DOSES OF MDMA ("ESCTACY") ON BIOGENIC AMINE LEVELS IN ADULT AND NEONATE RATS. D. J. Mokler, S.E. Robinson and J.A. Rosecrans Dept. of Pharmacol. and Toxicol., Va. Commonwealth Univ., Richmond, VA 23298

(±)MDMA was administered to adult rats as a single 40 mg/kg injection or 40 mg/kg (s.c.) every other day for 4 injections. Sixteen days after the last injection rats were killed rapidly and brain area biogenic amine and metabolite levels determined using HPLC techniques. MDMA produced significant depletions of 5-HT and its metabolite, 5-HIAA, in the hippocampus (Hp) and frontal cortex (FC). 5-HT was depleted to 30% of control values in the Hp following single doses. 5-HT levels were unaffected by MDMA in the hypothalamous suggesting a differential effect on 5-HT containing neurons. DA levels were significantly increased in the hypothalamous while frontal cortex NE levels were decreased to 73% of control values following 4 doses of MDMA. These data suggest that MDMA is neurotoxic to 5-HT neurons in the rat.

In a separate study neonate rats were administered MDMA in doses 10,20 and 40 mg/kg (s.c.) on days 4,6,8 and 10. An analysis of biogenic amine turnover (metabolite/-amine ratios) indicated that DA turnover was significantly increased 18 days after the last 4 doses of either 10 or 20 mg/ks (+18-27%), while 40 mg/kg of MDMA, induced a decrease in turnover. A similar increase in 5-HT turnover was observed at lower doses (10 and 20 mg/kg); 5-HT levels were also reduced by at least 25% in all MDMA treated rats. In addition there appeared to a dose-dependent decline in 5-HIAA levels suggestive of an MDMA-neurotoxic effect similar to that observed in the adult.

EFFECTS OF MDMA ON DOPAC AND 5-HIAA LEVELS

DOSE	DOPAC (ng/g)	5-HIAA (ng/g)
0	70.6	499
10	85.6 (+21%)	399 (-21%)
20	85.5 (+21%)	361 (-28%)
40	58.9 (-17%)	324 (-36%)

(D.M.J. was supported a NRSA Fellowship; 1F32DA 05260-01A1)

251.10 THE EFFECT OF MDA AND MDMA ("ECSTACY") ISOMERS IN COMBINATION WITH PIRENPERONE ON OPERANT RESPONDING IN MICE J. A. Rosecrans and R.A. Glennon*, Depts. of Pharmacol. and Toxicol. and Med. Chem., Va. Commonwealth Univ., Richmond, VA 23298.

The optical isomers of MDA and MDMA were evaluated as to their ability to disrupt operant behavior (FR-20) in the mouse. All agonists were administered (i.p.) 15 min prior to behavioral testing; animals received daily injections of saline except on test days which were conducted every 3rd day. Results were expressed as % of vehicle rates of operant responding; vehicle response rates from the day prior to the test session served as control. These compounds as well as S(+)-amphetamine (AMPH) and DOM disrupted behavior in a dose-related manner. ED-50 values indicated the order of potency amongst isomers to be as follows: S(+)-MDA >R(-)MDA>S-(+)MDMA>R(-)MDMA. AMPH was several times more potent than these isomers and disrupted behavior at <1 mg/kg. The preadministration (PRE) of the 5-HT-2 receptor antagonist, pirenperone (PIR), significantly antagonized DOM responding (0.1 mg/kg, s.c. 60 min. prior to 3 mg/kg DOM) supporting previous data obtained in rat drug discrimination studies. In the present studies, pirenperone was observed to antagonize only R(-)-MDA in the mouse operant. The results of this study are in accord with other research conducted in these laboratories. That is, the 5-HT-2 antagonist, PIR, is able to antagonize the effects of R(-)-MDA at a dose comparable to that which blocks the disruptive effects of DOM. On the other hand, this dose of PIR was unable to antagonize the effects of S(+)-MDA or of either optical isomer of MDMA. Apparently, the disruption of behavior produced by the isomers of MDA is via a different mechanism. In addition, the disruptive effects produced by the R(-)-isomer of MDMA appear to be via a mechanism that differs from that implicated for R(-)-MDA (i.e., a 5-HT-2 mechanism).

% DISRUPTION OF OPERANT BEHAVIOR IN PRESENCE OF PIR

ED-50 DOSE	APPROX. (MG/KG)	SALINE PRE	PIR PRE
DOM	3.0	38.6	90.8*
(+)MDA	2.5	53.2	58.2
(-)MDA	3.0	53.0	82.1*
(+)MDMA	3.1	57.9	57.8
(-)MDMA	11.2	48.0	49.5

(This was supported by a NIDA grant, DA-01642)