# Neurochemical Mechanisms Involved in Behavioral Effects of Amphetamines and Related Designer Drugs

*Lisa H. Gold, Mark A. Geyer, and George F. Koob*

## INTRODUCTION

The psychoactive drug 3,4-methylenedioxymethamphetamine (MDMA) has become increasingly popular as an abused substance (Beck and Morgan 1986; Peroutka 1987). Biochemically, MDMA is thought to release serotonin and to a lesser extent dopamine (Johnson et al. 1986; Nichols et al. 1982; Schmidt et al. 1987), while structurally, MDMA resembles both mescaline and amphetamine (Nichols et al. 1986; Shulgin 1978). MDMA is the N-methylated form of 3.4-methylenedioxyamphetamine (MDA), another substituted phenylethylamine with psychotropic properties that may have contributed to its popular name, "the love drug." MDA is considered to be frankly hallucinogenic and has been found to be highly toxic to serotonergic neurons (Ricaurte et al. 1985). Recently, long-term depletions of serotonergic markers have also been observed following single and multiple injections of MDMA in experimental animals, indicating a neurotoxic potential similar to that associated with MDA (Mokler et al. 1987; Schmidt 1987; Stone et al. 1986).

Interestingly, some psychotherapists have been using MDMA to enhance the psychotherapeutic process and to promote easy emotional communication in their patients (Grinspoon and Bakalar 1986). MDMA is characterized as evoking an altered state of consciousness with emotional and sensual overtones (Shulgin and Nichols 1978). This state is described as a pleasant state of introspection, a highly controllable experience that invites intensification of feelings (Grinspoon and Bakalar 1986) and greatly facilitates interpersonal communication (Nichols et al. 1986). Encouraged by these properties, the advocates of MDMA-assisted therapy argue that MDMA is a useful therapeutic tool. Unfortunately, sympathomimetic side effects are occasionally mentioned (Barnes 1988; Grinspoon and Bakalar 1986; Shulgin and Nichols 1978), and concern over a potential to induce arrhythmias in individuals with underlying cardiac disease has been expressed (Dowling et al. 1987).

To better understand the behavioral effects of MDMA, this drug and various analogs have been tested in several behavioral procedures in animals. Significant abuse potential for MDMA was demonstrated by animal self-administration of MDMA (Beardsley et al. 1986, Lamb and Griffiths 1987) and a lowering of self-stimulation thresholds by MDMA (Hubner et al. 1988). MDMA has also been reported to generalize to amphetamine in drug discrimination studies, indicating that MDMA may have subjective effects similar to those of amphetamine (Evans and Johanson 1986; Kamien et al. 1986; Oberlender and Nichols 1988). A more complex mechanism of action has been suggested by one report of generalization to the serotonin agonist fenfluramine (Schechter 1986) and another report that described drug-like responding following MDMA in rats trained on mescaline (Callahan and Appel 1987). Indeed, several authors have concluded that MDMA may produce discriminative stimulus effects that are different from both stimulants and hallucinogens (Glennon et al. 1988; Oberlender and Nichols 1988).

## LOCOMOTOR ACTIVITY AND PSYCHOSTIMULANT EFFECTS

Locomotor activity has historically been used as an index of psychostimulant effects. Simple assessment of amount of locomotor activity can provide the basis for anatomical as well as pharmacological analysis of the neural substrates that mediate the behavioral expression of stimulant action. More sophisticated behavioral measurement systems can record multiple measures of activity and describe spatial and temporal patterning of locomotion. In such systems, qualitative aspects of behavioral activation can be evaluated by examining the entire activity profile. A comparison of the effects of novel drugs with those produced by well-characterized substances may lead to a better understanding of their mechanisms of action and subjective properties.

### Neural Substrates of Psychostimulant Locomotion

The neural substrates of locomotor activation produced by psychomotor stimulants have been linked for some time to dopamine function in the nucleus accumbens. An early finding reported that direct injection of dopamine into the nucleus accumbens produced enhanced locomotor activity in rats (Pijnenburg and Van Rossum 1973), and the unconditioned motor activation produced by amphetamine was shown to be blocked by dopamine receptor antagonists (Pijnenburg et al. 1975). Destruction of dopamine terminals within the nucleus accumbens with 6-hydroxydopamine (6-OHDA) was found to attenuate the locomotion produced by indirect sympathomimetics (Joyce and Koob 1981; Kelly et al. 1975; Kelly and Iversen 1976) but not to disrupt the locomotor-activating properties of caffeine, scopolamine (Joyce and Koob 1981) (figure 1). corticotropin-releasing factor (CRF) (Swerdlow and Koob 1985). or heroin (Vaccarino et al. 1986) (figure 2) in rats. Thus, the locomotor stimulation produced by psychostimulant drugs

has been hypothesized to result from release of dopamine from the mesolimbic dopamine terminals in the region of the nucleus accumbens, but other drugs with locomotor-activating properties may interact with other parts of the limbic-nucleus accumbens-ventral pallidal circuitry known to be important for psychostimulant activation (Swerdlow et al. 1984; Swerdlow et al. 1986).

**Neural Substrates of Psychostimulant Reinforcement**

The locomotor-activating properties of psychomotor stimulants have been hypothesized to be one aspect of their reinforcing properties (Mucha

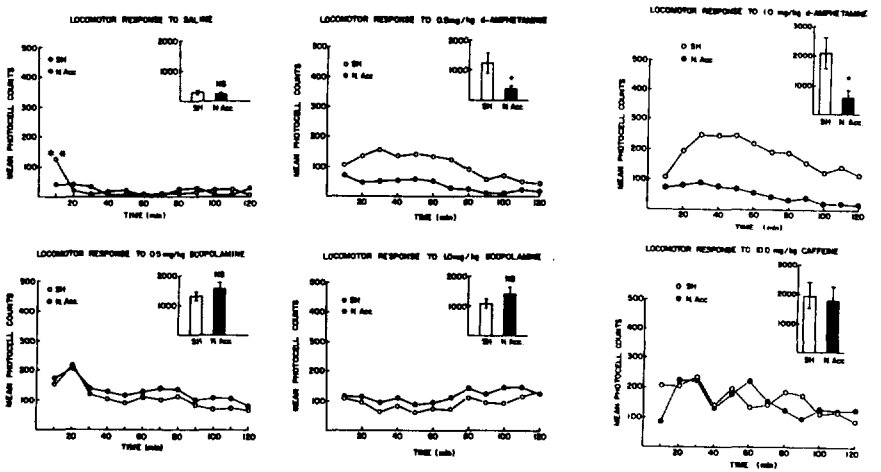

**FIGURE 1.** *Effects of amphetamine, scopolamine, caffeine, and saline on locomotor activity in rats with 6-OHDA lesions of the nucleus accumbens or sham-operated controls (n=8 rats/group)*

*Refers to a signficant group effect.

**Refers to a significant difference between the groups at 10 minutes postinjection, simple main effects.

KEY: Values in upper right corner of each panel represent mean ± SEM for the total activity over the 2-hour drug test.

SOURCE: Joyce and Koob, 1981, Copyright 1981, Springer-Verlag.

et al. 1982; Spyraki et al. 1982; Swerdlow and Koob 1984). Animals will learn to prefer an environment previously associated with drugs that produce hyperactivity, and pharmacological or surgical manipulations that block the locomotor-activating properties of psychomotor stimulants block this place preference. The nucleus accumbens, which has been demonstrated to be

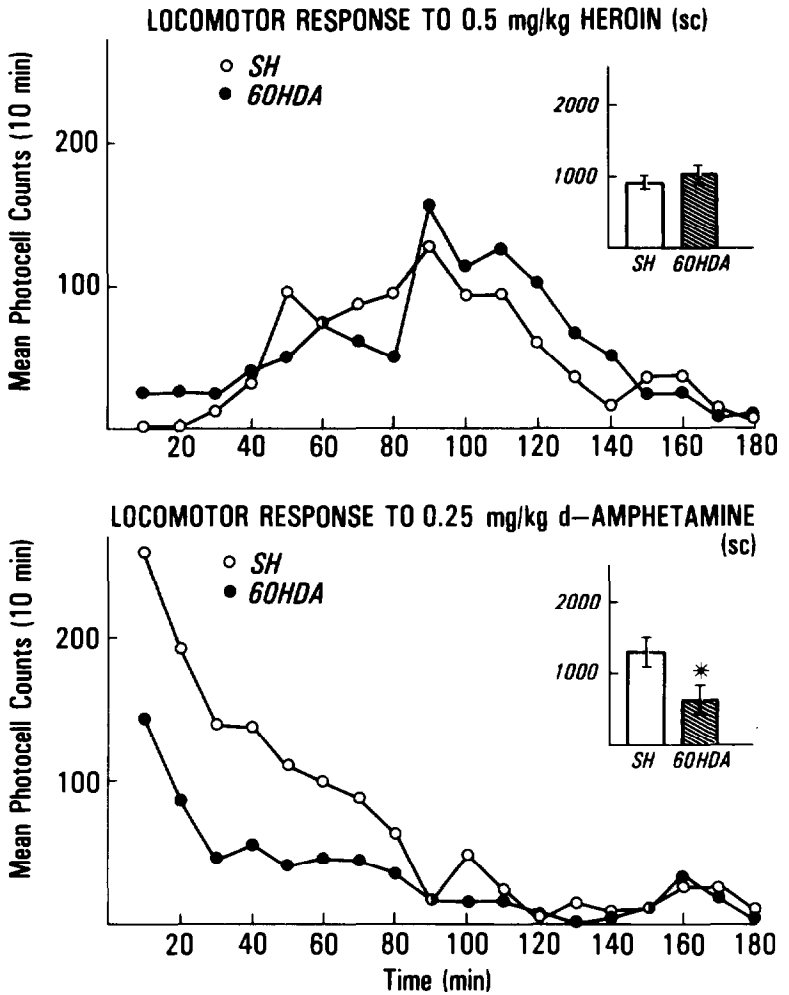


**FIGURE 2.** *Effects of 6-OHDA lesions of the nucleus accumbens on the locomotor response ajier SC injection of heroin (0.5 mg/kg) or amphetamine (0.25 mg/kg)*

*Significantly different from sham group. $p<0.05$.

NOTE: Rats were habituated to the photocell cages for 90 minutes. after which they were injected. Inserts show the mean ± SEM total counts for 180 minutes for eight rats in the sham and lesion group, respectively.

SOURCE: Vaccarino et al. 1986, Copyright 1986, Pergamon Press.

involved in a variety of the behavioral actions of stimulants and opiates, may act as a bridge between the limbic system and the extrapyramidal motor system, integrating limbic influences and motor activity (Mogenson and Nielson 1984; Swerdlow et al. 1986).

The reinforcing properties of psychomotor stimulants have also been linked to the activation of central dopamine neurons and their postsynaptic receptors. When the synthesis of catecholamines is inhibited by administering alpha-methyl-para-tyrosine, an attenuation of the subjective effects of euphoria associated with psychomotor stimulants occurs in man (Jonsson et al. 1971), and a blockade of the reinforcing effects of methamphetamine occurs in animals (Pickens et al. 1968). Furthermore, low doses of dopamine antagonists will increase response rates for intravenous injections of *d*-amphetamine (Risner and Jones 1976; Yokel and Wise 1975; Yokel and Wise 1976).

Noradrenergic antagonists such as phenoxybenzamine, phentolamine, and propranolol had no effect on stimulant (amphetamine) self-administration (DeWit and Wise 1977; Risner and Jones 1976; Yokel and Wise 1976). Wise and coworkers hypothesized that a partial blockade of dopamine receptors produced a partial blockade of the reinforcing effects of *d*-amphetamine. Thus, animals were thought to compensate for decreases in the magnitude of the reinforcer by increasing their self-administration behavior. Similar results have been observed with alpha-flupenthixol (Ettenberg et al. 1982) and many other dopamine receptor antagonists, including haloperidol, chlorpromazine, metoclopramide, thioridazine, and sulpiride (Roberts and Vickers 1984). Recently, the selective D-1 antagonist SCH 23390 was shown to increase cocaine self-administration at doses that did not impair motor function (Koob et al. 1987a), whereas spiperone, a D-2 selective compound, produced only small increases in responding at doses close to those that produced motor dysfunction. These results suggest that dopamine receptor blockade, particularly D-l receptor blockade, may be involved in the reinforcing effects of psychomotor stimulants in rats. It should be noted, however, that the SCH 23390 compound failed to produce this action consistently when administered intravenously to rhesus monkeys self-administering cocaine (Woolverton 1986).

The role of dopamine in the reinforcing properties of psychomotor stimulants was extended by the observations that 6-OHDA lesions of the nucleus accumbens produce extinction-like responding and a significant and long-lasting reduction in self-administration of cocaine and *d*-amphetamine over days (Lyness et al. 1979; Roberts et al. 1977). These effects were thought to be due largely to the depletion of dopamine, since rats pretreated with desmethylimipramine before the nucleus accumbens lesion (to protect norepinephrine neurons from destruction with the 6-OHDA) showed an identical extinction-like response (Roberts et al. 1980). Similar results were obtained following 6-OHDA lesions of the ventral tegmental area (Roberts and Koob

1982). Subsequent studies have shown that 6-OHDA lesions of the frontal cortex (Martin-Iverson et al. 1986) and corpus striatum (Koob et al. 1987b) do not significantly alter cocaine self-administration. Interestingly, lesions of specific subsets of the dopamine forebrain projections have been associated with facilitated acquisition of amphetamine self-administration (Deminiere et al. 1984; Deminiere et al. 1988), suggesting that some specific neuropathology within the dopamine system could sensitize individuals to the reinforcing actions of psychostimulants.

These results, showing facilitated acquisition of psychostimulant self-administration with lesions of subsets of the dopamine projections, emphasize the need for other measures of reinforcement besides a continuous reinforcement schedule. To this end, rats that had been trained to self-administer cocaine intravenously were subjected to a progressive-ratio procedure following 6-OHDA lesion to the nucleus accumbens or corpus striatum. The rats with a lesion of the nucleus accumbens showed a significant decrease in the highest ratio for which they would respond to obtain cocaine (figure 3) (Koob et al. 1987b). Complementary results have been obtained using a similar progressive-ratio procedure in which rats with 6-OHDA nucleus accumbens lesions increased significantly the highest ratios for which they would self-administer apomorphine (Roberts and Vickers 1988). This motivational probe thus avoids many of the problems associated with measuring local rates of responding. For example, the rats with 6-OHDA lesions showed a decrease in cocaine self-administration while on a continuous reinforcement schedule that superficially could be interpreted as either a decrease or increase in the reinforcing value of cocaine. The results in the progressive-ratio test suggest that this decrease in local rates of responding, previously observed with lesions to the region of the nucleus accumbens, does in fact represent a motivational deficit.

Both amphetamine and cocaine have also been reported to support intracranial self-administration in the mesolimbic/mesocortical dopaminergic system. Rats will self-administer cocaine into the medial prefrontal cortex (Goeders and Smith 1983). while amphetamine is self-administered into the orbitofrontal cortex of rhesus monkeys (Phillips and Rolls 1981) and the nucleus accumbens of rats (Hoebel et al. 1983; Monaco et al. 1981). These data indicate that the mesolimbic/mesocortical dopaminergic system is involved in the initiation of stimulant reinforcement processes, and this work suggests that the region of the nucleus accumbens, more specifically the mesolimbic dopamine system, may be an important substrate for reinforcing properties of several psychomotor stimulant drugs.

**Behavioral Profile of MDMA**

Both quantitative and qualitative aspects of the behavioral profile of motor activation produced by MDMA and methylenedioxyethylamphctamine

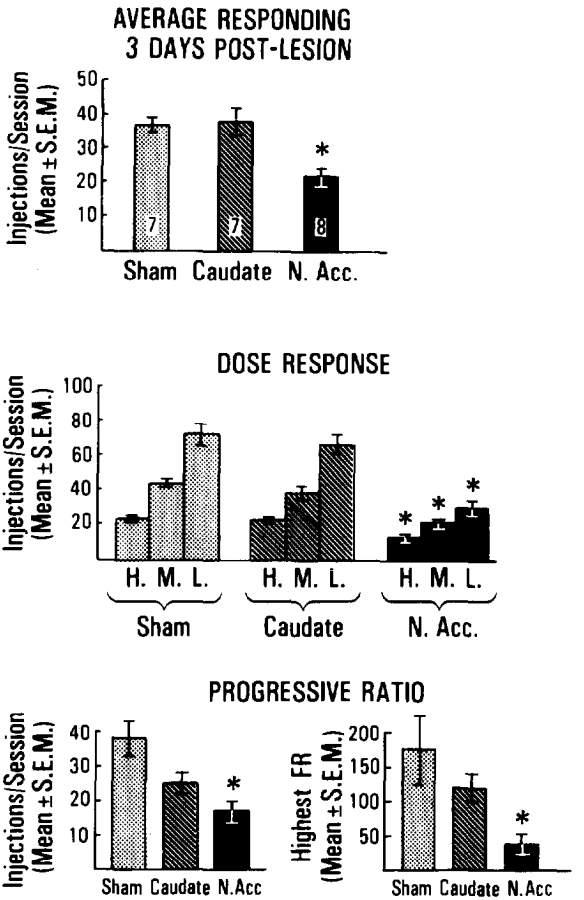


**FIGURE 3.** *Effects of 6-OHDA lesions to the nucleus accwnbens and corpus striatum on responding for rats self-administering cocaine*

*Significantly different from sham group. $p<0.05$ Newman-Keuls test.

KEY: H.=2 times the normal 0.75 mg/kg/injection dose; M=middle dose range, 0.75 mg/kg/injection; L=1/2 the 0.75 mg/kg/injection dose.

NOTE: Top panel shows continuous reinforcement data averaged over the first 3 days postlesion (means ± SEM). Sham, vehicle-injected (0.1 mg/mL ascorbic acid in saline) controls. Caudate, rats receiving 8 µg in 2 µL of 6-OHDA injected into the corpus striatum. N. Acc rats receiving 8 µg in 2 µL of 6-OHDA injected into the nucleus accumbens. Middle panel shows the dose-effect functions for each group. Bottom panel shows the mean rewards and mean highest ratio obtained by each group on the progressive ratio probe

SOURCE: Koob et al. 1987b. Copyright 1987, Raven Press.

(MDE) have been characterized and, the effects of these drugs compared with those of classic stimulants and hallucinogens (Gold et al. 1988). Exploratory activity was monitored in eight separate behavioral pattern monitor (BPM) chambers, each consisting of a 30.5 by 61 cm black Plexiglas holeboard with three floor holes, seven wall holes, and a steel touchplate 15 cm above the floor that detected rearings against the wall (figure 4) (Geyer et al. 1986). The frequency of photobeam breaks was used as a general measure of motor activity, and the number and duration of holepokes and rearings were cumulated.

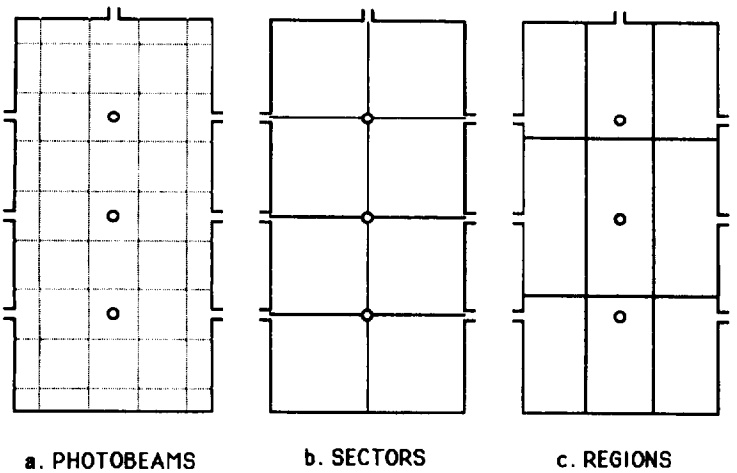


**FIGURE 4.** *Diagrammatic representation of the behavioral pattern monitor chamber. The positions of the seven wall and three floor holes are shown in each diagram*

KEY:
a. Infrared photobems are arranged in a Cartesian coordinate system on 7.6-cm centers and are sampled five times per second
b. Sectors are equal 15-cm squares and are used to define crossovers, a measure of horizontal locomotion.
c. Regions are unequal in size and are used primarily to define entries into the center region and for the CV9 analysis of spatial patterns of locomotion.

SOURCE: Geyer et al. 1987. Copyright 1981. Pergamon Press.

MDMA significantly altered the behavioral activity profile of rats. Figure 5A illustrates the timecourse of the effects of MDMA on crossovers resolved into 30-minute blocks across the 2-hour test session. Doses of 1.25, 2.5, 5.0, and 10.0 mg/kg produced significant increases in crossovers, which remained elevated at the end of the session at the two highest doses studied. Interestingly, during the first 10 minutes in the chamber (10 to 20 minutes postinjection), doses of 2.5 to 10 mg/kg did not significantly increase crossovers.

Concomitant with this total increase in horizontal locomotion, MDMA (1.25 to 10.0 mg/kg) caused alterations in measures of investigatory behavior. MDMA had a profound effect on the distribution of investigatory holepokes over time. Whereas the control animals exhibited a decrease in the number of investigatory holepokes as they habituated to the chambers during the session, the MDMA-treated rats demonstrated an initial decrease in the number of holepokes, followed by the tendency to increase investigatory holepoking over time (figure 5B). Similarly, MDMA (1.25 to 10.0 mg/kg) dramatically reduced the amount of rearing behavior measured. The amount and duration of this suppression of rearing was related to the dose of MDMA studied (figure 5C). Rearing in rats heated with MDMA was markedly reduced compared to control rats during the first 30 minutes.

More descriptive measures of the animals' behavior were provided by cumulating entries into and time spent in each of nine unequally sized regions, which included the center and the four comer regions (Geyer et al. 1986). Accompanying these changes in the amount of rearing and investigatory holepoking was an observable avoidance of the center of the experimental chamber. Thus, a significant decrease in average duration of center entries for the first 30 minutes was obtained following MDMA doses of 1.25 to 10.0 mg/kg.

MDE, the N-ethyl derivative of MDA, produced a behavioral profile similar to that described for MDMA. MDE increased the number of crossovers measured during a 1-hour experimental session (figure 5A). A transient decrease in the number of crossovers during the first 10 minutes in the chambers (0:549.1, 1.0:645.7, 3.0:313.1, 10.0:284.4) was noted for MDE at doses of 3.0 and 10.0 mg/kg. As with MDMA, the two highest doses of MDE tested (3.0 and 10.0 mg/kg) significantly decreased the total number of holepokes for the first 30 minutes. Rearing was also suppressed by these doses of MDE over a similar timecourse (figures 5B and 5C). At the 10 mg/kg dose of MDE, avoidance of the center was again observed as a significant decrease in the average duration of center entries.

For spatial pattern analyses, the data were reduced to sequences of X,Y positions as described elsewhere (Geyer et al. 1986). These sequences were used to produce video displays of the animal's position, rearings, and holepokes, which could be viewed from 1 to 20 times teal-time speed. The transition frequency between any of five areas (two ends, center, and two long wall areas) was calculated, as was the coefficient of variation (CV) for the relative transition frequencies (Geyer 1982). A related but slightly different procedure evaluated the sequence of position changes by calculating the number of occurrences of each of the 40 transitions among any of 9 specified regions. As an animal preferentially repeats certain transitions, the CV increases, while a more random pattern produces a lower CV. T'he CV thus reflects the extent to which the animal establishes a preferred pattern of locomotor activity over time.

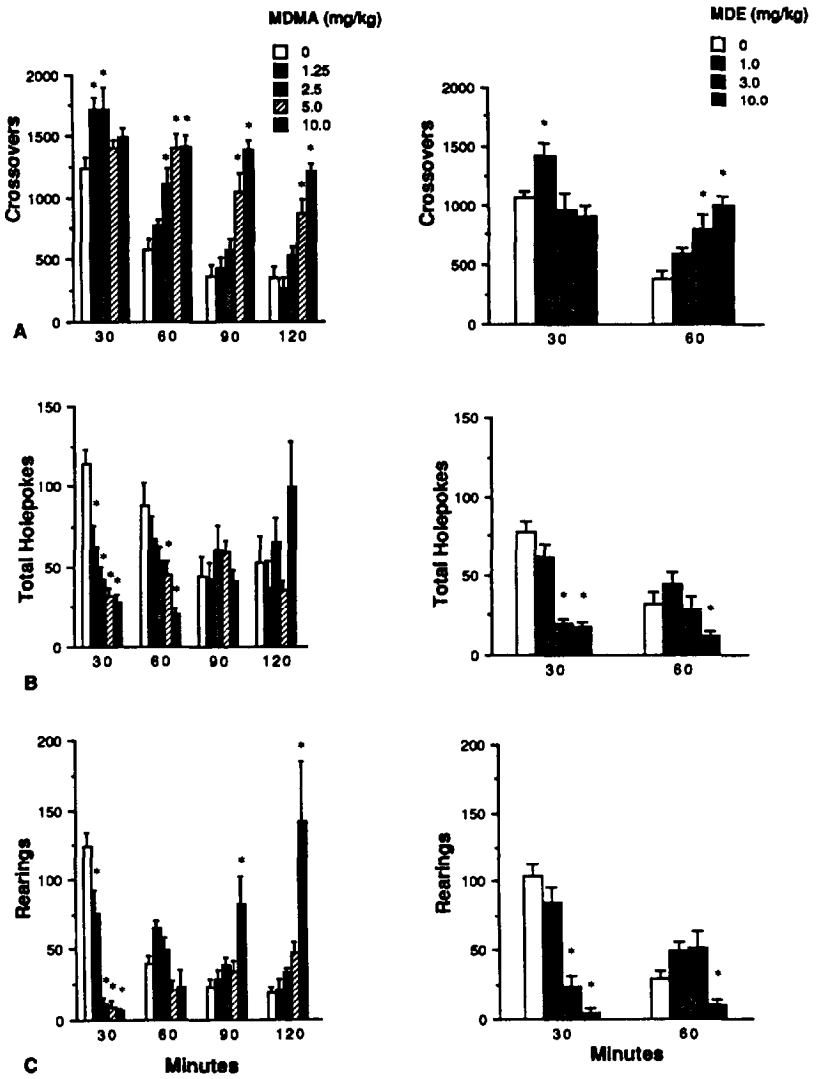


**FIGURE 5.** *Timecourse effects of MDMA (n=7 to 8 rats/group) and MDE (n=9 to 12 rats/group) on A (crossovers), B (total holepokes), and C (rearings) per 30 minutes in the BPM*

$p<0.05$.

NOTE: Animals were injected 10 minutes before being placed in the chambers. Effects of selected doses are shown as group means ±SEM.

Both MDMA and MDE caused some obvious qualitative changes in the locomotor patterns of rats. At moderate to high doses of MDMA, a definite avoidance of the center of the experimental chamber was frequently seen, and circling around the perimeter was the dominant behavior. This thigmotaxis is similar to that previously observed with apomorphine or scopolamine (Geyer et al. 1986). Although most rats had a predominant direction of rotation, occasionally the rats reversed direction for one or more revolutions. The impression of a disruption in locomotor patterns described above was corroborated by a significant change in the spatial CV measure. Both MDMA and MDE increased the spatial CV, which suggests a more perseverative nature of locomotor patterns (table 1). In contrast, doses of amphetamine (AMPH) that produced similar increases of horizontal locomotion tended to induce highly varied patterns of directional changes, which were reflected in a reduced spatial CV (Geyer et al. 1986).

**Neural Substrates for the Psychostimulant Actions of MDMA**

The neurochemical mechanisms for the stimulant properties of MDMA were examined in a photocell cage apparatus following pharmacological and neurochemical manipulations. Locomotor activity was measured in a bank of 16 wire cages 20 cm by 25 cm by 36 cm, each cage with two horizontal infrared beams across the long axis 2 cm above the floor. Total photocell beam interruptions and crossovers were recorded by a computer every 10 minutes. Before the drug series, each rat was habituated to the photocell cages overnight, and, prior to drug injection, the rats were habituated again to the photocell cages for at least 90 minutes.

A role for serotonin in the stimulant actions of MDMA was tested by examining the effects in rats of the serotonin antagonist methysergide on MDMA activation (Gold and Koob 1988). The locomotor-activating properties of MDMA. amphetamine, and methysergide are seen in figure 6. Drug doses for amphetamine and MDMA were selected to produce similar increases in activity, although MDMA appears to have a longer duration of action (Gold et al. 1988). Once the rats were habituated to the photocell apparatus, saline injection produced only transient arousal (lasting less than 20 minutes) followed by relative inactivity (figure 6C). MDMA at 10 mg/kg produced an increase in beam interruptions that lasted for at least 2 hours (figure 6A). Methysergide (2.5, 5, 10 mg/kg) significantly potentiated the locomotor hyperactivity produced by MDMA (10 mg/kg) when compared to MDMA injection alone (figure 6A). This enhancement of MDMA's locomotor effects was evident within the first 10 minutes and lasted for the full 2-hour session. In contrast, methysergide only slightly and nonsignificantly increased the locomotor hyperactivity produced by 0.5 mg/kg of amphetamine (figure 6B). Methysergide alone at these doses had no effect on locomotor activity (figure 6C).

**TABLE 1.** *Effects of MDMA, MDE, and AMPH on spatial CV*

| Dose (mg/kg) | CV5 | CV9 |
|---|---|---|
| 0 | .485 ± .02 | |
| MDMA 1.25 | .709 ± .1 | |
| MDMA 2.5 | .730 ± .17 | |
| MDMA 5.0 | 1.063 ± .21* | |
| MDMA 10.0 | .995 ± .13* | |
| 0 | | 1.723 ± .02 |
| MDE 1.0 | | 1.737 ± .05 |
| MDE 3.0 | | 2.209 ± .18* |
| MDE 10.0 | | 2.007 ± .11 |
| 0 | .522 ± .04 | |
| AMPH 0.25 | .379 ± .06* | |
| AMPH 0.5 | .376 ± .03* | |
| AMPH 1.0 | .373 ± .04* | |
| AMPH 2.0 | .506 ± .03 | |

*$p<0.05$, Dunnett's *t*-test

NOTE: Group means ± SEM are shown: an increase in spatial CV indicates a more repetitive pattern of movements in the BPM: a decrease indicates a more highly varied pattern.

The role of the mesolimbic dopamine system, which is known to be critical for amphetamine-stimulated locomotion, was investigated in MDMA-treated rats with 6-OHDA lesions of the nucleus accumbens (Gold et al., in press). Rats received bilateral injections of 6-OHDA (8 µg/2 µl, expressed as the free base) dissolved in saline containing ascorbic acid (0.1 mg/mL; lesion group) or injections of saline-ascorbic acid vehicle alone (sham group). Approximately 9 days following surgery, rats were injected with saline, and locomotor activity was measured for 120 minutes. In one study, rats (sham: n=8, lesion: n=8) were injected on the following day with 5 mg/kg MDMA, 3 days later with 0.5 mg/kg AMPH, and again with saline. Locomotor hyperactivity produced by MDMA was attenuated in the group with 6-OHDA lesions (figure 7A). When the rats were injected with 0.5 mg/kg AMPH, the sham-operated group showed a large increase in locomotor activity; this effect was significantly reduced in the rats with lesions.

Moreover, the hyperactivity seen in the sham rats was somewhat greater than that usually observed following this dose of AMPH, suggesting a cross-sensitization between MDMA and AMPH. The day after the AMPH injections, all the rats were reinjected with saline. At this time there was no significant difference between the sham- and lesion-operated rats.

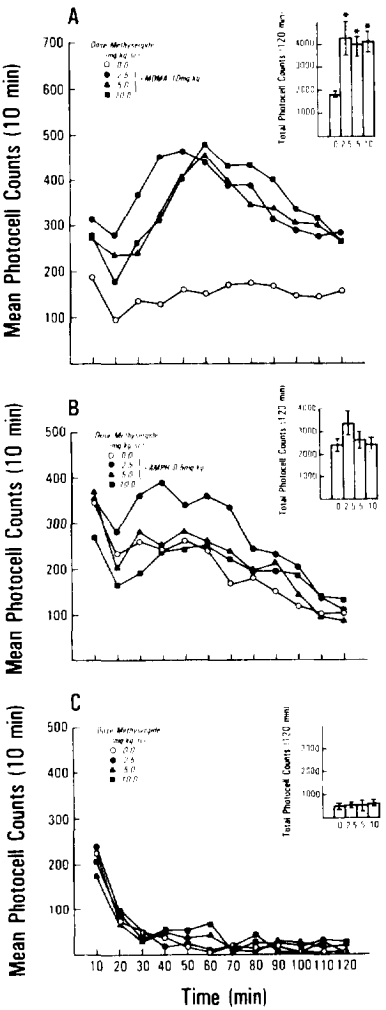


**FIGURE 6.** *Locomotor activity during 120-minute test session in the photocell cage apparatus*

*Significantly different from 0 methysergide dose, Newman-Keuls test following significant ANOVA main effect

KEY: Values in the upper right corner of each panel represent mean ±SEM for the total activity over the 2-hour drug test.

NOTE: Following a habituation period, rats were injected with methysergide (0-10 mg/kg, SC; C) and 2 minutes latex by (A) MDMA (10 mg/kg. SC). (B) amphetamine (0.5 mg/kg. SC).

SOURCE: Gold and Koob 1988, Copyright 1986, Pergamon Press.

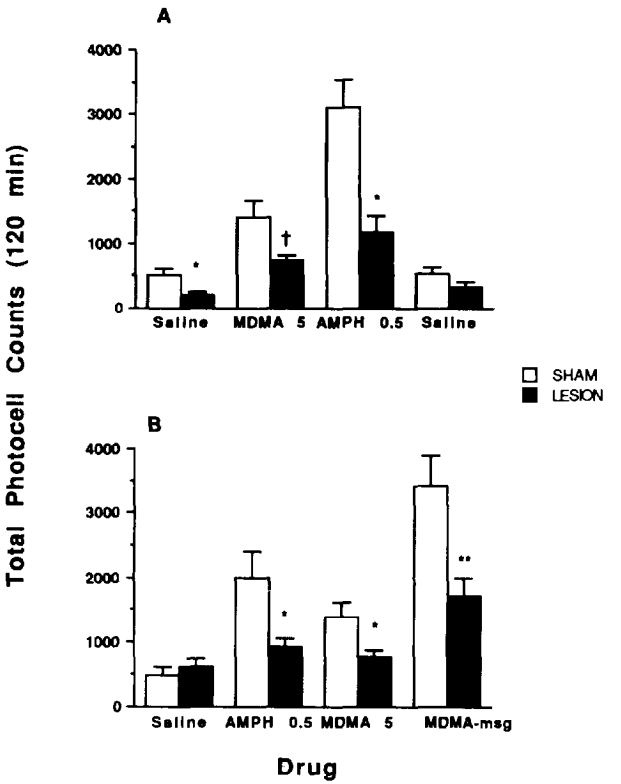


**FIGURE 7.** *Effects of 5 mg/kg MDMA, 0.5 mg/kg AMPH, or 5 mg/kg MDMA plus 25 mg/kg methysergide on locomotor activity in rats with 6-OHDA or sham lesions of the nucleus accumbens*

*p<0.05.

**Significant interaction.

†p.055.

KEY: Total photobeam interruptions, measured in photocell cage apparatus, for 120-minute test session, shown as group means ± SEM.

NOTE: A. The significant difference between sham-operated rats and those with 6-OHDA lesions following saline injection was attributed to a reduced response to the injection procedure in the lesion-operated group. Note that means for the two groups were almost identical (sham=576±84, lesion=524±55) for the 90-minute habituation period preceding saline injection. Sham group, n=8; lesion group, n=8. B. Sham group. n=8; lesion group, n=6.

SOURCE: Redrawn from Gold et al., in press.

In an additional study, following recovery and saline injection, rats (sham: n=8, lesion: n=8) were injected with 0.5 mg/kg AMPH on day 9 or 10 and 5 mg/kg MDMA 3 days later. On day 16 or 17 these rats received two injections: a serotonin antagonist, 2.5 mg/kg methysergide; and 5 mg/kg MDMA. Rats were injected with 0.5 mg/kg AMPH on the next day and, as in previous experiments, the locomotor hyperactivity produced by AMPH was attenuated in the group with 6-OHDA lesions (figure 7B). The mean ± SEMs per 120 minutes for the sham and lesion groups were 1,995.9±389.3 and 906±132, respectively. In the first experiment described above, the means for these groups were 3.111.9±421.8 and 1,176.5±248.1, respectively. When the rats were injected with 5 mg/kg MDMA 3 days later, the sham-operated group showed a large increase in locomotor activity; this effect was significantly reduced in the rats with lesions. The mean ± SEMs for the sham and lesion groups were 1,368±249.5 and 754.1±107.4, respectively. These values were not different from those described in the first experiment (sham: 1,401.3±257.8, lesion: 745.2±81.7). Therefore, a cross-sensitization from AMPH to MDMA was not evident. On the next day, locomotor activity was measured following injections of a serotonin antagonist and MDMA. Here, methysergide potentiated the effects of MDMA. Both the effects of surgery and the influence of methysergide were observed. However, a log transformation of the data eliminated the significant interaction between the two, which suggests that the interaction effect was due to scaling differences. Thus, the response of both the sham rats and the rats with lesions was increased by the serotonin antagonist.

Biochemical analyses of 6-OHDA-injected animals revealed a 93 percent depletion of dopamine. The tissue was assayed using electrochemical detection following separation by high-pressure liquid chromatography (Felice et al. 1978). recorded as ng/mg protein in the nucleus accumbens and compared to control rats with sham lesions (sham=65.5±4.4, lesion=4.9±1.5; t(39)=23.4). A lesion was defined as complete if 75 percent or more of the dopamine was determined to be depleted from the nucleus accumbens compared to mean sham group values.

## SUMMARY

The motor activation produced by psychomotor stimulants has been long associated with the midbrain dopamine systems. While focused stereotyped behavior produced by high doses of indirect sympathomimetics is blocked by removal of dopamine terminals in the corpus striatum (Creese and Iversen 1975), the locomotor activation produced by low doses of indirect sympathomimetics is blocked by removal of dopamine terminals in the region of the nucleus accumbens (Kelly et al. 1975). This dopaminergic substrate for psychostimulant effects appears selective for the indirect sympathomimetics in that dopamine lesions to the region of the nucleus

accumbens do not block caffeine, scopolamine, heroin, or CSF-induced locomotor activation (Swerdlow and Koob 1985; Vaccarino et al. 1986).

The neurochemical sites for psychomotor stimulant reward are likely to be the presynaptic dopamine terminals located in the region of the nucleus accumbens, frontal cortex, and other forebrain structures that originate in the ventral tegmental area. Note, however, that intracranial self-administration of cocaine is elicited from the frontal cortex, but not from the nucleus accumbens (Goeders and Smith 1983). Thus, concomitant activation of structures other than the nucleus accumbens may be an important part of the circuitry involved in initiation of cocaine intravenous self-administration, as has been hypothesized for the opiates (Smith and Lane 1983; Smith et al. 1982).

In addition, these neuropharmacological studies provide evidence to show that, in the rat, the neural/neurochemical substrates for processing the reinforcing and stimulant properties of psychomotor stimulants may be similar, if not identical. Parallel manipulations using dopamine receptor antagonists and 6-OHDA lesions produce parallel results. How far this parallelism continues in further processing is under current investigation; however, such an overlap brings additional impetus to earlier hypotheses relating reinforcement and motor function (Glickman and Schiff 1967).

The motor activation produced by MDMA and MDE has similarities to classic psychostimulants, but also some important differences. In the BPM system, the stimulant-like properties of these drugs were reflected in significant increases in horizontal locomotor activity measured across a wide dose range. Interestingly, medium to high doses of MDMA or MDE produced a transient decrease in horizontal locomotion for the first 10 minutes, followed by a sustained increase. The increase in holepokes and rearings that typically accompanies the increase in ambulation seen with amphetamine itself or other indirect sympathomimetics (Geyer et al. 1986) was not observed with MDMA or MDE. Instead, initial decreases in holepokes and rearings and a tendency to avoid the center were evident, a behavioral profile that is characteristic of hallucinogenic indoleamine or phenylethylamine derivatives (Adams and Geyer 1985a; Adams and Geyer 1985b; Geyer et al. 1979).

MDMA and MDE also produced locomotor patterns that differed significantly from other stimulants. Previous studies in rats have demonstrated that amphetamine-induced hyperactivity involves complex patterns of widely distributed locomotion with frequent directional changes (Geyer et al. 1986; Geyer et al. 1987). In contrast, similar levels of behavioral activation produced by scopolamine or apomorphine are associated with relatively smooth locomotor paths, in which the same movement patterns are frequently repeated. Other stimulants, such as caffeine or nicotine, increase the amount of locomotor activity without significantly altering its pattern (Geyer

et al. 1986). With LSD and other hallucinogens, the behavioral profile is characterized by an increase in the diversity of locomotor patterns and a concomitant suppression of the exploration of novel and open areas (Adams and Geyer 1985a). When evaluated on this basis, MDMA and MDE are similar to hallucinogens in producing an avoidance of the center. This effect is particularly notable in light of the simultaneous increases in the total amount of locomotor activity. Unlike LSD, however, MDMA produced a scopolamine- or apomorphine-like increase in perseverative and thigmotactic patterns of locomotion, reflected by increases in the spatial CV measures. The MDMA profile was also similar to that of apomorphine insofar as both drugs reduced holepoking and rearing, behaviors that are increased by scopolamine. However, relative to apomorphine, the MDMA-induced rotational patterns were less strictly unidirectional, and the reductions in investigatory responses were less complete. Rather, most animals injected with MDMA changed directions and exhibited investigatory responses at least occasionally, effects similar to those observed following various doses of scopolamine (Geyer et al. 1986). Hence, the behavioral profile engendered by MDMA and MDE appears to be unique among the various drugs that have been so characterized to date.

Investigation of the neurochemical substrates for the psychostimulant effects of MDMA suggests a role for the mesolimbic dopamine system. Destruction of dopamine terminal fields in the nucleus accumbens significantly attenuated the locomotor activation produced by MDMA. A similar blockade of amphetamine-induced locomotor hyperactivity is known and was observed following amphetamine injection in these same rats. Such results support the hypothesis that at least one component of MDMA-induced hyperactivity is dopamine mediated and suggest that mesolimbic dopamine specifically is the critical substrate. In this way, MDMA resembles other classical psychostimulants like amphetamine and cocaine. Interestingly, evidence for functional cross-sensitization was suggested in the study in which an injection of amphetamine followed MDMA injection.

The stimulant properties of MDMA were enhanced by the presence of a serotonin antagonist, methysergide. Thus, following serotonin-receptor blockade, profound locomotor hyperactivity was observed. This result can be viewed as a disinhibition of the dopamine neurons from serotonin modulation. These data are consistent with the hypothesis that MDMA acts predominantly as a serotonin agonist with weak dopamine activity. In this study, methysergide did not potentiate the effect of amphetamine. However, Hollister et al. (1976) reported that methysergide potentiated locomotion produced by 2 mg/kg amphetamine intraperitoneally. In fact, an enhancement of an amphetamine response after prior exposure to MDMA has also been observed. It is possible that previous exposure to MDMA may have resulted in neurotoxic damage to some serotonin neurons. Depletions of serotonin and its metabolites have been repotted following single injections of MDMA (Mokler et al. 1987; Schmidt 1987; Stone

et al. 1986). A decrease in serotonergic tone would also result in a disinhibition of dopamine neurons and may explain the enhanced amphetamine response. Indeed, evidence for such a "functional lesion" has been reported in an operant procedure in which MDMA-induced serotonin depletion was found to potentiate its psychomotor stimulant effects (Li et al. 1986). In the case where amphetamine was given first, followed by MDMA, no change in responsiveness would have been expected.

The stimulation of locomotor activity by MDMA and the importance of mesolimbic dopamine in this response reflect similarities with the prototype phenylethylamine stimulant, amphetamine. It is important to note that these parameters are frequently associated with rewarding aspects of drugs and drug abuse. Additionally, the behavioral profiles of MDMA and MDE share certain characteristics with hallucinogen-like agents. This unique mixture of stimulus properties and neurochemical actions may contribute to a dangerous behavioral toxicity and neurotoxic potential for drugs like MDMA.

**DISCUSSION**

QUESTION: Can you get animals to self-administer cocaine into the nucleus accumbens?

ANSWER: No, I never tried that, but the literature there is complicated, as you know. Animals will, however, self-administer cocaine into the frontal cortex. Amphetamine is self-administered into the nucleus accumbens.

You have to know that we take out most of the mesocorticolimbic dopamine system with that lesion; we are not just taking out the nucleus accumbens dopamine projection. I am very careful to put the region of the nucleus accumbens on my slide.

I think the way Jim Smith and I have discussed this paradox is a follows: He thinks that the frontal cortex has something to do with initiation of cocaine self-administration, and I think probably the whole system may be involved in maintaining the behavior once the animals have learned it.

QUESTION: Have you tried MDMA into the nucleus accumbens?

ANSWER: No, we haven't tried self-administration of MDMA. I am not sure we would get rats to switch from cocaine to MDMA.

QUESTION: Have you had the opportunity to look at the impact of methysergide pretreatment on MDMA's effects on exploration and rearing?

ANSWER: No, we just put that on the books. We would really like to look in the behavioral pattern monitoring system. I predict that the lesion

is going to block the crossovers. But I don't know what methysergide would block. I believe it would be incredibly interesting if it would turn those rats into amphetamine-like rats, and they would explore and show less thigmotaxis and more nosepokes.

QUESTION: How can you dissociate the locomotor effects from the reinforcing effects? It has been agreed that lesions of the mesolimbic system affect locomotor activity and shown by Eberson with respect to the dopaminergic system. How do you know you don't have a rat that is motorically compromised and can't press the lever to get the cocaine? How can you dissociate that from the reinforcement efficacy?

ANSWER: I think the only thing I can really argue strongly is that we have made similar lesions in rats the lever pressed for heroin, so they are lever pressing in the exact paradigm as a reinforcer, and continue to take heroin, although the cocaine self-administration extinguishes. I have a slide of a rat who keeps plugging along on heroin self-administration and at the same time every other day is tested on cocaine. The paradigm was heroin on Monday, cocaine on Tuesday, heroin on Wednesday, cocaine on Thursday, His cocaine self-administration was completely extinguished, yet his heroin self-administration continued. This is one piece of evidence that looks like a real dissociation. The animals can lever press for another reinforcer, but they choose not to lever press for cocaine.

And the other part would be that they show locomotion with other drugs. It is just the indirect sympathomimetics where locomotion is blocked.

It could be said that the reason they are not pressing the lever for cocaine is that it doesn't do anything for them. And then you get into a circuit where it is the psychostimulant effects that produce the reinforcing effects.

COMMENT: Your data showed that, at least with that one model rat, there was a good extinction pattern and high levels of activity. I would consider that to be a better piece of evidence.

RESPONSE: Yes, it means that the animal is capable of moving around for apomorphine. But then it gets subtle. In people, too, there is initially a high level of activity to exhaust residual dopamine stores and then the activity goes down to a very low level. The apomorphine can reinstate some locomotion. I think the most convincing evidence is the heroin. It is not true motor activity.

QUESTION: Do you have any explanation for sensitization within the MDMA or the methysergide? There has been evidence of serotonergic inhibition.

ANSWER: I think there are two ways to look at it I would say one reason is MDMA doesn't look like amphetamine. Why doesn't MDMA look like amphetamine without any other drugs added on? The animal has the psychedelic repertoire, whatever that is, interfering. This is what Klaus Miczek and I were discussing. The animal perhaps has another behavioral repertoire interfering with the expression of motor activity, and that happens to be that the animal is hanging close to the side of the cage and for whatever reason, if it is LSD-like, he doesn't want to go into the center because it is frightening. He is hallucinating. I am speculating here. And if you then take away that competing behavior or competing brain Gestalt of psychedelic activity, then you are turning the drug into basically amphetamine. That is one way of looking at it.

Another way of viewing it would be as levers going off. Serotonin is inhibitory, dopamine is excitatory. That is naive, but there is evidence to suggest that in the neurochemistry of those compounds there has been a kind of yin and yang.

QUESTION: How do you explain MDMA sensitization for amphetamine?

ANSWER: There is evidence that even one exposure of MDMA at 10 mg/kg can cause some serotonin neurotoxicity. Dr. Seiden has shown in DRL procedures with repeated exposure that there is more of an amphetamine-like effect after some of the serotonin has been depleted.

QUESTION: Had you looked at that at all?

ANSWER: In terms of the biochemistry itself, no, not at all.

COMMENT: I am not sure the serotonin is inhibitory and dopamine excitatory is all that naive. There were clinical studies published where they showed that serotonin agonists could completely suppress the CNS stimulant effects of amphetamine clinically in humans. So you may be seeing the same thing. I am not sure that it has to be a psychedelic activity superimposed. It may simply be some kind of a synergistic attenuation.

COMMENT: Both Campbell and Harvey, in independent experiments, have shown if you take away the serotonin input you can exacerbate the psychomotor stimulant effects of amphetamines.

RESPONSE: Yes, and there is some recent study too that was done by Lyness showing that if the serotonin system is destroyed, toxicity and self-administration of amphetamines are increased. There is a lot of evidence that some of this interaction does occur at some level, but we don't know where yet.

## REFERENCES


Adams, L.M., and Geyer, M.A. A proposed model for hallucinogens based on LSD's effects on patterns of exploration in rats. *Behav Neurosci* 99:881-900, 1985a.

Adams, L.M., and Geyer M.A. Effects of DOM and DMT in a proposed animal model of hallucinogenic activity. *Prog Neuropsychopharmacol Biol Psychiatry* 9:121-132, 1985b.

Barnes, D. New data intensify the agony over Ecstasy. *Science* 239:864-866, 1988.

Beardsley, P.; Balster, R.; and Harris, L. Self-administration of methylenedioxymethamphetamine (MDMA) by rhesus monkeys. *Drug Alcohol Depend* 18:149-157, 1986.

Beck, J., and Morgan, P.A. Designer drug confusion: A focus on MDMA. *J Drug Educ* 16:287-302, 1986.

Callahan, P.M., and Appel, J.B. Differences in the stimulus properties of MDA and MDMA in animals trained to discriminate hallucinogens from saline. *Society for Neuroscience Abstracts* 13:1720, 1987.

Creese, I., and Iversen, S.D. The pharmacological and anatomical substrates of the amphetamine response in the rat. *Brain Res* 83:419-436, 1975.

Deminiere, J.M.; Simon, H.; Herman, J.P.; and Le Moal, M. 6-Hydroxydopamine lesion of the dopamine mesocorticolimbic cell bodies increases (+)-amphetamine self-administration. *Psychopharmacology* 83:281-284, 1984.

Deminiere, J.M.; Taghzouti, K.; Tassin, J.P.; Le Moal, M.; and Simon, H. Increased sensitivity to amphetamine and facilitation of amphetamine self-administration after 6-hydroxydopamine lesions of the amygdala. *Psychopharmacology* 94:232-236, 1988.

DeWit, H., and Wise, R.A. Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide, but not with the noradrenergic blockers phentolamine and phenoxybenzamine. *Can J Psychol* 31:195-203, 1977.

Dowling, G.P.; McDonough, E.T.; and Bost, R.O. "Eve" and "Ecstasy": A report of five deaths associated with the use of MDEA and MDMA. *JAMA* 257:1615-1617, 1987.

Ettenberg, A.; Pettit H.O.; Bloom, F.E.; and Koob, G.F. Heroin and cocaine intravenous self-administration in rats: Mediation by separate neural systems. *Psychopharmacology* 78:204-209, 1982.

Evans, S., and Johanson, C. Discriminative stimulus properties of (±)-3,4-methylenedioxymethamphetamine and (±)-3,4-methylenedioxyamphetamine in pigeons. *Drug Alcohol Depend* 18:159-164 1986.

Felice, L.; Felice, J.; and Kissinger, P. Determination of catecholamines in rat brain parts by reverse-phase ion-pair liquid chromatography. *J Neurochem* 31:1461-1465, 1978.

Geyer. M. Variational and probabilistic aspects of exploratory behavior in space: Four stimulant styles. *Psychopharmacol Bull* 18:48-51, 1982.

Geyer, M.A.; Light, R.K.; Rose, G.J.; Petersen, L.R.; Horwitt, D.D.; Adams, L.M.; and Hawkins, R.L. A characteristic effect of hallucinogens on investigatory responding of rats. *Psychopharmacology* 65:35-40, 1979.

Geyer, M.A.; Russo, P.V.; and Masten, V.L. Multivariate assessment of locomotor behavior: Pharmacological and behavioral analyses. *Pharmacol Biochem Behav* 25:277-288, 1986.

Geyer, M.A.; Russo, P.V.; Segal, D.S.; and Kuczenski, R. Effects of apomorphine and amphetamine on patterns of locomotor and investigatory behavior in rats. *Pharmacol Biochem Behav* 28:393-399, 1987.

Glennon, R.A.; Yousif, M.; and Patrick, G. Stimulus properties of 1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDA) analogs. *Pharmacol Biochem Behav* 29:443-449, 1988.

Glickman, SE., and Schiff, B.B. A biological theory of reinforcement. *Psychol Rev* 74:81-108. 1967.

Goeders. N.E., and Smith, J.E. Cortical dopaminergic involvement in cocaine reinforcement. *Science* 221:773-775, 1983.

Gold, L.H.; Hubner, C.B.; and Koob, G.F. A role for the mesolimbic dopamine system in the psychostimulant actions of MDMA. *Psychopharmacology,* in press.

Gold, L.H., and Koob, G.F. Methysergide potentiates the hyperactivity produced by MDMA in rats. *Pharmacol Biochem Behav* 29:645-648, 1988.

Gold, L.H.; Koob, G.F.; and Geyer, M.A. Stimulant and hallucinogenic behavioral profiles of 3,4-methylenedioxymethamphetamine (MDMA) and N-ethyl-3,4-methylenedioxyamphetamine (MDE) in rats. *J Pharmacol Exp Ther* 247:547-555, 1988.

Grinspoon, L., and Bakalar, J. Can drugs be used to enhance the psychotherapeutic process? *Am J Psychother* 40:393-404, 1986.

Hoebel, B.G.; Monaco, A.P.; Hemandez, L.; Aulisi, E.F.; Stanley, B.G.; and Lenard, L. Self-injection of amphetamine directly into the brain. *Psychopharmacology* 81:158-163, 1983.

Hollister, A.; Breese, G.; Moreton Kuhn, C.; Cooper, B.; and Schanberg, S. An inhibitory role for brain serotonin-containing systems in the locomotor effects of *d*-amphetamine. *J Pharmacol Exp Ther* 198:12-22, 1976.

Hubner, C.B.; Bird, M.; Rassnick, S.; and Kometsky, C. The threshold lowering effects of MDMA (ecstasy) on brain-stimulation reward. *Psychopharmacology* 95:49-51, 1988.

Johnson, M.P.; Hoffman, A.J.; and Nichols, DE. Effects of the enantiomers of MDA, MDMA and related analogs on [$^3$H] serotonin and [$^3$H] dopamine release from superfused rat brain slices. *Eur J Pharmacol* 132:269-276, 1986.

Jonsson, L.E.: Anggard, E.; and Gunne, L.M. Blockade of intravenous amphetamine euphoria in man. *Clin Pharmacol Ther* 12:889-896. 1971.

Joyce, E.M., and Koob, G.F. Amphetamine-, scopolamine-, and caffeine-induced locomotor activity following 6-hydroxydopamine lesions of the mesolimbic dopamine system. *Psychopharmacology* 73:311-313, 1981.

Kamien, J.; Johanson, C.; Schuster, C.; and Woolverton, W. The effects of (±)-3,4-methylenedioxymethamphetamine and (±)-3,4-methylenedioxy-amphetamine in monkeys trained to discriminate (+)-amphetamine from saline. *Drug Alcohol Depend* 18:139-147, 1986.

Kelly, P.H., and Iversen, S.D. Selective 6-OHDA-induced destruction of mesolimbic dopamine neurons: Abolition of psychostimulant-induced locomotor activity in rats. *Eur J Pharmacol* 40:45-56, 1976.

Kelly, P.H.; Seviour, P.; and Iversen, S.D. Amphetamine and apomorphine response in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. *Brain Res* 94:507-522, 1975.

Koob, G.F.; Le. H.T.; and Creese, I. D-l receptor antagonist SCH 23390 increases cocaine self-administration in the rat. *Neurosci Lett* 79:315-321. 1987a.

Koob, G.F.; Vaccarino, F.J.; Amalric, M.; and Bloom, F.E. Positive reinforcement properties of drugs: Search for neural substrates. In: Engel, J., and Oreland, L., eds. *Brain Reward Systems and Abuse.* New York: Raven Press, 1987b. pp. 35-50.

Lamb, R., and Griffiths, R. Self-injection of d,1-3,4-methylenedioxy-methamphetamine (MDMA) in the baboon. *Psychopharmacology* 91:268-272, 1987.

Li, A.; Marek, G.; Vosmer, G.; and Seiden, L. MDMA-induced serotonin depletion potentiates the psychomotor stimulant effects of MDMA on rats performing on the differential-reinforcement-of-low-rate (DRL) schedule. *Society for Neuroscience Abstracts* 12:609, 1986.

Lyness, W.H.; Friedle, N.M.; and Moore, K.E. Destruction of dopaminergic nerve terminals in nucleus accumbens: Effect on *d*-amphetamine self-administration. *Pharmacol Biochem Behav* 11:553-556, 1979.

Martin-Iversen, M.T.; Szostak, C.; and Fibiger, H.C. 6-Hydroxydopamine lesions of the medial prefrontal cortex fail to influence intravenous self-administration of cocaine. *Psychopharmacology* 88:310-314, 1986.

Mogenson, G.J., and Nielson, M.A. Neuropharmacological evidence to suggest that the nucleus accumbens and subpallidal regions contribute to exploratory locomotion. *Behav Neural Biol* 42:52-60, 1984.

Mokler, DJ.; Robinson, S.E.; and Rosecrans, J.A. (±)3,4-Methylenedioxy-methamphetamine (MDMA) produces long-term reductions in brain 5-hydroxytryptamine in rats. *Eur J Pharmacol* 138:265-268, 1987.

Monaco, A.P.; Hemandez, L.; and Hoebel, B.G. Nucleus accumbens: Site of amphetamine self-injection: Comparison with the lateral ventricle. In: Chronister, R.B., and DeFrance, J.F., eds. *The Neurobiology of the Nucleus Accumbens.* Brunswick, ME: Haer Institute Press, 1981. pp. 338-342.

Mucha, R.F.; van der Kooy, M.; O'Shaughnessy, M.; and Bucenieks, P. Drug reinforcement studied by the use of place preference conditioning in rat. *Brain Res* 243:91-105, 1982.

Nichols, D.; Lloyd, D.; Hoffman, A.: Nichols, M.; and Yim, G. Effects of certain hallucinogenic amphetamine analogs on the release of [$^3$H] serotonin from rat brain synaptosomes. *J Med Chem* 25:530-535, 1982.

Nichols, D.E.; Hoffman, AJ.; Oberlender, R.A.; Jacob, P.; and Shulgin, A.T. Derivatives of 1-(1,3-benxodioxol-5-yl)-2-butanamine: Repre sentatives of a novel therapeutic class. *J Med Chem* 29:2009-2015, 1986.

Oberlender, R.. and Nichols, D.E. Drug discrimination studies with MDMA and amphetamine. *Psychopharmacology 95:71-76,* 1988.

Peroutka, S. Incidence of recreational use of 3,4-methylenedioxymetham-phetamine (MDMA, "Ecstasy") on an undergraduate campus. *N Engl J Med* 317:1542-1543, 1987.

Phillips, A.G., and Rolls, E.T. Intracerebral self-administration of amphetamine by rhesus monkeys. *Neurosci Lett* 24:81-86, 1981.

Pickens, R.; Meisch, R.A.; and Dougherty, J.A. Chemical interactions in amphetamine reinfomement. *Psycho1 Rep* 23:1267-1270, 1968.

Pijnenburg, A.J.J.; Honig, W.M.M.; and van Rossum, J.M. Inhibition of *d*-amphetamine induced locomotor activity by injection of haloperidol into the nucleus accumbens of the rat. *Psychopharmacologia (Berlin)* 41:87-95, 1975.

Pijnenburg, A., and van Rossum, J. Stimulation of locomotor activity following injection of dopamine into the nucleus accumbens. *J Pharm Pharmacol* 25:1003-1005, 1973.

Ricaurte, G.; Bryan, G.; Strauss, L.; Seiden, L.; and Schuster, C. Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. *Science* 229:986-988, 1985.

Risner, M., and Jones, B.E. Role of noradrenergic and dopaminergic processes in amphetamine self-administration. *Pharmacol Biochem Behav* 5:477-482, 1976.

Roberts, D.C.S.; Corcoran, M.E.; and Fibiger, H.C. On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. *Pharmacol Biochem Behav* 6:615-620, 1977.

Roberts, D.C.S., and Koob, G.F. Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats. *Pharmacol Biochem Behav* 17:901-904, 1982.

Roberts, D.C.; Koob, G.F.; Klonoff, P.: and Fibiger, H.C. Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. *Pharmacol Biochem Behav* 12:781-787, 1980.

Roberts, D.C.S., and Vickers, G. Atypical neuroleptics increase self-administration of cocaine: An evaluation of a behavioral screen for antipsychotic activity. *Psychopharmacology* 82:135-139, 1984.

Roberts, D.C.S., and Vickers, G. Increased motivation to self-administer apomorphine following 6-hydroxydopamine lesion of the nucleus accum-bens. In: Kalivas, P.W., and Nemeroff, C.B., eds. *The Mesocortico-limbic Dopamine System.* Vol. 537. New York: Annals of the New York Academy of Science, 1988. pp. 523-524.

Schechter, M. Discriminative profile of MDMA. *Pharmacol Biochem Behav* 24:1533-1537, 1986.

Schmidt, C. Neurotoxicity of the psychedelic amphetamine, methylene-dioxymethamphetamine. *J Pharmacol Exp Ther* 240:1-7, 1987.

Schmidt, C.J.; Levin, J.A.: and Lovenberg, W. In vitro and in vivo neurochemical effects of MDMA on striatal monoaminergic systems in rat brain. *Biochem Pharmacol* 36:747-755. 1987.

Shulgin, A.T. Psychotomimetic drugs: Structure-activity relationships. In: Iversen, L.; Iversen, S.; and Snyder, S., eds. *Handbook of Psychopharmacology.* Vol. 11. New York: Plenum Press, 1978. pp. 243-336.

Shulgin, A.T., and Nichols, D.E. Characterization of three new psychotomimetics. In: Stillman. R.C. and Willette. R.E., eds. *The Pharmacology of Hallucinogens.* New York Pergamon Press, 1978. pp. 74-83.

Smith, J.E.; Co, C.; Freeman, M.E.; and Lane, J.D. Brain neurotransmitter turnover correlated with morphine-seeking behavior of rats. *Pharmacol Biochem Behav* 16:509-519, 1982.

Smith, J.E., and Lane, J.D. Brain neurotransmitter turnover correlated with morphine self-administration. In: Smith, J.E., and Lane, J.D., eds. *The Neurobiology of Opiate Reward Processes.* Amsterdam: Elsevier, 1983. pp. 361402.

Spyraki, C.; Fibiger, H.C.; and Phillips, A.G. Dopaminergic substrates of amphetamine-induced place preference conditioning. *Brain Res* 253: 185-193, 1982.

Stone, D.; Stahl, D.; Hanson, G.; and Gibb, J. The effects of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) on monoaminergic systems in the rat brain. *Eur J Pharmacol* 128:41-48, 1986.

Swerdlow, N.R., and Koob, GF. Restrained rats learn amphetamine-conditioned locomotion, but not place preference. *Psychopharmacology* 84:163-166, 1984.

Swerdlow, N.R., and Koob, G.F. Separate neural substrates of the locomotor-activating properties of amphetamine, heroin, caffeine and corticotropin releasing factor (CRF) in the rat. *Pharmacol Biochem Behav* 23:303-307, 1985.

Swerdlow, N.R.; Swanson, L.W.; and Koob, G.F. Substantia innominata Critical link in the behavioral expression of mesolimbic dopamine stimulation in the rat. *Neurosci Lett* 50:19-24, 1984.

Swerdlow, N.R.; Vaccarino, F.J.; Amalric, M.; and Koob, G.F. The neural substrates for the motor-activating properties of psychostimulants: A review of recent findings. *Pharmacol Biochem Behav* 25:233-248, 1986.

Vaccarino, FJ.; Amalric, M.; Swerdlow, N.R.; and Koob, G.F. Blockade of amphetamine but not opiate induced locomotion following antagonism of dopamine function in the rat. *Pharmacol Biochem Behav* 24:61-65, 1986.

Woolverton, W.L. Effects of a D1 and D2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. *Pharmacol Biochem Behav* 24:531-535, 1986.

Yokel, R.A., and Wise, R.A. Increased lever pressing for amphetamine after pimozide in rats: Implications for a dopamine theory of reward. *Science* 187:547-549, 1975.

Yokel, R.A., and Wise, R.A. Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. *Psychopharmacology* 48:311-318, 1976.

## ACKNOWLEDGMENTS

This work was supported in part by National Institute of Mental Health Research Scientist Development Award MH00188, National Institute on Drug Abuse Awards DA 02925 and DA 04398, and a Parkinson's Disease Summer Fellowship.

## AUTHORS

Lisa H. Gold, B.S.
Predoctoral Fellow
Division of Preclinical Neuroscience and Endocrinology
Department of Basic and Clinical Research
Research Institute of Scripps Clinic
La Jolla, CA 92037

Mark A. Geyer, Ph.D.
Associate Professor of Psychiatry
Department of Psychiatry, T-004
University of California, San Diego
La Jolla, CA 92093

George F. Koob, Ph.D.
Associate Member
Division of Preclinical Neuroscience and Endocrinology
Department of Basic and Clinical Research
Research Institute of Scripps Clinic
La Jolla, CA 92037