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BEHAVIORAL PSYCHOPHARMACOLOGY OF MDMA AND MDMA-LIKE DRUGS: A REVIEW OF HUMAN AND ANIMAL STUDIES

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Since being classified as a Schedule I controlled substance, MDMA (3,4-methylenedioxy-N-methylamphetamine; "ecstasy") has been the subject of controversy regarding its potential therapeutic usage, increased use by young people in the "Rave" culture, and issues of potential neurotoxicity. This review article summarizes much of the animal and human studies of the general behavioral effects of MDMA and MDMA-like drugs, as well as studies using specific locomotor activity and startle/prepulse inhibition paradigms. MDMA and related serotonergic drugs produce a unique behavioral profile in both humans and animals. The precise sites of action and mechanisms for these behavioral effects are still being studied. Carefully conducted studies of MDMA and related compounds in animal and human subjects will provide invaluable information that can be used to elucidate mechanisms underlying drug abuse, cognition, arousal, and motor activity, as well as mechanisms of neurotoxicity and the possible therapeutic value of MDMA.

Keywords: MDMA; Human; Rat; Startle; Prepulse inhibition; Locomotor activity

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NEUROPHARMACOLOGY OF MDMA

The behavioral properties of MDMA ("ecstasy") and MDMA-like drugs have received attention in the scientific community, as well as by the public, as these drugs have gained popularity within the "Rave" culture. Most of the focus of the attention, however, has been on issues of neurotoxicity and epidemiology rather than basic behavioral pharmacology studies of MDMA (Hatzidimitriou *et al.*, 1999; Christophersen, 2000; Ricaurte *et al.*, 2000). This review will summarize some of the behavioral literature with regard to both animal and human studies. MDMA influences two neurotransmitter systems in the brain: serotonin and dopamine via reuptake mechanisms. Reuptake functions as a regulatory system in which a neuron can determine the concentration of the neurotransmitter in the synaptic cleft and can alter the rate of reuptake accordingly to regulate the amount of neurotransmitter available. MDMA enters a neuron through a reuptake channel and acts by increasing the amount of neurotransmitter released by the neuron. MDMA is a more potent releaser of serotonin than dopamine (Schmidt and Kehne, 1990). In addition, effects of MDMA on dopamine systems may be dependent upon serotonergic mechanisms, based on observations that depletion of serotonin attenuates the effects of MDMA on dopamine levels (Gazzara *et al.*, 1989). Thus, while MDMA increases both serotonin and dopamine release, it is primarily referred to as a serotonin releaser.

The role of serotonin is not confined to any one specific physiological process or behavior. Manipulations of serotonergic systems in the central nervous system affect a wide range of physiological processes, including sleep (Nicholson *et al.*, 1989), feeding and appetite (Lucki *et al.*, 1988), body temperature regulation (Komiskey and Rudy, 1977), sensory perception (Yaksh and Wilson, 1979), aggression (Lucki, 1998), sex (Lucki, 1998), and mood (Kroeze and Roth, 1998).

In stark contrast to the current laws and opinions of MDMA use, MDMA was initially available as a legal drug and used by therapists in conjunction with psychotherapy. In 1985, however, the Drug Enforcement Administration placed MDMA into Schedule I of the Controlled Substances Act (Lawn, 1985). Schedule I drugs are classified as having a high potential for abuse, with no currently accepted medical use, and a lack of accepted safety for use under medical supervision

(Drug Enforcement Administration, 1996). This classification of MDMA banned all medical use without explicit permission from the Food and Drug Administration. This about-face was prompted by data providing evidence of neurotoxicity, as indicated by serotonin nerve terminal degeneration, with administration of MDA, a compound closely related to MDMA (Ricaurte *et al.*, 1985).

EFFECTS OF MDMA IN HUMANS

The effects of MDMA and related drugs differ from those of stimulants, such as amphetamine ("speed"), or traditional hallucinogens or psychedelics, such as LSD ("acid"). In humans, amphetamine administration produces wakefulness and increases responsivity to environmental stimuli. Human subjects have reported that the behavioral effects of MDMA administration are distinct from those experienced with amphetamine administration, instead producing intense changes in levels of emotion, empathy, and affiliative bonds with other persons (Anderson *et al.*, 1978; Greer and Strassman, 1985; Shulgin, 1986). MDMA also differs from hallucinogens, too. Reports from human subjects characterize MDMA as lacking the profound sensory disruptions associated with traditional hallucinogenic compounds (Naranjo *et al.*, 1980). On the basis of these human reports, it has been suggested that MDMA and related compounds represent a new class of compounds, termed "Entactogens" for their ability to heighten, but not distort, sensory perceptions (Nichols *et al.*, 1986). Hence, information gathered from human reports supports the hypothesis that the behavioral effects of MDMA-like compounds in humans differ from those of either stimulants or traditional hallucinogens.

Therapists have argued that MDMA can be a useful tool in psychotherapy, producing an enhancement in mood, communication, and introspection (Greer and Tolbert, 1986). The classification of MDMA as Schedule I, however, has hindered a thorough clinical investigation of MDMA in human subjects. Despite the scheduling of MDMA, there are several studies currently being conducted in the United States and abroad investigating the psychobiologic effects of MDMA in humans, including a Food and Drug Administration-approved Phase 1 dose-response safety study conducted by Dr.

Charles Grob and colleagues at the University of California Los Angeles Medical Center. A listing of current studies is maintained by the Multidisciplinary Association for Psychedelic Studies (MAPS) and can be found on the Internet (www.maps.org), illustrating efforts by researchers to better characterize the safety profile and potentially beneficial effects of MDMA in human subjects.

In December 1998, the Novartis Foundation held a meeting in London to discuss ongoing studies of MDMA-induced neurotoxicity. In addition to the scientific session, the Foundation held a press conference to highlight presentations at this meeting that included evidence that was interpreted as suggesting that a single dose of MDMA causes neurotoxicity in the human brain. Also discussed were the long-term functional consequences of this neurotoxicity for MDMA users (The Novartis Foundation, 1998; Hatzidimitriou *et al.*, 1999). A special MDMA issue of *Neuropsychobiology* was published, that included several papers authored by meeting participants (June 2000, Vol. 42, No. 1). Potential negative effects of MDMA use were discussed, including depression, mood swings, memory problems, sleep disturbance, and anxiety disorders. Some participants argued that the assertion that "one dose of MDMA is sufficient to produce a neurotoxic lesion" is misleading. One conference participant, Dr. Madhu Kalia, argued that what is actually evaluated in these toxicity studies "...are measures of depletion of the serotonin transporter and metabolite. They are not measures of brain lesions. There is no evidence that there are real lesions in the brain. There is no evidence of gliosis, that there is any scarring, that any neurons are lost... we are not seeing brain lesions in animals" (The Novartis Foundation, 1998). Furthermore, proponents of psychotherapy-associated use of MDMA argued that the assertion that no documented evidence of the medical utility of MDMA exists was true only because of a lack of permission to conduct proper methodological investigations, despite numerous case reports of MDMA therapeutic efficacy. Thus, the debate of whether MDMA is a potential therapeutic tool, or potent neurotoxin, or both, is ongoing. As a consequence of this debate the vast majority of scientific studies have focused on toxicity rather than the acute effects (and the mechanisms underlying them) that have contributed to the popularity of MDMA as a recreational drug of abuse.

Despite the focus on issues of toxicity, preclinical behavioral animal studies of MDMA and MDMA-like drugs are being conducted investigating the behaviors these compounds produce and what these drugs are doing in the brain to produce these behavioral effects. The remainder of this chapter will review some of these acute administration studies in animals conducted in our laboratory and discuss the relevance of these studies to the work in humans.

EFFECTS OF DRUGS IN ANIMALS

Assessing the effects of drugs in animals can be difficult. As animals cannot explicitly "tell" experimenters what they are experiencing, it is up to experimenters to design paradigms for examining animals' behavior and then make interpretations based on the data obtained from these tests. Many different kinds of behavior can be assessed, depending upon the interest of the experimenter and the types of drugs being used. As the behavioral effects of hallucinogens in humans are defined primarily by subjective and variable reports, studies in animals have used various behavioral paradigms to provide additional insight into hallucinogen-induced behavioral profile. This chapter will review animal studies investigating the effects of MDMA, and MDMA-like drugs, on rodent locomotor activity, investigatory behavior, and sensorimotor gating.

LOCOMOTOR ACTIVITY

Locomotor activity is a term used to describe the amount and/or quality of locomotion of an animal. In this laboratory, locomotor activity is measured by placing the rat into a 30.5 × 61 cm chamber (referred to as the Behavioral Pattern Monitor, or BPM) which is equipped with a photobeam grid that records the animal's location in the chamber at any given time. These recordings are saved by a computer and can later be examined and quantified into specific measures of how much the rat moves within the chamber and where it moves in the chamber. More complicated analyses have been developed within our laboratory that characterize the locomotor pattern or path the

rat follows in moving around the BPM chamber. These measures have allowed us to more fully characterize the qualitative aspects of the locomotor activity of the rat. We have found that the pattern of locomotion can be influenced in different ways, with or without affecting the amount, or quantitative aspect, of locomotor activity. Additionally, the chambers are specifically designed with photobeam-equipped holes that allow us to measure investigation by the rat when it pokes its nose into the hole. Burrowing animals, such as rodents, frequently investigate their environment by poking their noses into discrete areas of their environment. Another type of rodent investigative behavior is that of rearings. Rearings occur when the rat raises its front paws up and "stands" on its hind legs to investigate an area or object. The BPM can also measure rearings. Thus, the BPM presents us with the opportunity to measure three aspects of rat behavior: the amount of locomotor activity (locomotor activity), the quality of locomotor activity (locomotor patterns), and amount of holepokes and rearings (investigatory activity).

EFFECTS OF MDMA ON RAT LOCOMOTOR ACTIVITY

MDMA produces a very characteristic profile of locomotor and investigatory behavior when it is administered to rats. MDMA administration, like amphetamine, *increases* the amount of locomotor activity in rats, such that rats are more active within the BPM chamber. A closer examination, however, reveals that the MDMA-induced spatial pattern of locomotion *differs* from that produced by amphetamine. Normally, rats explore the entirety of the BPM chamber (see Fig. 1A). Amphetamine-treated rats also explore the entire chamber (Geyer *et al.*, 1986) (see Fig. 1B). Rats given MDMA, however, avoid the center of the BPM chamber and circle the walls of the BPM (see Fig. 1C) (Paulus and Geyer, 1992). There are also differences in investigatory activity produced by either amphetamine or MDMA. Amphetamine treatment in rats *increases* investigatory holepokes and rearings at doses that increase locomotor activity. In contrast, MDMA-treated rats do not investigate the holes of the BPM chamber or rear as much as rats given saline (Callaway *et al.*, 1990, 1991; Callaway and Geyer, 1992). Thus, unlike amphetamine

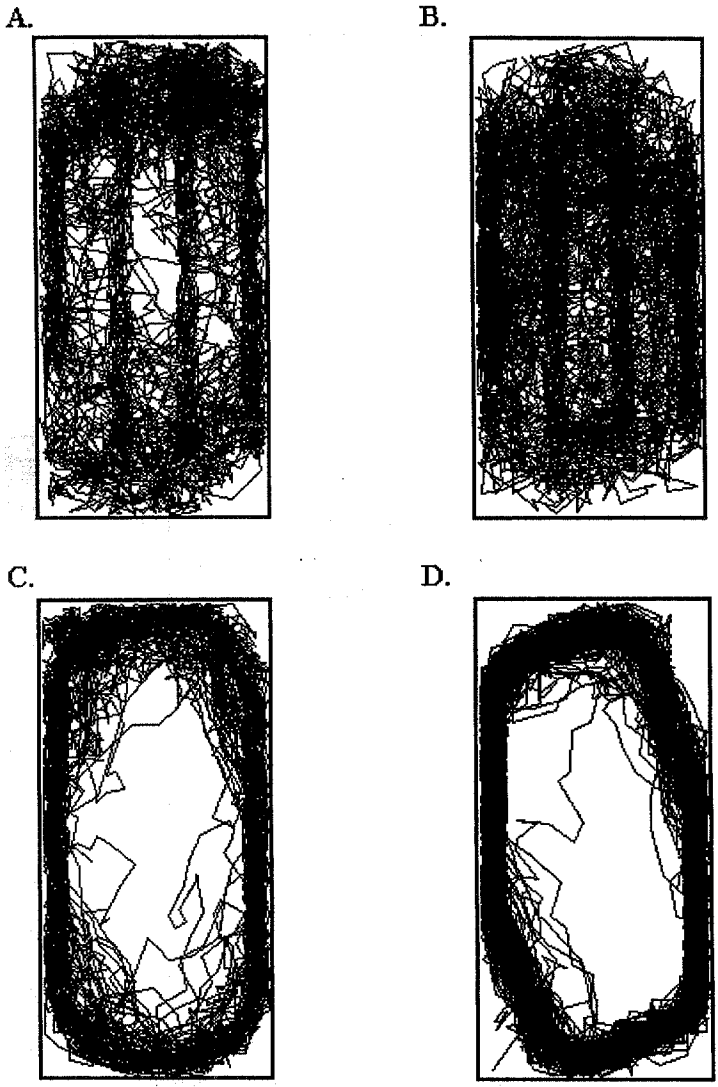

FIGURE 1 Representative plots of individual animals treated with (A) saline, (B) amphetamine, (C) the serotonin releaser, MDMA, and (D) the direct 5-$HT_{1A/1B}$ agonist, RU24969. The reconstructed plot consists of plotted *x-y* positions during the course of a 60-minute test session. The plot of the saline-treated animal (A) shows no preference for any area of the test chamber. The plotted pattern of the amphetamine-treated animal (B) illustrates the increased activity and, like the saline treated animal, exhibits no preference for any area of the chamber. The MDMA-and RU24969-treated animals (C and D respectively) ambulated around the perimeter of the chamber, while avoiding the center.

(Geyer *et al.*, 1987), MDMA-treated rats exhibit a *decrease* in the number of holepokes and rearings at the same doses that elicit increases in locomotor activity (Gold *et al.*, 1988). Taken together, these studies suggest that MDMA administration produces a behavioral profile different from that of amphetamine. Thus, these three aspects of rat locomotor activity and investigatory behavior make up the behavioral profile of MDMA: increased locomotor activity, circular locomotor patterns, and decreased investigatory activity.

EFFECTS OF MDMA-LIKE COMPOUNDS ON RAT LOCOMOTOR ACTIVITY

Studies in rats have shown that other serotonin releasers have effects similar to those of MDMA. The selective serotonin releaser MBDB (which has minimal dopamine-releasing properties) and the tryptamine derivative, alpha-ethyltryptamine (AET), both produce similar behavioral effects on rat locomotor and investigatory behavior, despite being derived from different chemical families (Callaway *et al.*, 1991b; Callaway and Geyer, 1992; Krebs and Geyer, 1993). These compounds also increase rat locomotor activity, decrease investigatory behavior, and produce the characteristic patterns of locomotion elicited by MDMA. AET is a monoamine oxidase inhibitor and potent serotonin-releasing agent. AET has been reported to produce MDMA-like effects in human subjects and has been sold illicitly as a substitute for MDMA on the street (Drug Enforcement Administration, 1993). In addition, AET substitutes for MDMA in rats trained to discriminate the effects of MDMA (Glennon, 1993). Previous studies have demonstrated that AET administration produces effects on unconditioned locomotor behavior and exploratory behavior in rats similar to the effects of serotonin releasers such as MDMA and dissimilar from the effects of dopamine releasers such as amphetamine (Geyer, 1995; Krebs and Geyer, 1993).

The locomotor activating effects of both MDMA and AET, but not amphetamine, are blocked by pretreatment with fluoxetine, a selective serotonin uptake inhibitor (SSRI), suggesting that these two structurally different compounds may share a presynaptic mechanism of action that differs from that of amphetamine (Callaway *et al.*, 1990;

Krebs and Geyer, 1993). An SSRI is a compound that binds to the uptake site on a serotonergic neuron and prevents serotonin that has already been released into the synapse from being taken back up into the neuron; thus it is no longer available to act upon other neurons' receptors. The overall effect, therefore, of an SSRI is to leave the serotonin neurotransmitter in the synapse for a longer period of time. It is important to understand that this effect is very different from an *increase* in the *release* of serotonin. SSRIs do not release serotonin and thus do *not* have MDMA-like effects. The mechanism whereby fluoxetine blocks the effects of serotonin releasers like MDMA is by interfering with the ability of MDMA to enter into a neuron to produce serotonin release. Fluoxetine binds to the uptake carrier, which is the method that MDMA uses to enter into a neuron, and blocks the entry of MDMA into the serotonin terminal via the uptake carrier, which prevents MDMA-induced serotonin release (Hekmatpanah and Peroutka, 1990; Schmidt and Kehne, 1990; Schmidt and Taylor, 1990). The fact that fluoxetine blocks the effects of MDMA and AET supports the hypothesis that the locomotor-activating effects of MDMA and AET are attributable specifically to the ability of each drug to release presynaptic serotonin. It remains unclear whether pretreatment with fluoxetine prevents the entactogenic effects of MDMA in humans (McCann and Ricaurte, 1993). If not, one could suggest that serotonin release is not responsible for the effects of MDMA in humans. It must be recognized, however, that the doses of fluoxetine used in animals to block the serotonin-releasing effect of MDMA are typically as large or larger than the doses of MDMA. Thus, to block the effects of MDMA, one would likely require a dose of fluoxetine that is several times that used clinically. Nevertheless, recent data from human studies indicate that an SSRI pretreatment does reduce the psychological effects of MDMA (Liechti *et al.*, 2000).

SEROTONIN RECEPTOR SUBTYPE INVOLVEMENT IN EFFECTS OF MDMA AND MDMA-LIKE COMPOUNDS ON LOCOMOTOR AND INVESTIGATORY ACTIVITY

Studies have demonstrated that MDMA is taken up into serotonergic neurons and then causes serotonin to be released from this neuron

into the synapse. The released serotonin is then free to bind to a variety of serotonin receptors on neighboring neurons. There are at least 14 serotonin receptor subtypes identified. Although researchers have not conclusively identified which serotonin receptors are involved in these effects of MDMA, previous studies have addressed the hypothesis that MDMA and MDMA-like compounds (such as MBDB and AET) increase locomotor activity by activating serotonin (5-HT) 5-HT_{1B} receptors (Callaway *et al.*, 1992; Rempel *et al.*, 1993). The 5-HT_{1B} receptors are thought to be involved in the effects of MDMA because systemic administration of the direct 5-$HT_{1A/1B}$ agonist RU24969 produces MDMA-like increases in locomotor activity, decreases in investigation, and changes in locomotor patterns in the rat (Rempel *et al.*, 1993) (see Fig. ID for locomotor pattern changes). RU24969 has a five-fold degree of selectivity for 5-HT_{1B} receptors over 5-HT_{1A} receptors. In addition, MDMA shows behavioral cross-tolerance with RU24969. A rat treated repeatedly with MDMA will have a decreased response to the next treatment with MDMA (Callaway and Geyer, 1992). Additionally, when a rat is treated repeatedly with MDMA, the rat will no longer show the same behavioral profile associated with RU24969, and vice versa. There was no cross-tolerance between amphetamine and MDMA or between the 5-HT_{1A} receptor agonist 8-OH-DPAT and MDMA (Callaway and Geyer, 1992). These data indicate that MDMA and RU24969 share a similar mechanism of action: RU24969 activates 5-HT_{1B} receptors directly and MDMA releases serotonin, which activates 5-HT_{1B} receptors indirectly. These results also support the idea that neither MDMA and amphetamine, nor MDMA and 8-OH-DPAT, share a mechanism of action in their effects on locomotor activity.

Studies in this and other laboratories have used antagonist studies to identify the neural substrates responsible for RU24969-induced changes in behavior. Systemic studies of RU24969 with 5-HT_{1A} and 5-HT_{1B} receptor antagonists, WAY100,635 and GR127,935 respectively, have produced evidence of a complex interaction between these two 5-HT_1 receptor subtypes (Martinez and Geyer, 1997a; O'Neill and Parameswaran, 1997). To explore the neural circuitry underlying the RU24969-induced behavioral profile, ongoing studies are examining the effects of direct injections of various 5-HT_{1A} and 5-HT_{1B} agonists and serotonin releasers into areas of the brain known to

possess high densities of 5-HT_{1B} receptors and/or be involved with production of locomotor activity (Martinez and Geyer, 1998; 1999). Preliminary data (Martinez and Geyer, 1999) have provided evidence for multiple-site mediation of the locomotor-activating effects of RU24969. In addition, these experiments have demonstrated that activations of different serotonin receptor subtypes are involved in the production of specific locomotor and investigatory components of the RU24969-induced behavioral profile. Taken together, systemic and central studies of the MDMA-like drug RU24969 indicate that where some drug-induced effect on the brain takes place should be as carefully considered as by what mechanism these effects occur (i.e. 5-HT_{1A} or 5-HT_{1B} receptor activation).

SENSORIMOTOR GATING

In addition to changes in locomotor and investigatory behaviors, MDMA and MDMA-like compounds also produce specific effects on sensorimotor gating, a specific form of sensory information processing (Geyer and Callaway, 1994). Focusing on selected environmental stimuli is a fundamental aspect of sensory information processing. Unconditioned responses to sensory stimuli have been classified as orienting responses to mild, information-laden stimuli and as defensive responses elicited by powerful stimuli. Startle has been considered to be a prototypical defensive response (Davis, 1984; Ison and Hoffman, 1983) and denotes a pattern of reflex responses to sudden intense stimuli. Thus, the startle response is a reflexive response to strong exteroceptive stimuli. These stimuli can be auditory, tactile, or in other modalities. All of these stimuli can produce the startle reflex in humans and animals, reflected in an eyeblink or a whole body jump, respectively. The startle reflex can be altered, and thus exhibits plasticity in the forms of habituation and prepulse inhibition (PPI). PPI is the normal suppression of the startle reflex when the startling stimulus is preceded by a weaker prestimulus (see Fig. 2) (Graham, 1975; Hoffman and Searle, 1968).

Prepulse inhibition is unlearned, as it can occur the very first time a smaller stimulus is paired with a larger stimulus, and it is present across species. The startle response, habituation, and prepulse inhibition are

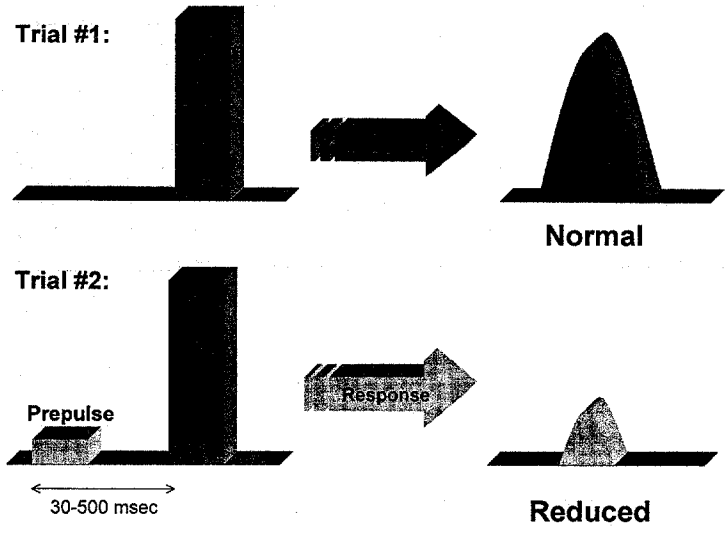

FIGURE 2 Trial #1 illustrates the startle response (R) that is elicited when a "pulse" stimulus is presented. Trial #2 demonstrates prepulse inhibition (PPI) of the startle response (r). PPI is a profound decrease in startle magnitude that occurs when the startling "pulse" is preceded by a weak "prepulse". The degree of PPI is expressed as: $100([r/R] \times 100)$.

easily measured in both humans and animals and, therefore, cross-species modeling of the phenomena represents a unique opportunity to explore and compare the neural substrates governing sensorimotor gating in humans and animals. In humans, the eyeblink response to startling stimuli is measured using electromyography of the muscles surrounding the eye. In animals, a specially designed movement-sensitive chamber measures the whole-body jump produced by exposure to the startling stimulus. In mammals, the underlying neural circuitry governing the startle response consists of three synapses linking the auditory nerve with the spinal motor neuron (Davis *et al.*, 1982), and this circuit is influenced by other areas of the brain involved in PPI and/or habituation (Bakshi and Geyer, 1998, 1999; Caine *et al.*, 1992; Sipes and Geyer, 1997; Swerdlow *et al.*, 1992).

SENSORIMOTOR GATING IN HUMANS

Studies of PPI and habituation of startle have proven to be useful methods for assessing the behavioral influences of various psychoactive substances, environmental or experiential manipulations, or psychiatric conditions on startle reactivity, habituation, or prepulse inhibition. An advantage of using such models is that they have been studied in depth and thus their modulation via pharmacologic manipulations, especially of monoaminergic systems such as serotonin or dopamine, is well documented. In particular, PPI and startle habituation have been used as operational measures of sensorimotor gating and habituation functions, respectively, in both human and animal explorations of attentional deficits characteristic of schizophrenia patients (Braff *et al.*, 1978, 1992; Braff and Geyer, 1990; Geyer and Braff, 1982). In addition, the pathophysiologies of Obsessive Compulsive Disorder and Huntington's disease include abnormalities in brain regions that modulate PPI in rats. Accordingly, PPI deficits have been observed in patients with both these disorders (Swerdlow *et al.*, 1993, 1995), as well as patients with schizophrenia (Braff *et al.*, 1992) and schizotypal personality disorder (Cadenhead *et al.*, 1993).

SENSORIMOTOR GATING IN ANIMALS

There are several hypotheses as to which neurotransmitter systems might be affected in disorders such as schizophrenia. In accordance with the dopamine theory of schizophrenia, deficits in PPI can be produced in animals treated with dopamine agonists and prevented with typical antipsychotics (which have a clinical efficacy that is predicted by dopamine D2 receptor binding). In addition to the involvement of the dopamine system, animal studies have provided evidence to suggest that multiple neurotransmitter systems are involved in the startle response, habituation, and PPI. Animal studies have demonstrated that PPI is modulated by multiple interacting neurotransmitters, including dopaminergic, noradrenergic, serotonergic, cholinergic, GABAergic, and glutamatergic systems within cortical, limbic, and striatal brain structures (Mansbach *et al.*, 1989, 1998; Swerdlow *et al.*, 1990; Caine *et al.*, 1991; Sipes and Geyer, 1995,

1997; Gaggi *et al.*, 1997; Bakshi and Geyer, 1998, 1999; Carasso *et al.*, 1998).

EFFECTS OF MDMA AND MDMA-LIKE COMPOUNDS ON SENSORIMOTOR GATING

In addition to the changes in locomotor and exploratory behaviors, MDMA and MDMA-like compounds produce specific effects in startle reflex paradigms. Serotonin releasers, such as MDMA, MDEA, AET, fenfluramine, and PCA disrupt PPI in rodents (Mansbach *et al.*, 1989; Dulawa and Geyer, 1996; Kehne *et al.*, 1996; Padich *et al.*, 1996; Martinez and Geyer, 1997b; Vollenweider *et al.*, 1999). Startle habituation refers to the decrement in responding when the same stimulus is presented repeatedly in the absence of any contingencies and has been deemed the simplest form of learning. Startle habituation is reduced in rats treated with hallucinogens (Geyer and Tapson, 1988) or serotonin releasers. MDMA and AET administration produce dose-related decreases in acoustic and tactile startle habituation in rats (Kehne *et al.*, 1992; Martinez and Geyer, 1997b). A study comparing the effects of MDMA on PPI of acoustic startle in rats versus healthy human volunteers has produced surprising results (Vollenweider *et al.*, 1999). It was hypothesized that MDMA would disrupt PPI in both rats and humans. The results, however, showed that MDMA produced opposite effects in rats and humans. Earlier results demonstrating an MDMA-induced disruption of PPI in rats were replicated, but comparable doses increased PPI in humans. This discrepancy could be explained by a species-specific difference in the mechanism of action of MDMA or a difference in the behavioral expression of a similar pharmacological effect of MDMA. In any case, these data provide additional justification of the need for controlled studies of the acute effects of MDMA in humans, within appropriate ethical constraints.

The effects of MDMA and other serotonin-releasing agents on both habituation and PPI reflect indirect agonist actions due to the stimulation of presynaptic serotonin release. Fluoxetine pretreatment prevented the AET-induced disruption of PPI and reduced the AET-induced disruption of startle habituation (Martinez and Geyer,

1997b). As explained in the locomotor activity section, fluoxetine works to block the effects of MDMA because it prevents MDMA from being taken up into the neuron's terminal. Thus, MDMA is not able to release serotonin when fluoxetine is bound to the uptake carrier. As noted before, the blockade of reuptake produced by fluoxetine has no effect on serotonin release per se and thus does not produce an MDMA-like effect. The PPI disruptive effects of other serotonin releasers were also reduced by serotonin uptake blockade (Padich *et al.*, 1996), indicating that, like locomotor activity, MDMA and MDMA-like compounds affect sensorimotor gating via the release of serotonin. In accordance with animal studies, there are now data from human subjects demonstrating that MDMA-induced increases in PPI in humans are prevented by pretreatment with another SSRI, citalopram (Liechti *et al.*, 2000). These data indicate that both rat decreases and human increases in PPI induced by MDMA administration are mediated by serotonin release. Together with animal studies, the human data support the hypothesis that differences in effects of MDMA administration in humans and animals can be attributed to a difference in the behavioral expression (increase or decrease in PPI) of a similar pharmacological effect (serotonin release).

SEROTONIN RECEPTOR SUBTYPE INVOLVEMENT IN EFFECTS OF MDMA AND MDMA-LIKE COMPOUNDS ON SENSORIMOTOR GATING

Although not studied very extensively, it appears that the effects of MDMA and related serotonin releasers on sensorimotor gating measures may be attenuated by antagonism of specific serotonin receptors. Antagonism of 5-HT_{2A} receptors reduced the effects of MDMA and fenfluramine, another serotonin releaser, on PPI (Padich *et al.*, 1996). Additionally, mice that were genetically designed to lack 5-HT_{1B} receptors exhibited a reduced response to MDMA, MBDB, and AET (Dulawa *et al.*, 1998). Thus, it appears that 5-HT_{1B} receptors and 5-HT_{2A} receptors may play roles in the effects of MDMA and other serotonin releasers on startle reactivity.

NOT ALL SEROTONIN RELEASERS ARE EQUAL – THE CASE OF FENFLURAMINE

Human Reports

Of the serotonin-releasing compounds we have discussed thus far, MDMA has received the most attention both within the scientific community, as well as by the public media. Another serotonin releaser, fenfluramine, has received a great deal of attention for a reason other than psychoactive effects. The U.S. Food and Drug Administration (FDA) first approved fenfluramine in 1973. From 1992 until recently, fenfluramine and another drug, phentermine, were being referred to as fen-phen, and touted as the magic drug combination for weight reduction. Fenfluramine is believed to increase the release of the brain chemical serotonin, which controls satiety, or a feeling of fullness, thereby reducing the food intake of a patient and resulting in weight loss. Fenfluramine administration has several side effects, such as drowsiness, fatigue, and dizziness (Gotestam and Gunne, 1972; Muldoon *et al.*, 1996; Aman *et al.*, 1997), and the second drug, phentermine, is administered in conjunction with fenfluramine to reduce some sedative effects of fenfluramine. In addition to anti-drowsiness properties, phentermine, which acts on dopamine, increases the body's metabolism. Both drugs were approved separately by the FDA as short-term diet aids. In 1997, researchers reported that some patients using both of these medications concurrently had developed leaking of their heart valves (McCann *et al.*, 1997). This report prompted the FDA to issue a warning regarding the combined use of fenfluramine and phentermine (fen-phen). In September 1997, the data linking fen-phen with an increased risk for heart disease were sufficiently convincing for the manufacturers of fenfluramine and a related drug, dexfenfluramine (Redux), to voluntarily withdraw these drugs from the market. Phentermine, produced by three different manufacturers, is still available.

Since these initial reports, the results from additional studies have indicated that the heart-related problems are not as prevalent as initially reported and furthermore, that there may be some recovery from such problems (Harvard Heart Letter, 2000). In addition to heart valve problems, patients who took fen-phen may have also sustained

brain injuries. A recent review article summarized the available literature on studies of the effects of fenfluramine on animal brain nerve cells (McCann *et al.*, 1997). The researchers found long-term, and perhaps permanent, damage to the serotonin axons. The drug dosages and lengths of time that the animals took the drugs were comparable to those common to human use. The authors pointed out that although no similar human studies have been done, several articles (Preval and Pakyurek, 1997; Raison and Klein, 1997) have been published that report psychotic behavior in humans who have taken fenfluramine or Redux. In both reports, however, it should be noted that there was either a prior history of alcohol and drug abuse, or a familial history of psychiatric disorders. The authors of the article declined to speculate whether the type of nerve cell destruction observed in animals would be found in humans or could explain neurological or behavioral changes in humans. In 1998 a review of fenfluramine and dexfenfluramine was published that cited thirty-one case reports of neuropsychiatric problems ranging from mood disorders to psychotic episodes (McCann *et al.*, 1998). Included in this report were patient self-reports of short-term memory loss (19 patients out of 31). One of the more common symptoms associated with fenfluramine administration in humans is sedation, unlike MDMA (Gotestam and Gunne, 1972; Griffith *et al.*, 1975).

Animal Studies of Fenfluramine

The serotonin-releasing properties of fenfluramine have been examined both *in vitro* (Garattini *et al.*, 1975; Kannengiesser *et al.*, 1976; McKenna *et al.*, 1991) and *in vivo* (Schwartz *et al.*, 1989). Like MDMA, fenfluramine-induced serotonin release can be prevented by selective serotonin reuptake inhibitors thereby indicating that fenfluramine releases serotonin via a carrier-mediated mechanism (Hekmatpanah and Peroutka, 1990). As previously mentioned, the appetite-suppressant effects of fenfluramine are thought to be due to its serotonin-releasing properties. Animal studies have demonstrated that the appetite suppressant effect of fenfluramine can be blocked by prior depletion of serotonin (Samanin *et al.*, 1972; Kleven *et al.*, 1988).

Locomotor studies of fenfluramine present a very *different* drug-induced profile than that induced by MDMA treatment. Fenfluramine treatment *reduces* the amount of motor activity in animals (Ziance *et al.*, 1972), just as it produces sedation in humans (Lindquist and Gotestam, 1977; Aulakh *et al.*, 1988). In studies of locomotor activity in animals, serotonin traditionally has been believed to inhibit motor output, hence exerting an influence directly opposite to the activation of motor output produced by increased activity of dopaminergic and noradrenergic systems. The locomotor-reducing effects of fenfluramine have been cited as evidence in support of this traditional view. Additional evidence, however, suggests the possibility that some endogenous serotonergic systems may be involved in the *activation* of motor activity, rather than the inhibition of motor output (Geyer and Callaway, 1994; Jacobs and Fornal, 1997; Rueter *et al.*, 1997). Studies have demonstrated the dependence of locomotion on an intact serotonergic system (Salles and Salles, 1980). This finding is in agreement with a subsequent study demonstrating a decrease in locomotor activity produced by chemical (5,7-DHT) lesions of the serotonergic system (Lipska *et al.*, 1992). Thus, the traditional view that serotonin is associated with reduced activity, a view supported by the effects of fenfluramine, is *not* supported by other evidence.

Our studies have provided evidence of this non-traditional view of the role of serotonin in locomotor activity. Studies of fenfluramine administration in the Behavioral Pattern Monitors indicate that serotonin release does *not* account for the reduction in rat behavioral activity produced by fenfluramine (Callaway, 1992). In accordance with previous reports, fenfluramine treatment *did* reduce locomotor activity. Pretreatment with the serotonin reuptake inhibitor fluoxetine, however, *failed* to block these locomotor-depressant effects. The fact that fluoxetine did not antagonize the effects of fenfluramine, but did block the locomotor activating effects of MDMA, indicates that these activity-reducing effects of fenfluramine were *not* dependent on the serotonin carrier. Hence, the locomotor effects of fenfluramine are due to a nonserotonergic mechanism.

The effects of MDMA and fenfluramine in the BPM paradigm are more consistent than other animal models with the effects observed in humans. That is, experimental data from animal studies, such as in drug discrimination, neuroendocrine studies, and anorectic effects,

implicate an underlying serotonin releasing mechanism for fenfluramine. In particular, in animal studies of drug discrimination of fenfluramine versus MDMA, animals generalize the stimulus cue of fenfluramine to MDMA (Schecter, 1986), while subjective reports from humans administered fenfluramine indicate that the effects of fenfluramine differ from those of MDMA (Gotestam and Gunne, 1972; Griffith *et al.*, 1975; Muldoon *et al.*, 1996; Aman *et al.*, 1997). Hence, drug discrimination paradigms may be detecting serotonin release produced by either MDMA or fenfluramine, but these paradigms are not predictive of human experience because the effects of fenfluramine and MDMA in humans are so different. Taken together, these data suggest that while fenfluramine and MDMA can both be described as serotonin releasers, the pharmacological mechanisms of the two compounds differ enough to have different effects in some paradigms (locomotor activity), while having similar effects in others (animal drug discrimination). In addition, results from human studies appear to support the hypothesis that fenfluramine has an additional pharmacological action, independent of serotonin release, that produces sedative effects that override the entactogenic effects of released serotonin.

CONCLUSIONS AND FUTURE DIRECTIONS

In summary, MDMA and related serotonergic releasing drugs produce a unique behavioral profile in both humans and animals with one notable exception. Specifically, MDMA and fenfluramine, both serotonin releasers, differ in their overall *pharmacologic* profiles (i.e. potency of serotonin versus dopamine release or distribution of released serotonin) such that the overall *behavioral* profiles that result from treatment with either MDMA or fenfluramine also differ. Further studies of MDMA and MDMA-like drugs in animals may provide specific evidence of neural mechanisms underlying their behavioral effects. If the behavioral effects produced by these drugs are dependent on serotonin release there are at least two additional questions that must be addressed to further understand MDMA and MDMA-like drugs and the behavioral effects resulting from administration in animals *and* humans. When a serotonin releaser is

taken up via the uptake carrier and causes serotonin to be released, which serotonin receptor subtype(s) does this released serotonin bind to, and where in the brain does this occur? Studies addressing these two questions are currently being conducted in animals by this laboratory. Furthermore, carefully conducted studies of MDMA and related compounds in human subjects will provide invaluable information that, together with data from animal studies, can be used to elucidate mechanisms underlying drug abuse, cognition, arousal, and motor activity, as well as mechanisms of neurotoxicity and the possible therapeutic value of MDMA.

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