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Neuropsychopharmacological Investigations of MDMA/Cocaine Combinations

John J. Panos

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NEUROPSYCHOPHARMACOLOGICAL INVESTIGATIONS OF MDMA/COCAIN COMBINATIONS

by

John J. Panos

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Faculty of The Graduate College
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John J. Panos
Despite the popularity of polydrug abuse among recreational MDMA users, relatively few controlled experimental studies have documented the neurobehavioral effects of MDMA in combination with other abused substances. In this study, the neurochemical and behavioral effects of MDMA/cocaine combinations were assessed using in vivo microdialysis with simultaneous measurement of locomotor activity (LMA). Rats were administered cocaine (10 mg/kg or 20 mg/kg, IP), MDMA (1.5 mg/kg or 3.0 mg/kg, IP) or combinations of cocaine and MDMA during microdialysis experiments. Microdialysis samples were collected every 30 min for three hours prior to drug injections. Following drug administration, six additional 30 min samples were collected over a three-hour period. Samples were analyzed by HPLC with electrochemical detection. Locomotor activity was monitored in microdialysis chambers equipped with infrared emitters and detectors. The results of this study suggest the possibility that MDMA and cocaine produce additive or synergistic neurochemical and behavioral effects. This preclinical study may have important clinical implications and may help explain the common practice of polydrug use among MDMA users.
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INTRODUCTION

Background Statement

Despite increased public awareness regarding the health risks of substance abuse, recreational drug use and abuse continues to be a major problem, especially among adolescents and young adults. The increased accessibility of "club drugs" to young adults is a growing problem in our society. In club settings, known as "raves", the use of multiple drugs in combination is very common. In particular, MDMA ("Ecstasy") is commonly used in combination with other drugs, such as cocaine. Unfortunately, relatively little experimental research exists on the neurobehavioral consequences of these drug combinations. A review of the electronic literature databases revealed a significant gap in the literature with respect to animal models of polydrug abuse that correspond to human drug abuse patterns. A recent article by (Cowan et al., 2003) that examined MDMA use and polydrug use in humans stressed a need for animal studies on the effects of MDMA and combined polydrug administration. Therefore, the aim of the proposed study is to examine the neurobehavioral effects of MDMA in combination with cocaine, and to determine the extent to which these effects differ from those of either drug alone. This study may lead to a greater understanding of the neurobehavioral consequences of polydrug abuse.

Polydrug Use

Polydrug use has become a rampant problem in modern society (Barret, Darredeau, & Pihl, 2006; Gouzoulis-Mayfrank & Daumann, 2006; Montgomery, Fisk, Newcombe, & Murphy, 2005; Wish, Fitzelle, O'Grady, Hsu, & Arria, 2006). Ecstasy or 3, 4-methylenedioxymphetamne (MDMA) has the potential of being a "gateway" drug initiating further exploration with illicit substances. Wish et al (2006) conducted a self-report based study on college students; their results infer that MDMA users are more
likely to have used cocaine, heroin, LSD, other hallucinogens, and inhalants. In relation
to psychostimulant use, MDMA preceded cocaine use in 46% of the individuals surveyed
(Wish, Fitzelle, O'Grady, Hsu, & Arria, 2006).

The medical complications of MDMA and cocaine use are documented and
include cerebral oedema and hepatic liver failure (Kramer et al., 2003). Polydrug use of
psychostimulants such as cocaine and MDMA may present several other possible
complications for the user which include high abuse potential, neurotoxic effects on the
dopaminergic and serotinergic systems, and the possibility of experiencing an
amphetamine-type psychosis. The hypothesized neurotoxic damage may impact on
cognitive and motor system function. There exists a possibility that this neurotoxic effect
could result after a single exposure to a high dose of MDMA or even to a lower dose if
taken in combination with another psychostimulant drug. It is hypothesized that these
negative effects may result from excessive neurotransmitter release elicited by an
additive or synergistic effect of simultaneous polysubstance use (SPU).

A review of the current literature has found relatively few studies that examine
SPU (N = 19). Several researchers have called for further investigations of polysubstance
use including human (Barret, Darredeau, & Pihl, 2006; Gouzoulis-Mayfrank &
Daumann, 2006; Wish, Fitzelle, O'Grady, Hsu, & Arria, 2006) and animal studies
(Gouzoulis-Mayfrank & Daumann, 2006).

Polydrug use among MDMA users is common, especially MDMA use in
combination with psychostimulant drugs, such as amphetamine, methamphetamine, or
cocaine (Khorana, Pullagurla, Young, & Glennon, 2004; Riley, James, Gregory, Dingle,
& Cadger, 2001; Williams, Dratcu, Taylor, Roberts, & Oyefeso, 1998; Winstock,
Griffiths, & Stewart, 2001). Presumably, users take other psychostimulants in combination with MDMA to prolong or enhance its euphoric effects. Scholey et al., (2004) reported significantly greater psychoactive drug use among experienced MDMA users compared to nonusers based on an internet survey. Specifically, survey data revealed that cocaine use was greatest among heavy Ecstasy users (81%) compared to novice (44%) and moderate (61%) MDMA users. Lua, Lin, Tseng, Hu, and Yeh (2003) investigated polydrug abuse with MDMA in Taiwan. These investigators analyzed urine samples from police detainees and found evidence for a high rate of MDMA use in combination with other illicit drugs. Despite the apparent prevalence of polydrug abuse among MDMA users, only a few controlled experimental studies have documented the neurobehavioral effects of MDMA in combination with other drugs.

**MDMA**

3,4-Methylenedioxymethamphetamine (MDMA) is a ring substituted phenylisopropylamine, and a structural analog to amphetamine. Also known as “Ecstasy” on the street, MDMA is commonly used as a recreational drug among young adults. Originally documented in Merck’s laboratory records, MDMA was referred to as “Methylsafrylamin” (Bernschneider-Reif, Oxler, & Freudenmann, 2006; Freudenmann, Oxler, & Bernschneider-Reif, 2006), patented by Merck in 1912 under its chemical structure as an intermediate product in the development of a vasoconstrictive drug (Berschneider-Reif, Oxler, & Freudenmann, 2006; Freudenmann, Oxler, & Bernschneider-Reif, 2006; Pentney, 2001). During the 1970’s, MDMA was used as an adjunct to psychotherapy (Greer & Tolbert, 1986; Meehan, Gordon, & Schechter, 1995), reportedly to enhance communication and “self-examination”. A psychotherapy study
reported that subjective effects of MDMA include altered states of consciousness with emotional components such as empathy, acceptance, and insight (Kemmerling, Haller, & Hinterhuber, 1996). In the early 1980's, MDMA became a popular recreational drug and was sold legally, typically through mail order (Eisner, 1989; Ray & Ksir, 1999). Citing nationwide abuse and the potential health problems of MDMA, the Drug Enforcement Agency (DEA) established MDMA a Schedule I controlled substance in 1988 (Lawn, 1988). Despite increased public awareness of the health risks associated with MDMA, its use has continued to rise in recent years, particularly among young people.

MDMA users have consistently reported the subjective effects of this substance to include elevated mood, feelings of closeness and intimacy, increased empathy, insightfulness, mild alterations in perception, accelerated thinking, jaw clenching, and appetite suppression (Greer & Tolbert, 1986; Grinspoon & Bakalar, 1986; Peroutka, Newman, & Harris, 1988). MDMA has been of great interest to behavioral pharmacologists due to its unique profile of subjective effects.

Cocaine

Cocaine is an alkaloid obtained from the leaves of the coca plant (Vetulani, 2001). Coca leaves have a long history of use by civilizations in the southern hemisphere (Das, 1993; Johanson & Fischman, 1989; Vetulani, 2001). There is evidence that coca leaves were used in religious ceremonies, as medicine, and to relieve the pain of hunger (Johanson & Fischman, 1989). It was not until after the process of chemically isolating cocaine from the coca leaf in the 19th century was developed that the implications of cocaine as a powerful psychostimulant became apparent in the western hemisphere (Johanson & Fischman, 1989). The purification of cocaine from its naturally occurring
plant form is a multi step process. In this process, the intermediate precursor cocaine-sulfate is extracted by washing crushed coca leaves in sulfuric acid or an aromatic solvent. Cocaine-sulfate is then transformed into cocaine-hydrochloride, a water soluble white powder. Cocaine-HCl can be administered by snorting or by dissolving in water and then injecting or drinking the solution. The snorting or injection of cocaine produces rapid psychostimulant and euphoric effects.

**Neuropharmacology of Psychostimulants**

The pharmacological classification of psychostimulants includes a large variety of compounds, including but not limited to cocaine and the amphetamines. In general, the actions of these compounds fall under the psychomotor stimulant theory of addiction (Wise & Bozarth, 1987). The psychomotor stimulant theory of addiction is heavily based on the principles of Skinnerian operant reinforcement. Wise and Bozarth (1987) state; “The crux of the theory is that the reinforcing effects of drugs, and thus their addiction liability can be predicted from their ability to induce psychomotor activation” (p. 474). In advancing beyond the standard Skinnerian approach of considering psychostimulants as environmental variables, the psychostimulant theory of addiction examines the activation of dopaminergic pathways and its relevance to forward locomotion (Wise & Bozarth, 1987).

The psychostimulants, amphetamine and cocaine, have been indicated in the activation of brain reward circuitry and in particular activation of dopamine pathways in the nucleus accumbens (Wise & Bozarth, 1984). Furthermore, the psychostimulants cocaine and the amphetamines increase catecholamine levels in the extracellular fluid space (Bozarth, 1986).
Nucleus accumbens dopamine has been implicated in the study of motivation and reward (Salamone, 1996; Salamone, Correa, Mingote, & Weber, 2003; Sokolowski, Conlan, & Salamone, 1998). It is well documented that most drugs of abuse, including cocaine, ethanol (Doyon et al., 2003; Mcdowell & Kleber, 1994; Yan, 1999) and MDMA (Bankson & Yamamoto, 2004; Hser, Huang, Chou, Teruya, & Anglin, 2003; Koch & Galloway, 1997), increase extracellular dopamine (DA) in the nucleus accumbens (NAc). Acute administration of MDMA increases the release of both DA and 5-HT in awake-behaving rats (Gough, Ali, Slikker, & Holson, 1991; Hiramatsu & Cho, 1990; Kankaanpaa, Meririnne, Lillsunde, & Seppala, 1998; Yamamoto & Spanos, 1988), and NAc DA release may be modulated by 5-HT (Filip & Cunningham, 2002; Koch & Galloway, 1997). Recent studies have shown that MDMA acts at nerve terminals to modulate release and re-uptake mechanisms of DA and 5-HT (Bankson & Yamamoto, 2004).

Cocaine exerts its actions primarily through blocking DA re-uptake in the central nervous system. It is well documented that cocaine increases extracellular DA levels in the nucleus accumbens shell (David, Zahniser, Hoffer, & Gerhardt, 1998). Previous microdialysis studies have shown that both systemic and local injections of cocaine increase synaptic 5-HT in the NAc (Teneud, Baptista, Murzi, Hoebel, & Hernandez, 1996). Serotonin and DA interactions on open-field and stereotypical behaviors in rats following cocaine administration, and the functional importance of increased monoamine release on behavioral activation have also been established (Broderick & Phelix, 1997). At the present time, there are no published microdialysis studies on the effects of acute MDMA/cocaine combinations.
Rationale for Current Study

It is of great importance to closely approximate human drug use when developing an animal testing model of drug abuse. The current study simultaneously examined locomotor activity and neurochemical changes using *in vivo* microdialysis sampling techniques to investigate the combined effects of MDMA and cocaine. The locomotor activity (LMA) testing paradigm is based upon the activation of brain mechanisms associated with movement. Example behaviors are increased exploratory behavior and rearing. Due to the association of motor system activation with drugs that produce reward, the locomotor activity test is often used as a preliminary assessment prior to more extensive investigations of the behavioral effects of drugs. *In vivo* microdialysis and High Performance Liquid Chromatography (HPLC) are commonly used to analyze and quantify extracellular levels of neurotransmitters in the behaving organism. The analysis of drug-induced changes in neurotransmitter levels combined with measures of LMA offers a valuable strategy to assess simultaneously the neurochemical and behavioral actions of drugs. With respect to drugs of abuse, it is of particular interest to examine the release of monoamines in the mesocorticolimbic system. Two factors that are highly related when examining the abuse potential of a drug are behavioral activation and the release of dopamine in the nucleus accumbens. By using both LMA and microdialysis, the present study investigated behavioral and neurochemical effects of acute MDMA-cocaine combinations.
METHOD

Animals

Eighty-four male Sprague-Dawley rats served as subjects (Sasco, Portage, MI). Each rat weighed approximately 500 g at the start of the experiment. All rats were individually housed with standard rat chow and water available ad libitum. Rats were maintained on a 12L:12D cycle (lights on at 0700h/lights off at 1900 h), at a constant temperature (20 ± 2° C) and humidity (50 ± 5%). Animals were allowed to recover for four days prior to testing. Six animals were eliminated from the study due to surgical complications or problems related to microdialysate sample volume. All procedures were approved by Western Michigan University’s Institutional Animal Care and Use Committee. In accordance with university policy, all efforts were made to minimize pain and distress and the number of animals used.

Surgical Procedures

Rats were injected with 1.0 mg/kg atropine-sulfate (Calbiochem, San Diego, CA) 15 min. prior to being anesthetized with sodium pentobarbital 51.0 mg/kg (Sigma-Aldrich, St. Louis, MO). Animals were then placed in a Kopf small animal stereotaxic device (David Kopf Instruments, Tujunga, CA) and maintained at 37.5° C using a Gaymar T/PUMP heat therapy pump (Gaymar Industries Inc, Orchard Park, NY). Removable guide cannulae (Bioanalytical Systems Inc, West Lafayette, IN) were stereotaxically implanted in the nucleus accumbens (AP + 1.70, ML -1.50, DV -6.20) with the incisor bar adjusted to achieve the flat skull position (Paxinos and Watson,
Guide cannula were secured in place with three small jewelers screws (Bioanalytical Systems Inc, West Lafayette, IN) and dental cement (PERM, Hygenic Corp, Akron, OH).

**Behavioral Procedures**

Locomotor activity assessment and in vivo microdialysis procedures were conducted in six identical Plexiglas chambers (16”l x 16”w x 16”h) equipped with a Versamax® Activity Monitoring System (Accuscan Instruments Inc., Columbus, OH). All locomotor data were collected in 30 minute intervals that coincided with microdialysis sample collection times.

**Microdialysis Procedures**

BAS BR-2 microdialysis probes (Bioanalytical Systems Inc, West Lafayette, IN) were flushed with artificial cerebral spinal fluid (aCSF) (147.2 mM NaCl, 1.2 mM CaCl₂, 2.7 mM KCl, 1.0 mM MgCl₂) at a flow rate of 0.5 µl/min 12 hours prior to calibration using BAS BEE syringe pump (Bioanalytical Systems Inc, West Lafayette, IN). At 0600h probes were placed in a calibration solution (1.5 µm DOPAC, 15 nM DA, 760 nM HVA, 300 nM 5-HIAA, 15 nM 5-HT) at a flow rate of 1.5 µl/min, a 30 minute calibration sample was collected. At 0700 – 0800h microdialysis probes were inserted into the guide cannulae and the rats were tethered to an Instech fluid swivel (Plymouth Meeting PA) attached to a counter-balanced arm and placed in the locomotor activity chambers. Microdialysis flow rates were maintained at 1.5 µl/min for the entire experiment. Following insertion, the probes were allowed to equilibrate for three hours prior to testing. At approximately 1100 h, microdialysis sample collection began. Samples
were collected at 30 minute intervals and immediately flash frozen and stored in a -80 °C freezer until HPLC-EC analysis. The sampling regimen consisted of six 30 minute baseline samples, one 30 minute vehicle sample, one 30 minute drug injection sample, and five post injection 30 minute samples.

**Histology**

At the conclusion of the microdialysis procedure, rats were euthanized by injection of a solution containing sodium pentobarbital (50 mg/kg) dissolved in a 60% ethanol and then perfused at a constant pressure of 300 mm/hg with a 10% sucrose solution followed by a 10% formalin solution using a Perfusion One pressurized perfusion system (myNeuroLab, St Louis, MO). The microdialysis guides were removed after the perfusion and the brains were removed from the skulls and stored in 10% formalin. A Vibratome 1500 sectioning system (Ted Pella Inc, Redding, CA) was used to slice coronal sections at a thickness of 70 µm. Coronal sections were mounted on microscope slides and histological placement was confirmed. All probe placements were within the nucleus accumbens target.

**HPLC-EC**

Dopamine was detected by reverse phase high performance liquid chromatography coupled to electrochemical detection. The HPLC-EC system consisted of an ESA Coulochem II Model 5200 detector, ESA 582 solvent delivery module, ESA 540 autosampler and PC running ESA 501 chromatography software, MD-150/RP-C18 column (particle size 3µm, 3.0 x 150 mm i.d.) and a model 5014 analytical cell (ESA, Chelmsford, MA). The detector settings were: guard cell 350 mv, CH1: -175 mv and
CH2: 250 mv, all filter settings were set to 5 sec. A commercially prepared mobile phase, MD-TM (ESA, Chemlsford, MA) was used consisting of 75 mM sodium dihydrogen phosphate monohydrate, 1.7nm 1-octanesulfonic acid, 100 µL/L triethyllamine, 25 µm EDTA, 10% acetonitrile, and adjusted to a pH = 3.0 with phosphoric acid.

Drugs

Cocaine-hydrochloride and 3,4-Methylenedioxymethamphetamine (MDMA) were obtained from the National Institute on Drug Abuse (Rockville, MD). Sodium pentobarbital was purchased from Sigma-Aldrich (St. Louis, MO). Atropine sulfate was purchased from Calbiochem (San Diego, CA). All drugs were dissolved in 0.9% sterile saline and administered by intraperitoneal injection.

Statistical Analysis

The dependent measures of interest in this study included distance traveled (cm) and dopamine concentrations during each 30 minute sampling period. These data were graphed over the 13 sampling periods, which included six baseline samples, one sample following the vehicle injection, and six samples following the drug injection. For dopamine concentrations, averages were calculated from the baseline samples and data points were expressed as a percentage of the baseline average. Analysis of both locomotor activity and dopamine concentrations was performed by calculating individual regression line equations for time periods 8 to 13 for each individual subject. The slopes of the lines were grouped according to drug treatment condition. The slope of the regression lines for treatment groups based on the LOG of dopamine concentrations were compared using a One-Way ANOVA and Fisher-Hayter pairwise comparisons were calculated for treatment effects.
RESULTS

Figure 1 represents the total distance traveled during each 30 minute sampling period. Note that drug injections were administered at the beginning of the eighth sampling period. Both doses of cocaine produced significant increases in locomotor activity. In comparison, MDMA produced only moderate increases in locomotor activity. The combined effects of either MDMA dose with 10 mg/kg cocaine were similar to the effects of this dose of cocaine when administered alone. However, the combined administration of 20 mg/kg cocaine and 3.0 mg/kg MDMA produced greater locomotor activity compared to either dose alone.

**Locomotor Activity**

![Locomotor Activity](image)

**Figure 1. Locomotor Activity**

The slope of the regression lines (see Figure 2) for treatment groups based on the LOG of distance traveled (cm) were compared by using a One-Way ANOVA. A significant drug effect was obtained (F(7, 70) = 4.54, p<.01). Fisher-Hayter pairwise comparisons were calculated for treatment effects and qFH exceeded the critical value.
(q_{05,J, 1N, J}) for [MDMA 1.5 vs. MDMA 1.5 + COC 10.0], and [MDMA 1.5 vs. MDMA 3.0 + COC 20.0].

**Figure 2.** Regression Lines Log of Locomotor Activity

Figure 3 shows extracellular dopamine (DA) levels in the nucleus accumbens (NAc) represented as a percentage of the average baseline concentration for each 30 minute sampling period. When administered alone, cocaine increased NAc DA levels to 265% or 450% of baseline following a dose of 10 or 20 mg/kg, respectively. MDMA increased NAc DA levels to 155% or 194% following 1.5 or 3.0 mg/kg, respectively. When administered in combination with 1.5 mg/kg MDMA, 10 mg/kg cocaine increased NAc DA levels by 370% and cocaine 20 mg/kg increased these levels by 532%. When administered in combination with 3.0 mg/kg MDMA, 10 mg/kg cocaine increased NAc DA levels by 316% and cocaine 20 mg/kg increased these levels by 700%. Thus, the combined actions of MDMA and cocaine appeared to increase NAc DA levels to a greater extent than either drug alone.
The slope of the regression lines (see figure 4) for treatment groups based on the LOG of dopamine concentrations were compared by using a One-Way ANOVA. A significant drug effect was obtained $F(7, 64) = 4.90, p<.01$ Fisher-Hayter pairwise comparisons were calculated for treatment effects. $q_FH$ exceeded the critical value ($q_{.05,J-1, N-J}$) for [MDMA 3.0 vs. MDMA 3.0 + COC 20.0], [MDMA 3.0 vs MDMA 3.0 + COC 10.0], and [MDMA 1.5 vs. MDMA 3.0 + COC 20.0]. These results are indicative of cocaine’s actions to produce a dose-dependent temporal and quantal augmentation of extracellular dopamine elicited by injection of MDMA 3.0 mg/kg.
Figure 4. Regression Lines Log of Nucleus Accumbens Dopamine Levels

DISCUSSION

Cocaine and MDMA produced the anticipated increase in extracellular NAc DA levels and locomotor activity resulting from activation of the mesocorticolimbic system (Bozarth, 1986; Bozarth & Wise, 1986). In concordance with the literature, MDMA produced locomotor system activation and dopamine efflux to a lesser extent than cocaine (Koch & Galloway, 1997). With respect to a combinatorial effect of MDMA and cocaine, MDMA 3.0 mg/kg co-injected with cocaine 20 mg/kg produced dopamine levels and locomotor activity greater than that of either drug alone. These results are indicative of a possible MDMA/cocaine synergistic effect which is dose dependent.

The individual effects of cocaine and MDMA on extracellular dopamine efflux are well documented. Cocaine increases dopamine efflux in the nucleus accumbens shell (Morgan, Horan, Dewey, & Ashby, 1997; Morgan et al., 1997; Shimada, Yamaguchi, & Yanagita, 1996) (Bradberry, 1994, 2002). MDMA has also been demonstrated to enhance dopamine transmission (Cadoni et al., 2005; Green, Mechan, Elliott, O'Shea, & Colado, 2003; Koch & Galloway, 1997), although the mechanisms related to the efflux of extracellular dopamine levels differ. It is important to distinguish the action of cocaine from the action of amphetamine-analogs such as MDMA. Cocaine’s action of blocking
monoamine transporters generates an increase in extracellular dopamine, whereas amphetamine analogs reverse monoamine transporter activity and in turn increase dopamine efflux (Metzger, Hanson, Gibb, & Fleckenstein, 1998). It is hypothesized that MDMA may affect dopamine release by several different mechanisms; (1) by producing action analogous to amphetamine on dopamine terminals (Cadoni et al., 2005) (2) and releasing serotonin by acting on 5-HT₂ receptors (Bradberry, 1994; Cadoni et al., 2005; Koch & Galloway, 1997).

The neurobehavioral actions of MDMA and cocaine, when co-administered, have not been thoroughly investigated. The results of the current study bear some similarity to findings reported by Morgan et al. (1997) who administered cocaine to rats four hours following the administration of the cocaine analog RTI-55. RTI-55 has been demonstrated to have a high binding affinity for the dopamine transporter and the serotonin transporter. Our results are consistent with those of Morgan and colleagues (1997), who demonstrated an increase in NAc dopamine levels of 458% over basal levels following 20 mg/kg cocaine and a 758% increase in dopamine levels following the administration of both RTI-55 and cocaine. In addition, the RTI/cocaine data parallel our findings with respect to an augmented temporal duration of the drug combinations on extracellular NAc dopamine levels. Given the results of Morgan et al (1997) it is hypothesized that MDMA may augment the effects of cocaine via dopamine transporters.

These results have important implications for future lines of research. Future research should include the investigation of the appetitive and aversive properties of MDMA/cocaine combinations. Although these combinations produce increases in extracellular dopamine, which is highly relevant in relation to reward mechanisms,
excessive dopamine release may induce a psychological state similar to a drug-induced amphetamine psychosis, which in turn may be experienced as an aversive condition. To examine the aversive and appetitive effects of these combinations, the conditioned place preference paradigm may be employed. To assess the abuse potential of these drug combinations in animal models, a self-administration study could be conducted to examine whether these combinations will be readily administered and if the rate of administration is greater for the combination compared to either drug alone. Further neurochemical investigations ought to be conducted simultaneously with behavioral experiments to assess the relationship between dopamine release and behavioral effects of MDMA/cocaine combinations. In addition to the aforementioned studies, immunohistochemical investigations of the dopamine transporter and tyrosine hydroxylase activity could be examined. These neurochemical and behavioral studies may also be extended to examine the chronic effects of combined MDMA and cocaine administration with respect to their possible neurotoxic consequences.

These preclinical data may generalize to the population of polydrug abusers who frequently use MDMA in conjunction with other drugs of abuse. The preclinical data demonstrated an increased effect of cocaine's action on dopamine efflux. This increase in extracellular dopamine may augment the subjective feeling of euphoria that humans experience in association with psychostimulant use. MDMA may also extend the temporal effects of psychostimulant actions in humans, causing a prolonged subjective euphoric effect. The increase in intensity and temporal elongation of drug action may contribute to the abuse potential of polydrug use.
CONCLUSION

Recent reports of human polydrug abuse have demonstrated the popularity of MDMA use in conjunction with cocaine (Chinet, Stephan, Zobel, & Halfon, 2007; Marsden et al., 2006). MDMA and cocaine are psychostimulants that individually produce forward locomotion and elevations in extracellular dopamine. In combination, these drugs produce a significant increase in extracellular dopamine levels and locomotor activity greater than either drug alone. The relevant importance of investigating the neurobehavioral effects of this particular drug combination is becoming readily apparent. Further study of the neurochemical, neurobehavioral, and neurotoxic actions of MDMA/cocaine combinations is warranted.
REFERENCES


APPENDIX

Institutional Animal Care and Use Committee Approval Form
Date: October 15, 2004

To: Lisa Baker, Principal Investigator

From: Robert Eversole, Chair

Re: IACUC Protocol No. 04-09-01

Your protocol entitled “Microdialysis Studies Of Polydrug Administration” has received approval from the Institutional Animal Care and Use Committee. The conditions and duration of this approval are specified in the Policies of Western Michigan University. You may now begin to implement the research as described in the application.

The Board wishes you success in the pursuit of your research goals.

Approval Termination: October 15, 2005