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Cocaine and methamphetamine produce different patterns of subjective and cardiovascular effects☆

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Abstract

The stimulant effects of cocaine and methamphetamine are mediated by changes in synaptic concentrations of brain monoamines; however, the drugs alter monoamine levels via different mechanisms. This study examined the subjective and cardiovascular responses produced by investigational administration of cocaine or methamphetamine, in order to examine the onset and patterns of subjective and cardiovascular responses. Subjects included 14 non-treatment seeking cocaine-dependent and 11 non-treatment seeking methamphetamine-dependent volunteers. As part of ongoing research studies, cocaine and methamphetamine subjects received cocaine (40 mg, IV) or methamphetamine (30 mg, IV), respectively. Subjective and cardiovascular responses were assessed for 30 min and 60 min, respectively. The data reveal significant within groups differences for all subjective effects and cardiovascular effects ($p<0.05$). Significant between group differences in subjective effects were observed for "Any Drug Effect" ($p<.008$ for group, and $p<.029$ for group × time), for "High" ($p<.002$ for group, and $p<.0001$ for group × time) and for "Stimulated" ($p<.001$ for group, and $p<.006$ for group × time). Significant between group differences in cardiovascular effects were observed for Systolic blood pressure ($p<.0001$ for group, and $p<.002$ for group × time), Diastolic blood pressure ($p<.0001$ for group, though $p=$NS for group × time), and for Heart Rate ($p<.0001$ for group, and $p<.0001$ for group × time). The only difference between the groups for placebo was for heart rate, where there was a significant group × time effect ($p<.005$). Taken together, the data reveal that the subjective effects of cocaine tended to peak and then decline more rapidly than those produced by methamphetamine. The subjective effects of methamphetamine tended to rise more slowly, and remain elevated longer. Cardiovascular effects of cocaine and methamphetamine had similar onset, but effects of cocaine tended to decline more rapidly. Overall, the results reveal differences in the onset, pattern, and duration of subjective and cardiovascular responses following cocaine or methamphetamine administration in stimulant addicted patients. We predict that these differences may impact drug use and relapse patterns, and may have implications in medications development for these addictive disorders.

Keywords: Cocaine; Methamphetamine; Subjective effects

1. Introduction

The psychostimulant effects of drugs such as cocaine and methamphetamine are thought to reflect the ability of these compounds to increase the concentration of extrasynaptic monoamines, including dopamine (DA), in mesolimbic brain regions (Kuhar et al., 1991; Wise, 1996). However, the mechanisms by which these drugs increase synaptic monoamine levels differ. Reuptake inhibitors, such as cocaine, bind to transporters (e.g., the DA transporter: DAT) and inhibit the reuptake of DA into the presynaptic terminal (Woolverton and Johnson, 1992). In contrast, methamphetamine enters the presynaptic terminal to promote the release of neurotransmitters by interfering with vesicular storage and promoting carrier-mediated exchange (Rudnick and Clark, 1993). Cocaine and methamphetamine differ markedly in their pharmacokinetics, as well. The

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elimination half-life of cocaine is about 90 min (Czoty et al., 2002; Jeffcoat et al., 1989), whereas the elimination half-life of methamphetamine is 11–12 h (Cook et al., 1993).

Given the marked differences in the manner in which these drugs influence neurobiological functioning, it is reasonable to hypothesize that the effect profiles of these drugs will differ. The cardiovascular and subjective effects of cocaine are well documented (Abreu et al., 2001; Foltin and Fischman, 1992; Mendelson et al., 2002; Preston et al., 1993; Preston et al., 1992; Schlaepfer et al., 1997; Volkow et al., 2000). Maximal effects appear to follow the time course of the appearance of cocaine in the venous circulation, peaking within the first several minutes following intravenous (IV) administration. Although the cardiovascular and subjective effects of experimentally administered methamphetamine in humans have not been studied as extensively, available reports indicate that these effects peak between 10 and 20 min following IV administration, though systolic blood pressure may peak earlier (Drevets et al., 2001; Laruelle et al., 1995; Mendelson et al., 1995).

To date, there have been no reports directly comparing effects produced by these two stimulants. One possible comparison would involve administering both cocaine and methamphetamine to include participants who use both drugs. Available evidence, however, suggests that most dependent individuals use *either* cocaine or methamphetamine, and not both (Simon et al., 2002); and this is our clinical impression as well. Also, given the differing mechanisms of the drugs, it is likely that chronic use produces neuroadaptations that alter the effects produced by these stimulants. Thus, administration of methamphetamine to a cocaine user may have quite different effects than administration of methamphetamine to a methamphetamine user, and vice versa. A remaining approach is to compare the effects of each drug in well-characterized users of each drug when examined under controlled conditions after a known period of detoxification. Important insights that may be gained from such a study include assessment of differences in subjective effects that may account for the unique dependence patterns produced by the drugs, and assessment of differences in cardiovascular effects that may contribute to the differences in toxicity produced by the drugs. Each of these may contribute to a more complete understanding of the mechanisms and time-course by which these drugs act to produce these effects.

In this study, we pooled data from several protocols conducted by our clinical research group that involved IV cocaine or methamphetamine administration. Subjective and cardiovascular data were collected consistently across all protocols. Different groups of volunteers were recruited for each drug, based on their primary drug of abuse, for reasons noted above and in order to limit participants' exposure to drugs on which they were not already dependent. Based on differing pharmacokinetics, pharmacodynamics, and drug use patterns, we hypothesized that the time course for the subjective and cardiovascular effects of these drugs would differ.

2. Methods

2.1. Subjects

Subjects were 14 non-treatment-seeking cocaine-dependent and 12 non-treatment-seeking methamphetamine-dependent volunteers recruited from the community for inpatient phase I clinical trials. Complete subjective effects data were available from 14 cocaine users and 11 methamphetamine users; complete cardiovascular data were available from 13 cocaine users and 12 methamphetamine users. All procedures reported here were carried out prior to the administration of any investigational medications. All subjects met DSM-IV criteria for cocaine or methamphetamine dependence (but not both drugs concurrently), and did not meet criteria for other current Axis I psychiatric disorders or dependence on other drugs of abuse, other than nicotine (DSM-IV, 1994). All potential participants were screened by a physician for histories of exclusionary concurrent medical illnesses, as well as HIV seropositivity. Laboratory testings, including CBC, electrolytes, liver and kidney function tests, were all within clinically acceptable limits. An ECG was used to exclude subjects with serious cardiac abnormalities. Positive urine toxicologies at study entry confirmed self-reported drug use. At the time of admission, a full drug screen demonstrated either undetectable or falling benzoylecgonine or methamphetamine levels, with repeated urine toxicology screens during the study ensuring abstinence illicit drug use. As previously reported, methamphetamine-dependent volunteers were male, white and averaged approximately 30 years of age. Cocaine-dependent volunteers were predominantly male, African-American, and were on average approximately 40 years of age. All subjects provided informed consent after the risks of the study had been fully explained, and subjects were paid for their participation upon completion of the study.

2.2. Procedure

Subjects were hospitalized for 3 days of stabilization and detoxification, after which they received either cocaine or methamphetamine, depending on their prior drug use history, and placebo. Cocaine (40 mg) and matched placebo were administered over 1 min. Methamphetamine (30 mg) and matched placebo were administered over 2 min. These doses were selected on the basis of published findings (Mendelson et al., 1995; Newton et al., 1999, 2001) and were predicted to produce physiological and subjective responses of similar magnitude. A single administration of each drug was utilized in an effort to determine the acute effects produced by each compound on physiological

function and subjective effects. A slightly longer duration of administration of methamphetamine (2 min) versus cocaine (1 min) was selected to be conservative, as there was less experience administering methamphetamine intravenously in the human laboratory. Drug administration was performed using a single-blind design. The drugs were administered IV because smoking (generally the preferred route of administration) is associated with variable and incomplete bioavailability (Cook et al., 1993; Hatsukami et al., 1990).

2.3. Drugs

Cocaine HCl and D-methamphetamine solutions for human administration were obtained from a NIDA-contracted vendor. Solutions were diluted in sterile saline and administered using a syringe pump under the supervision of a physician. Saline was utilized as a placebo control.

2.4. Measures

Subjective effects were rated using visual analogue scales (VAS) ranging from 0 to 100 mm, where 0 was indexed as "no drug effect" and 100 as "most drug effect ever". Subjects provided ratings for the following adjectives: "High", "Stimulated", "Drug Effect", "Depressed" and "Anxious". Ratings were obtained at baseline (arbitrarily set at −15 min), 3, 6, 10, 15, 20, and 30 min following drug administration. Heart rate and blood pressure were assessed using an automatic monitoring system at baseline, 3, 6, 10, 20, 30, and 60 min following drug administration. The first 30 min of subjective effects data are presented because the effects produced by cocaine returned (on average) to baseline at that time. The presentation of cardiovascular data was truncated at 60 min because data collection for the cocaine group was stopped at that time.

2.5. Assurances

All procedures in the experimental protocol were approved by the UCLA Institutional Review Board for the use of human subjects in research and all procedures were in compliance with the Declaration of Helsinki for human subjects.

2.6. Data analysis

Data were analyzed with SPSS using a repeated measures analysis of variance (ANOVA). Time and group × time effects were then calculated using Huynh–Feldt sphericity correction. Variables showing significant time or time-× group effects were further analyzed using one-way ANOVAs for each time point. Because the analysis was intended to be primarily descriptive, there was no correction for multiple comparisons.

3. Results

3.1. Within-subjects effects

Significant effects were observed for *cocaine* compared to placebo for subjective effects ratings of "Any Drug Effect" ($p<.0001$ for time and $p<.0001$ for group × time), "High" ($p<.001$ for time and $p<.001$ for group × time), and "Stimulated" ($p<.005$ for time and $p<.004$ for group × time). Similar effects were observed for *methamphetamine* compared to placebo for "Any Drug Effect" ($p<.004$ for time and $p<.015$ for group × time), for "High" ($p<.001$ for time and $p<.006$ for group × time), and for "Stimulated" ($p<.002$ for time and $p<.012$ for group × time). Significant effects were observed for *cocaine* compared to placebo for the cardiovascular measures of Systolic blood pressure (BP) ($p<.0001$ for time and $p<.0001$ for group × time), Diastolic BP ($p<.0001$ for time and $p<.003$ for group × time) and for Heart Rate ($p<.0001$ for time and $p<.0001$ for group × time). Significant effects were observed for *methamphetamine* compared to placebo for the cardiovascular measures of Systolic BP ($p<.001$ for time and $p<.037$ for group × time), Diastolic BP (NS for time and $p<.002$ for group × time), and for Heart Rate ($p<.0001$ for time and $p<.0001$ for group × time).

3.2. Between-subjects effects

Significant between group differences in subjective effects were observed for "Any Drug Effect" ($p<.008$ for group and $p<.029$ for group × time), for "High" ($p<.002$ for group and $p<.0001$ for group × time) and for "Stimulated" ($p<.001$ for group and $p<.006$ for group × time). Significant between group differences in cardiovascular effects were observed for Systolic BP ($p<.0001$ for group and $p<.002$ for group × time), Diastolic BP ($p<.0001$ for group though $p=$NS for group × time), and for Heart Rate ($p<.0001$ for group and $p<.0001$ for group × time). The only difference between the groups for placebo was seen for heart rate, where there was a trend for time ($p<.095$) and a significant group × time effect ($p<.005$).

Follow-up ANOVAs evaluating differences between effects of cocaine and placebo or methamphetamine and placebo at each time-point are shown in Fig. 1A, B, and C for subjective effects and in Fig. 2A, B, and C for cardiovascular effects. The pattern of significant differences at each time point is indicated in the legend of Figs. 1 and 2. Overall, subjective effects of cocaine tended to peak and then decline more rapidly than those produced by methamphetamine. The subjective effects of methamphetamine tended to rise more slowly, and remain elevated longer. Cardiovascular effects of cocaine and methamphetamine had similar onset, but effects of cocaine tended to decline more rapidly.

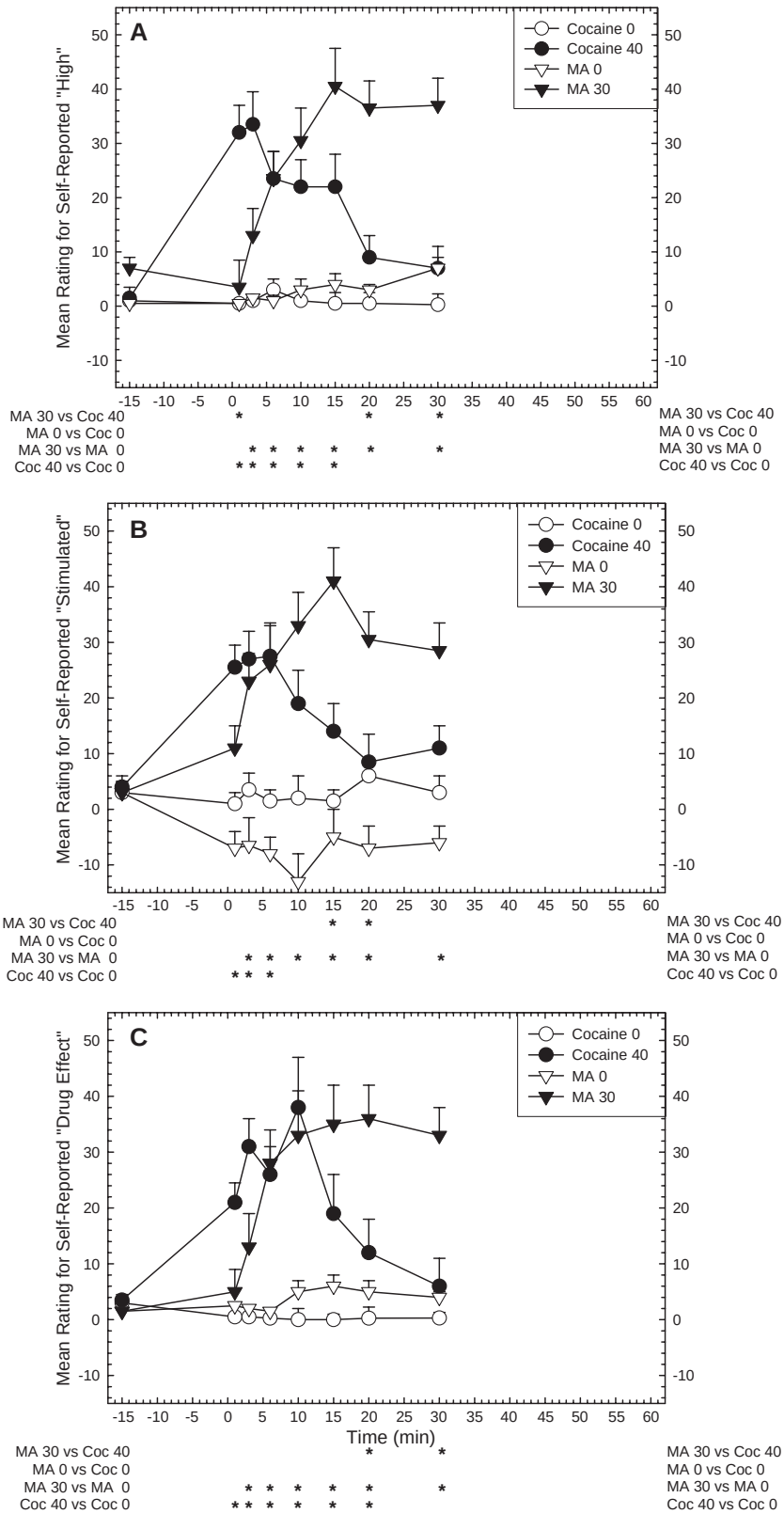

Fig. 1. (A) Mean ratings for self-reported “high”. All data in this and subsequent figure expressed as means ± standard error. For all comparisons, significance is denoted by * ($p<0.05$) as indicated in the table below each panel. (B) Mean ratings for self-reported “stimulated”. (C) Mean ratings for self-reported “drug effect”.

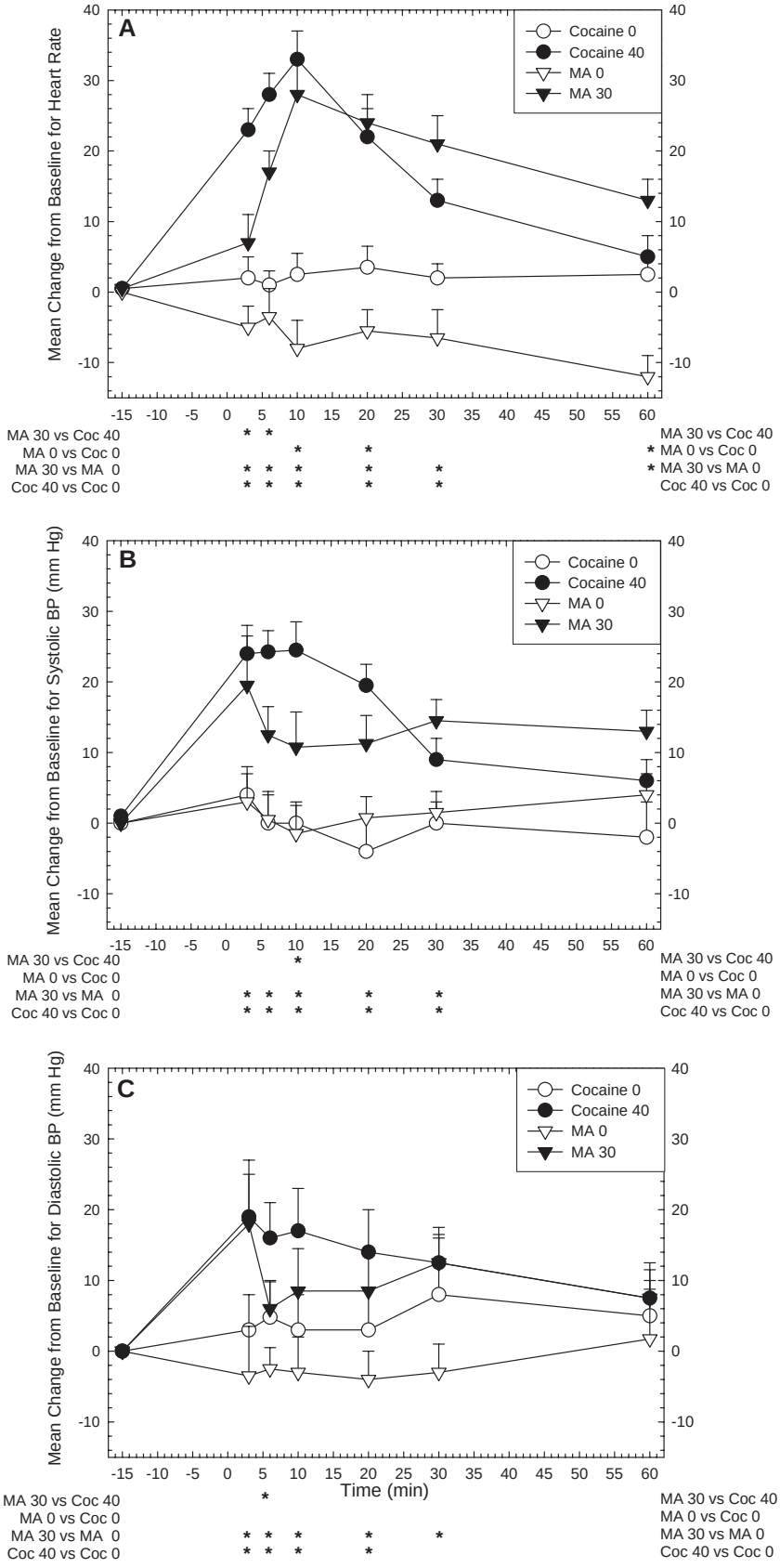

Fig. 2. (A) Mean change from baseline for heart rate. (B) Mean change from baseline for systolic blood pressure. (C) Mean change from baseline for diastolic blood pressure.

4. Discussion

The current report illustrates distinct patterns of subjective and cardiovascular changes in response to acute administration of cocaine versus methamphetamine. Characteristic stimulant effects (increases in ratings of "High" and related measures) peaked early following cocaine administration, and returned to baseline relatively quickly. Stimulant effects emerged more slowly following methamphetamine administration, and remained elevated throughout the 30-min period of observation. As reported previously (Newton et al., 2001; Wachtel et al., 2002), there were minimal effects of these stimulants on ratings of "Depressed" or "Anxious".

The cardiovascular changes produced by cocaine and methamphetamine emerged nearly in parallel, with peak effects occurring at 10 min. The changes to heart rate and blood pressure returned to baseline by 30 min following cocaine administration, whereas those produced by methamphetamine remained elevated at this time point. Continued clinical observation of the methamphetamine-dependent participants suggested that these subjective and cardiovascular effects persisted for several additional hours beyond the formal assessment period (data not shown). Cardiovascular responses following administration of placebo were also distinct in these groups, with methamphetamine-dependent participants exhibiting reduced heart rate over time in comparison to the responses observed in cocaine-dependent participants.

As a whole, the data presented correspond well with previous reports of cocaine- (Abreu et al., 2001; Foltin and Fischman, 1992; Mendelson et al., 2002; Preston et al., 1992, 1993; Schlaepfer et al., 1997; Volkow et al., 2000) or methamphetamine-induced cardiovascular and subjective effects (Drevets et al., 2001; Laruelle et al., 1995; Mendelson et al., 1995).

Differences in patterns of cardiovascular and subjective changes produced by cocaine as opposed to methamphetamine may contribute to distinct use patterns and addiction profiles associated with these stimulants. Although this has not been extensively documented, a preliminary report indicated that methamphetamine-dependent individuals use the drug on most days in a given month, and at spaced intervals throughout each of those days. By contrast, cocaine-dependent individuals have been characterized by intermittent use patterns, and more often engaging in binge use (Simon et al., 2002). The duration of action of methamphetamine (half-life ~11 h) as opposed to cocaine (half-life ~90 min) likely influences patterns of self-administration of these stimulants, such that dosing is either spaced throughout the day (methamphetamine) or is one of binging (cocaine).

Potential explanations for the differing temporal profiles of the cardiovascular and subjective effects produced by acute cocaine or methamphetamine administration in the current study include differences in rate of administration, differences in the rate of CNS penetration, differences in clearance, and differences in pharmacodynamics between the drugs. Differences in the rate of administration are unlikely to account for the unique profiles of subjective effects. In the current study, methamphetamine was administered over 2 min, whereas cocaine was administered over 1 min. This 1-min difference is a mere fraction of the 10 min difference observed in the onset of subjective effects, and is therefore unlikely to account for the distinct profiles exhibited. In another study, however, injection of cocaine over 2 s produced greater effects than injecting cocaine over 60 s (Abreu et al., 2001), so rate of administration cannot be conclusively ruled out as contributing to the profiles established in this report. Differences in the rate of brain entry could contribute to the more rapid effects produced by cocaine. Cocaine doses similar to those used here bound between 60% and 77% of striatal DAT sites, and the time course for "high" paralleled cocaine concentration within the striatum (Volkow et al., 1997). A PET study examining brain entry of the drug in which cocaine and methamphetamine users received both cocaine and methamphetamine would be very instructive in this regard. So far as we are aware, it has not been technically feasible to measure brain entry of methamphetamine in humans (presumably due to high, non-specific binding of labeled methamphetamine), so it cannot be determined if delayed brain entry contributes to the observed differences in the onset of subjective effects. Studies using non-human primates or rodents would be useful to clarify the role of the rate of brain entry for methamphetamine in producing behavioral effects.

Differences in clearance between cocaine and methamphetamine are unlikely to explain the rapid declines in subjective effect ratings observed following cocaine administration. First, the differences in rate of decline observed in subjective effect ratings appear larger that those observed for cardiovascular indices. Second, the period of observation described here, up to 30 min following administration for the subjective effects measures, is short compared to the elimination half-life of cocaine. Given a half-life of 90 min, the plasma cocaine concentration would be expected to be just under 80% of maximum at 30 min, so the rapid decline in self-rated "High" following cocaine administration is unlikely to be explained by this decrease in plasma concentration. Similar considerations apply to declines in the cardiovascular effects produced by methamphetamine. It is, therefore, more likely that differing pharmacodynamics, rather than differing pharmacokinetics, accounts for the observed differences in subjective and cardiovascular effects between cocaine and methamphetamine.

Potential pharmacodynamic differences between cocaine and methamphetamine include differing mechanisms by which these drugs enhance dopaminergic neurotransmission, and also their potential to produce long-term synaptic changes that result in altered signal transduction. As noted, methamphetamine facilitates the release of DA, NE, and serotonin (5-HT) through the process of carrier-mediated

exchange, thus increasing extracellular levels of these neurotransmitters (Rudnick and Clark, 1993). Administration of neurotoxic doses of methamphetamine to rats and non-human primates has been shown to produce relatively rapid (within 2 weeks) and significant (over 70%) reductions in DAT availability (Melega et al., 2000; Ricaurte et al., 1980; Villemagne et al., 1998; Woolverton et al., 1989). These changes are greater in ventral striatum as opposed to dorsal striatum, which may explain why motor function is spared. Significant, but less marked, reductions have been reported in humans with methamphetamine dependence (McCann et al., 1998; Sekine et al., 2001; Volkow et al., 2001b,c), but not in those with cocaine dependence (Volkow et al., 1996). Thus, if a reduction in DAT availability results in slowed carrier-mediated release of stored monoamines, the effects produced by methamphetamine may be delayed for these individuals. This discussion extends to specific receptors for DA, including data illustrating lower levels of DA D_2 receptors in methamphetamine (Volkow et al., 2001a) and cocaine users (Volkow et al., 1993). Less is known about the effects of chronic stimulant treatment on NE and 5-HT systems in humans, though preclinical data suggest that cocaine and methamphetamine administration are each associated with unique pharmacodynamic effects on these neurotransmitter systems (Kuczenski et al., 1997; Kuczenski and Segal, 1999).

Reductions in second messenger systems may account for some of the differences observed between the two stimulants. For example, selective reductions of DA and $G_{\alpha i}$ and $G_{\alpha o}$ proteins within the nucleus accumbens have been reported in methamphetamine users, but not cocaine users (McLeman et al., 2000; Wilson et al., 1996).

Methamphetamine and cocaine produce opposite effects on the vesicular monoamine transporter (VMAT), with methamphetamine producing rapid reductions in VMAT activity (Sandoval et al., 2003) and cocaine producing rapid increases in VMAT activity (Brown et al., 2001). As such, slower sequestration of monoamines could account, in part, for the prolonged effects produced by methamphetamine, as compared to cocaine.

The time-courses for cocaine-induced subjective and cardiovascular effects differed considerably from those produced by methamphetamine. According to published data, these stimulants act similarly in both the central and peripheral nervous systems, so the reported differences are difficult to interpret. In addition, there is substantial evidence that the cardiovascular effects produced by stimulants are primarily due to central actions of the drugs (Vongpatanasin et al., 1999). One possible explanation for delayed subjective effects of methamphetamine may be that regionally specific changes in DAT occurred in brain regions (i.e., ventral striatum) involved in mediating subjective effects (Drevets et al., 2001; Melega et al., 2000; Ricaurte et al., 1980; Villemagne et al., 1998; Woolverton et al., 1989), but did not affect regions involved in sympathetic control, though this remains to be confirmed.

While the findings presented in this report reveal important temporal differences for the cardiovascular and subjective effects produced by cocaine versus methamphetamine, some important limitations should be noted. Foremost, while the procedures for cocaine and methamphetamine testing were similar, they were not identical. An ideal design may be a randomized, double-blind, within-subjects crossover study assessing a range of doses of each drug under identical procedures. This design, however, would be confounded by drug-specific neuroadaptations present in each group. In this study, we emphasized evaluation of the effects of acute stimulant administration, and concede that additional research is required to explore changes produced by chronic or binge dosing.

In conclusion, this study demonstrates that there are notable differences in the onset, pattern, and duration of subjective and cardiovascular responses following cocaine or methamphetamine administration in the laboratory. These differences may relate to the effects produced by chronic methamphetamine on the DAT, which have been previously documented. The differences in change over time in stimulant-induced subjective effects may contribute to previously described differences in use patterns between methamphetamine- or cocaine-addicted patients seeking treatment (Rawson et al., 2000; Simon et al., 2002). As mentioned above, methamphetamine addicts report using the drug daily (or nearly every day) throughout each day, whereas cocaine users typically engage in binges, occurring most often in the evening (Wilkins et al., 2004). The distinct patterns of use, coupled with differences in pharmacokinetics and pharmacodynamics, have implications for the development of pre-clinical models for the study stimulant dependence (Cho and Melega, 2002; Cho et al., 2001). Moreover, these considerations may impact the development of medication treatments for these two very different stimulants.

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