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Intravenous (+)-methamphetamine causes complex dose-dependent physiologic changes in awake rats

Harendra Arora [a], S. Michael Owens [b,*], W. Brooks Gentry [a,b]

[a] *Department of Anesthesiology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA*
[b] *Department of Pharmacology and Toxicology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA*

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Abstract

Hemodynamic and temperature dose–response relationships were characterized in freely moving rats following i.v. (+)-methamphetamine administration to mimic the rapid onset of effects experienced by many human users. Rats received saline and (+)-methamphetamine in a repeated-measures, mixed-sequence design at 22 ± 1 °C. Significantly greater blood pressure and heart rate elevations were observed after 1.0 and 3.0 mg/kg (+)-methamphetamine vs. 0.1 and 0.3 mg/kg. The time to peak hemodynamic values and the duration of effects were significantly greater after 3.0 mg/kg vs. the lower doses. The time to peak temperatures was significantly longer after 1.0 mg/kg vs. the lower doses. Following 3.0 mg/kg, all rats experienced temperature decreases before having elevated temperatures. The duration and magnitude of the delayed temperature elevations were significantly greater after 3.0 mg/kg vs. the lower doses. In conclusion, the (+)-methamphetamine-induced hemodynamic and temperature effects were not temporally synchronized, and the complex responses were not linearly related to dose.

Keywords: Hemodynamics; (Intravenous dosing); Methamphetamine; Radiotelemetry; (Rat); Temperature

1. Introduction

As many as 90% of (+)-methamphetamine users prefer to self-administer the drug by one or more of the rapid routes of administration, i.v. injection, smoking or intranasal ingestion (snorting), because these routes of administration result in rapidly occurring effects (Domier et al., 2000). The perceived rapid increases in energy, euphoria and heightened awareness result in a profound "rush" that appears to play a major role in the reinforcing effects of the drug (Cook et al., 1993). Unfortunately, these effects are frequently accompanied by detrimental side effects such as hypertension, tachycardia (Albertson et al., 1999; Richards et al., 1999) and hyperthermia (Callaway and Clark, 1994), which too often necessitate emergency medical treatment (Buchanan and Brown, 1988; Lan et al., 1998; Perez et al., 1999).

While reported total doses associated with these clinically detrimental effects are as high as 2.5–15 g/day (Cho, 1990; Hong et al., 1991), most chronic users appear to prefer individual i.v. doses as low as 10–50 mg (i.e., 0.1–0.8 mg/kg in a 70-kg person) (Beebe and Walley, 1995; Cho, 1990). These low doses are important because controlled human studies have shown that i.v. (+)-methamphetamine doses as small as 30 mg can result in significant elevations in heart rate and blood pressure (Mendelson et al., 1995). Nevertheless, a clear understanding of the dose–response relationships associated with these symptoms is difficult to determine because controlled human studies of doses high enough to produce serious symptoms are not possible due to the risk of addiction and potential for adverse side effects and neurotoxicity (Fumagalli et al., 1998). Thus, animal models of i.v. (+)-methamphetamine dose–response relationships for hemodynamic and temperature effects are needed.

A previous study has investigated dose–hemodynamic response relationships of i.v. (+)-methamphetamine in squirrel monkeys using a range of doses that mimic those used by humans (0.1–3.0 mg/kg) (Schindler et al., 1992). In this study, the authors report that the magnitude and time course of (+)-methamphetamine-induced blood pres-

* Corresponding authors. S.M. Owens is to be contacted at Tel.: +1-501-686-5487; fax: +1-501-686-5521. W. Brooks Gentry, Department of Anaesthesiology, University of Arkansas for Medical Sciences, 4301 West Markham St., Slot 515, Little Rock, AR 72205, USA. Tel.: +1-501-686-7611; fax: +1-501-603-1951.

E-mail addresses: owenssamuelm@uams.edu (S.M. Owens), gentrywilliamb@uams.edu (W. Brooks Gentry).

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sure responses increase with increasing dose. However, while increases in heart rate are observed following low (e.g., 0.2 mg/kg) i.v. doses, higher doses (1–2 mg/kg) result in decreases in heart rate values. Thus, this primate study shows that hemodynamic responses to i.v. administration of (+)-methamphetamine are complex, and that a range of relevant doses should be studied to fully characterize its effects.

Similar dose–response studies of the effects of i.v. (+)-methamphetamine on body temperature have not been reported to our knowledge. However, available studies on the temperature effects of (+)-methamphetamine administered via the i.p. route show that the dose–temperature response relationships are also complex. For example, Bowyer et al. (1992) show elevations in body temperature when rats receive (+)-methamphetamine (5 mg/kg, i.p. every 4 h for four doses) at an ambient temperature of 23 °C, but decreases in body temperature when given at an ambient temperature of 4 °C. Although data such as these are helpful in understanding the complex effects of (+)-methamphetamine, the i.p. route in rats should not be assumed to be a good model for the preferred human routes of administration (i.v., smoking, intranasal), which avoid first-pass hepatic metabolism. This is especially important since a principle metabolite of (+)-methamphetamine is (+)-amphetamine, which is also pharmacologically active.

The goal of our studies was to characterize hemodynamic and temperature dose–response relationships of i.v. (+)-methamphetamine in freely moving rats. Our hypothesis was that these relationships are complex, and not readily predictable based on dose. We used i.v. doses in these studies to mimic the rapid onset of drug effects experienced by humans who use rapid routes of administration. In addition, since restraint and environmental stress alter hemodynamic and temperature responses to a variety of stimuli (Irvine et al., 1997; Schnell and Wood, 1993), we used freely moving animals to allow for more realistic characterization of the actual (+)-methamphetamine-induced changes in heart rate, blood pressure and temperature without stress-inducing handling and restraint of the animals. Using radiotelemetry devices, we were able to continuously measure the physiologic parameters heart rate, blood pressure and peritoneal temperature over a 30-fold range of (+)-methamphetamine doses.

2. Methods

2.1. Animals

Adult male Sprague–Dawley rats with an indwelling jugular venous cannula (Dow Corning silastic tubing, 0.020″ inside diameter; 0.037″ outside diameter) in the right external jugular vein were purchased from Hilltop Laboratory Animals (Scottsdale, PA). Each animal was fed a controlled diet to maintain its body weight at approximately 300 g, and maintained in an animal care facility with a 12 h light/dark cycle (7:00 a.m.–7:00 p.m.). All animal experiments were carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health, and the University of Arkansas for Medical Sciences Institutional Animal Care and Use Committee.

2.2. Monitoring system and implantation of radiotransmitters

The Dataquest ART System 1.10 (Data Sciences International, St. Paul, MN) was used to collect the hemodynamic and temperature data. The T11CXT P50 transmitters used for these studies are capable of continuously measuring arterial blood pressure, heart rate, and peritoneal temperature in freely moving rats by telemetry. Radiotransmitter implantation was performed as outlined in literature available from Data Sciences International (http://www.datasci.com/index.html) and in a previous study by Brockway et al. (1991).

2.3. Animal protocol for (+)-methamphetamine dose–response studies

The experiments were carried out in open-top polyethylene chambers ($60 \times 45 \times 40$ cm; l × w × h) which provided adequate room for free movement. Each chamber was used for only one rat for the duration of the experiment to increase familiarity with the environment and reduce extraneous stimulating odors. The rats were placed in the chambers every day for approximately 6 h for the duration of the experiments.

On each study day, the rats were placed in the chambers at least 2 h prior to saline or (+)-methamphetamine administration for acclimatization. Investigators entered the study room (ambient temperature 22 ± 1 °C) during each study only to place the animals in the study chambers and to give the (+)-methamphetamine or saline injections since hemodynamic responses in rats as measured by telemetry are sensitive to environmental stimuli (Schnell and Wood, 1993). Each animal received saline and four doses of (+)-methamphetamine (0.1, 0.3, 1.0 and 3.0 mg/kg, i.v.) in a randomized, mixed sequence design. The animals were allowed 72–96 h to recover between treatments. The physiologic parameters heart rate, systolic and diastolic blood pressures, and temperature were recorded every 10 s and averaged over consecutive 2-min intervals. At time 0 (approximately 10:00 a.m. in every study), saline or (+)-methamphetamine was injected i.v. in a single 10-s rapid infusion followed by 0.2 ml of saline to flush the catheter. Data for saline- or (+)-methamphetamine-induced effects were collected for 6 h.

2.4. Data analysis

The peak measured value for each physiologic parameter, the time at which this value occurred, and the duration of effect for each (+)-methamphetamine dose in each rat was recorded to characterize the effect vs. time relationships. For elevations in heart rate, blood pressure and temperature, the duration of effect was defined as the time from drug administration until the first of two consecutive 2-min intervals in which the effect was less than the mean + 1 S.D. of the baseline value (Hardin et al., 1998). For decreases in temperature, the duration of effect was defined as the time from drug administration until the first of two consecutive 2-min intervals in which the temperature exceeded the mean − 1 S.D. of the baseline value. The baseline value for each physiologic parameter in each rat at each dose was defined as the average value for the 30-min time period from $t = -40$ min to $t = -10$ min.

All values are reported as the mean ± S.D. All statistical analyses were conducted using SigmaStat v. 2.01 (Jandel Scientific, San Rafael, CA). A one-way repeated-measures analysis of variance was used to quantify differences among the groups. If tests for normality failed, a Friedman repeated measures analysis of variance on ranks was used. Student–Neuman–Keuls post-hoc testing was used to compare differences among groups receiving different doses of (+)-methamphetamine. Statistical significance was considered to be achieved at a level of $P < 0.05$.

3. Results

3.1. General experimental observations

All rats ($n = 9$) tolerated the radiotransmitter implantations and appeared to be fully recovered within 3–4 days, but were allowed 7–10 days before starting (+)-methamphetamine injections to ensure full recovery. The baseline values for all pharmacologic parameters were within the range of published normal values for rats (Spector, 1956), and they were consistent within and between animals prior to each (+)-methamphetamine dose for the duration of the studies. The average baseline heart rate was 351 ± 37 beats/min, the average systolic and diastolic blood pressures were 124 ± 8 and 95 ± 8 mm Hg, respectively, and the average baseline temperature was 38.4 ± 0.4 °C. Because the radiotransmitters provided consistent measurements over the 2–3-week period of each study, the animals could be used as their own controls.

In preliminary experiments, we observed a period of stabilization (i.e., slow, steady decrease in values after i.v. injection of saline) of the physiologic parameters that lasted approximately 100 min for the hemodynamic effects and continued throughout the experiments for the temperature effects (Figs. 1–3). We continued to measure each animal's hemodynamics and temperature on non-study days between each (+)-methamphetamine dose and did not observe any changes in these stabilization periods from day to day (data not shown). Although these effects could have been influenced by factors such as handling during injection or circadian rhythms, the exact mechanisms are unclear. Consequently, we used a simple mathematical correction to allow a clearer picture of the (+)-methamphetamine-induced effects to emerge. This was accomplished by subtracting the physiologic parameter value at each 2-min time point in the saline treatment from the value obtained at the corresponding 2-min time point with each (+)-methamphetamine dose. This additional analysis allowed us to better characterize the physiologic effects of (+)-methamphetamine over time because maximum differences between (+)-methamphetamine and saline values did not always reflect the peak measured value for physiologic parameter, and they did not always occur at the time of the peak measured value.

3.2. Hemodynamic measurements

The onset of hemodynamic effects occurred immediately after (+)-methamphetamine injection, but the time course of effects varied with dose. The times to peak heart rate values were significantly longer following 3.0 and 1.0 mg/kg (+)-methamphetamine (at 100 and 49 min, respectively) than the lower doses and saline (Fig. 1). The times to maximum heart rate differences from saline were signif-

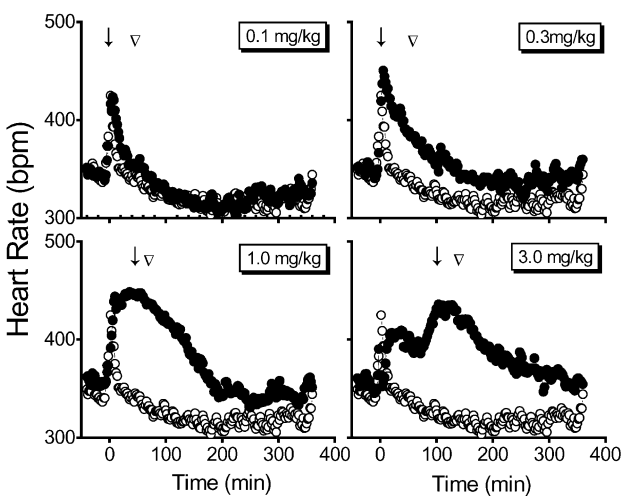

Fig. 1. Average heart rate responses of the rats ($n = 9$) to saline and four increasing i.v. doses of (+)-methamphetamine over a 360 min (6 h) period. S.D. values are not shown to avoid cluttering the graphs. Saline or (+)-methamphetamine was injected at time $t = 0$ in all rats. The (+)-methamphetamine dose is noted in the right upper corner of each panel. The responses to (+)-methamphetamine are shown as closed circles (●) and to saline as open circles (○). The down arrow (↓) shows the time of peak measured value and the down triangle (▽) shows the time of maximum difference from saline values. Note the apparent biphasic effects of the 3.0 mg/kg (+)-methamphetamine dose.

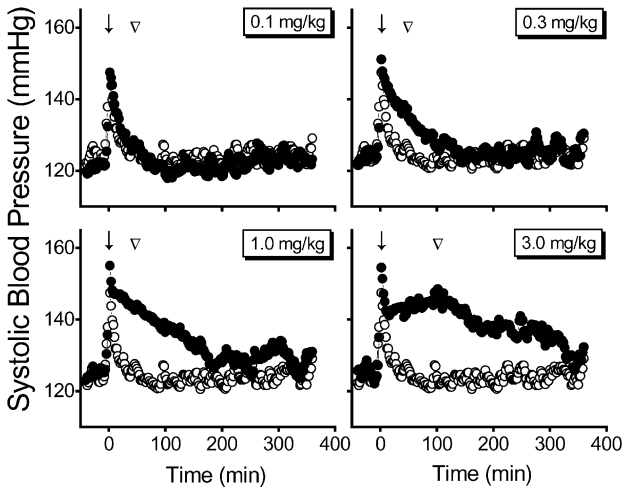

Fig. 2. Average systolic blood pressure responses of the rats ($n = 9$) to saline and four increasing i.v. doses of (+)-methamphetamine over a 360 min (6 h) period. S.D. values are not shown to avoid cluttering the graphs. Saline or (+)-methamphetamine was injected at time $t = 0$ in all rats. The (+)-methamphetamine dose is noted in the right upper corner of each panel. The responses to (+)-methamphetamine are shown as closed circles (●) and to saline as open circles (○). The down arrow (↓) shows the time of peak measured value and the down triangle (▽) shows the time of maximum difference from saline values.

icantly longer following 3.0 mg/kg (+)-methamphetamine at 132 min than the lower doses. In addition, the effect vs. time curve for heart rate was different after 3.0 mg/kg than after 1.0 mg/kg. The effect vs. time curve after 3.0 mg/kg was biphasic, with two distinct peaks occurring at approximately 38 min (53 beats/min above baseline) and 147 min (146 beats/min above baseline) (Fig. 1). While the times to peak diastolic and systolic blood pressure values did not differ among the doses, the time of maximum difference from saline was significantly greater after 3.0 mg/kg (+)-methamphetamine than after the lower doses (at 121 and 99 min for diastolic and systolic blood pressures, respectively; Fig. 2).

The magnitudes of peak heart rate values were not different among the doses, but the peak values for systolic and diastolic blood pressures were significantly greater after 1.0 mg/kg than after 0.1 mg/kg (+)-methamphetamine and saline (Table 1). In addition, the magnitude of peak systolic blood pressure was significantly greater after 3.0 mg/kg (+)-methamphetamine than after 0.1 mg/kg and saline. The magnitudes of maximum differences from saline for all other hemodynamic parameters were significantly greater after 3.0 and 1.0 mg/kg (+)-methamphetamine than after 0.3 and 0.1 mg/kg, but the magnitudes of differences were not different for 3.0 and 1.0 mg/kg.

The duration of hemodynamic effect was significantly longer after 3.0 mg/kg (+)-methamphetamine than after all lower doses (Figs. 1 and 2). The heart rate remained elevated for an average of 275 min, while the diastolic and systolic blood pressures were elevated for 224 and 222 min, respectively, after 3.0 mg/kg (+)-methamphetamine. Heart rate effects were significantly longer after 1.0 mg/kg (+)-methamphetamine (at 184 min) than after 0.3 and 0.1 mg/kg (+)-methamphetamine (at 91 and 33 min, respectively). However, blood pressure effects were significantly longer only after 1.0 mg/kg (+)-methamphetamine (at 95 min for diastolic blood pressure and 129 min for systolic blood pressure) than after 0.1 mg/kg (+)-methamphetamine (at 24 and 38 min for diastolic and systolic blood pressures, respectively).

3.3. Temperature

The onset of (+)-methamphetamine-induced temperature effects also occurred immediately after injection, with temperature elevations following 1.0, 0.3 and 0.1 mg/kg (+)-methamphetamine (Fig. 3). The peak temperature value occurred significantly longer after 3.0 mg/kg (+)-methamphetamine (at 222 min after dosing) than after all lower doses and saline, but the times of peak values were not different for the three lower doses and saline. The highest peak temperature value occurred following 0.3 mg/kg (+)-methamphetamine (39.2 ± 0.2 °C), but the

Table 1
Magnitude of (+)-methamphetamine-induced hemodynamic and temperature effects in the rat[a]

Magnitude of effect	(+)-Methamphetamine dose (mg/kg)			
	0.1	0.3	1.0	3.0
Heart rate (beats/min)	440 ± 47 (66 ± 35.9)	462 ± 39 (98.2 ± 43.9[d])	464 ± 48 (140.1 ± 46.2[c])	457 ± 55 (146.3 ± 45.3[c])
Diastolic blood pressure (mm Hg)	112 ± 9 (9.3 ± 4.9)	117 ± 10 (14.6 ± 8.4)	119 ± 10[d] (18.7 ± 6[d])	116 ± 12 (23.4 ± 12.5[c])
Systolic blood pressure (mm Hg)	148 ± 11 (12.1 ± 7.3)	153 ± 11 (18.9 ± 7.6[d])	159 ± 11[d] (26.8 ± 7.3[c])	158 ± 12 (32.3 ± 11.3[c])
Temperature increase (°C)	38.9 ± 0.3 (0.4 ± 0.4)	39.2 ± 0.4 (0.8 ± 0.6)	38.9 ± 0.2 (1 ± 0.7[d])	38.8 ± 0.4 (1.3 ± 0.5[b])
Temperature decrease (°C)[e]				37.5 ± 0.2 (-1.3 ± 0.5)

[a] Peak values are shown with the maximum differences between (+)-methamphetamine and saline values in parentheses.
[b] $P < 0.05$ vs. 0.1, 0.3 and 1.0 mg/kg.
[c] $P < 0.05$ vs. 0.1 and 0.3 mg/kg.
[d] $P < 0.05$ vs. 0.1 mg/kg.
[e] The only observed temperature decrease occurred following the 3.0 mg/kg (+)-methamphetamine dose (see Fig. 3 for graphical representation of these data).

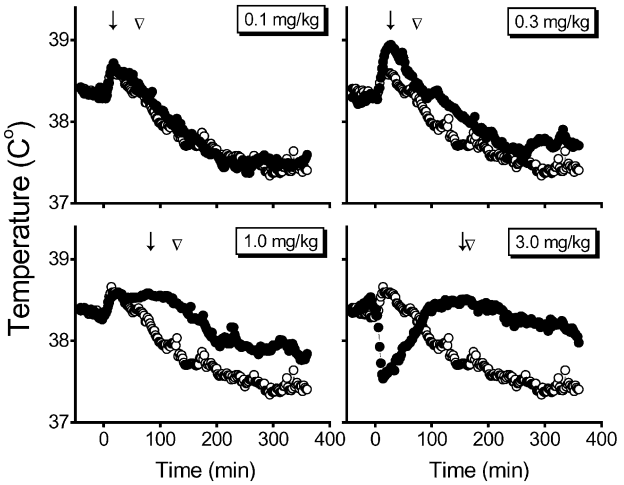

Fig. 3. Average temperature responses of the rats ($n = 9$) to saline and four increasing i.v. doses of (+)-methamphetamine over a 360 min (6 h) period. S.D. values are not shown to avoid cluttering the graphs. Saline or (+)-methamphetamine was injected at time $t = 0$ in all rats. The (+)-methamphetamine dose is noted in the right upper corner of each panel. The responses to (+)-methamphetamine are shown as closed circles (●) and to saline as open circles (○). The down arrow (↓) shows the time of peak measured value and the down triangle (▽) shows the time of maximum difference from saline values.

greatest maximum difference from saline occurred following 3.0 mg/kg (+)-methamphetamine (1.3 ± 0.5 °C). Both values were significantly higher than following all other doses. The maximum difference from saline was significantly greater after 1.0 mg/kg (+)-methamphetamine (1 ± 0.7 °C) than after 0.1 mg/kg.

Following 3.0 mg/kg, all rats experienced substantial temperature decreases before they experienced elevated temperatures (Fig. 3). The time to the temperature nadir was approximately 20 min after 3.0 mg/kg (+)-methamphetamine and the lowest temperature attained was 1.3 ± 0.5 °C below the saline baseline (Table 1). The durations of decreased and increased temperatures after 3.0 mg/kg were 65 and 282 min, respectively.

Comparison of the different temperature effect vs. time curves with increasing doses revealed changes from dose to dose that have not been reported previously (Fig. 3). Following 0.3 mg/kg, the temperature increased quickly above the saline values to peak at an average of 39.2 °C about 30 min after the injection. This effect was transient and the temperature quickly decreased to approximate the saline values for the duration of the study. Following 1.0 mg/kg, the average temperature increased immediately after the injection. Instead of decreasing immediately after peaking (as occurred after 0.3 mg/kg), the temperature remained above the saline values at a plateau for approximately 150 min after injection. Thereafter, the temperature decreased in parallel to the saline baseline, but remained above the saline values for the remainder of the study. Finally, following 3.0 mg/kg, the temperature decreased immediately after the injection to a nadir of 37.5 °C, which was the equal to the lowest measured temperature in any group. Thereafter, the temperature rose over approximately 2 h, and remained elevated for the duration of the study.

4. Discussion

This study characterized the hemodynamic and temperature dose–response relationships over a 30-fold range of i.v. (+)-methamphetamine doses in freely moving animals using radiotelemetry technology. (+)-Methamphetamine produced dose-dependent hemodynamic and temperature effects. However, the lowest dose (0.1 mg/kg) produced only minimal hemodynamic effects and no apparent temperature effects (Figs. 1–3). While the onset of (+)-methamphetamine-induced hemodynamic effects was immediate following all pharmacologically active doses, the effect vs. time relationship changed qualitatively as well as quantitatively with increasing (+)-methamphetamine doses.

At least one previous study has characterized the dose-dependent effects of i.v. (+)-methamphetamine using the same doses as the current study in an animal model. In a study using squirrel monkeys, Schindler et al. (1992) showed a rapid onset of similar blood pressure elevations to those observed in the current study. In addition, the relative magnitude of blood pressure elevations was similar in both studies at the higher (e.g., 3.0 and 1.0 mg/kg) doses. Finally, both studies also showed more complex heart rate changes with increasing (+)-methamphetamine dose. Following 1.0 mg/kg (+)-methamphetamine, the rats and monkeys demonstrated a slow rise in heart rate to peak at approximately 50 min. Following 3.0 mg/kg, the heart rate effect vs. time curve after the 3.0 mg/kg dose was different (Fig. 1). The heart rate effect vs. time curve was biphasic in the rats and monkeys after 3.0 mg/kg, with two distinct peaks in both, but the peaks occurred earlier in the monkeys than in the rats. However, while both studies showed similar curve shapes following 3.0 and 1.0 mg/kg (+)-methamphetamine, the heart rate decreased significantly in monkeys immediately after injection.

Peripheral hemodynamic effects of (+)-methamphetamine are due to a complex interplay of α_1-adrenergic, β_1-adrenergic and dopaminergic stimulation. Schindler et al. (1992) demonstrated in their previous study that α_1-adrenoceptors play a substantial role in hypertensive effects and that β_1-adrenoceptors play a substantial role in tachycardic effects. In addition, α_1-adrenoceptor-mediated effects tend to predominate over β_1-adrenoceptor-mediated effects as doses increase. Thus, the early relative bradycardia in rats and absolute bradycardia in monkeys after 3.0 mg/kg (compared to 1.0 mg/kg, Fig. 1) could be associated with a relative predominance of α_1-adrenoceptor stimulation at 3.0 mg/kg. Species differ-

ences in rats and monkeys likely accounted for the absolute differences in heart rate. It appears that monkeys may be more sensitive to the effects of (+)-methamphetamine. Indeed, Schindler et al. (1992) state that their monkeys did not tolerate the 3.0 mg/kg dose of (+)-methamphetamine well. This dose was given to only three subjects in their investigation, whereas eight subjects received all other doses. In contrast, we did not observe any apparent toxic effects in the rats at 3.0 mg/kg. Indeed, in previous studies (unpublished data) we do not see toxic effects until doses reach 5.6 mg/kg. At this dose, rats begin to self-mutilate.

The duration of (+)-methamphetamine-induced heart rate and temperature effects was consistent with the duration of (+)-methamphetamine-induced increases in locomotor activity we observed previously (Riviere et al., 1999). (+)-Methamphetamine doses of 0.3 and 1.0 mg/kg (i.v.) resulted in increased locomotor activity that lasted 100 and 175 min, respectively. However, the time to peak spontaneous locomotor effects occurs sooner after these doses (Riviere et al., 1999) than the peak hemodynamic effects observed in the current study. For instance, peak locomotor effects occur 6–14 min after 0.3 mg/kg and 28–34 min after 1.0 mg/kg (Riviere et al., 1999). Peak heart rate effects occurred at 37 and 67 min, respectively, following these doses and peak temperature effects occurred at 31 and 98 min in the current study. The most likely cause of increased hemodynamic and temperature effects following (+)-methamphetamine administration is increased energy utilization due to CV and CNS stimulation. Previous studies in freely moving rats show that oxygen consumption (an index of metabolism) doubles by 10–15 min after an i.p. dose of 1.0 mg/kg (+)-methamphetamine (Makisumi et al., 1998). Thus, it appears that increases in metabolism and locomotor activity (found in previous studies) precede and contribute to the observed increases in hemodynamics and temperature found in the current study.

At least one study has evaluated hemodynamic and temperature responses in freely moving rats after a single 1.0 mg/kg i.p. dose of (+)-methamphetamine (Yoshida et al., 1993). Their values for peak heart rate and blood pressure responses were similar to our findings at 1.0 mg/kg. However, this previous study reports peritoneal temperatures increase as much as 1.6 °C following a 1.0 mg/kg dose (vs. 1 °C in the current study after 1.0 mg/kg).

One possible reason for the lower observed temperature in the current study than in the previous study (Yoshida et al., 1993) after 1.0 mg/kg (+)-methamphetamine is the environmental temperature. The previous study (Yoshida et al., 1993) was performed at an environmental temperature of 26 °C. This is important because (+)-methamphetamine-induced changes in body temperature are altered by environmental temperatures. In a study of the effect of environmental temperature on (+)-methamphetamine-induced changes in body temperature and neurotoxicity, Bowyer et al. (1992) measured rectal temperature in rats with a digital thermometer every 30 min after administration of (+)-methamphetamine (5 mg/kg, i.p. every 4 h for four doses). Their results show rectal temperature decreases 2–4 °C over 2–3 h at an environmental temperature of 4 °C. When they administered the same (+)-methamphetamine doses at an ambient temperature of 23 °C, body temperature changed very little for the first 1.5 h and then increased 2–4 °C.

While the environmental temperatures in the current study (22 °C), the Bowyer study (23 °C) and the Yoshida study (26 °C) do not appear to be substantially different, these differences may have profound effect on the body temperature response to (+)-methamphetamine. Previous studies of the substituted amphetamine, (±)3,4-methylenedioxymethamphetamine, show small changes in environmental temperature result in profound differences in body temperature (Malberg and Seiden, 1998). In this previous study, freely moving rats were given (±)3,4-methylenedioxymethamphetamine (20 or 40 mg/kg, i.p.) at environmental temperatures ranging from 20 to 30 °C. These authors report that (±)3,4-methylenedioxymethamphetamine administered at environmental temperatures of 20 and 22 °C results in decreases in body temperature, while (±)3,4-methylenedioxymethamphetamine administered at 28 and 30 °C results in increases in body temperature. Malberg and Seiden (1998) and Bowyer et al. (1992) suggest that high stimulant doses interfere with the ability of the animals to autoregulate body temperature, and that the temperature response is therefore significantly altered by environmental temperature. Thus, the environmental temperature in the current study (22 °C) may be low enough to result in the observed decreases in body temperature following the highest dose of (+)-methamphetamine.

Another important difference between the current study and the previous studies of (+)-methamphetamine effects (Bowyer et al., 1992; Malberg and Seiden, 1998; Yoshida et al., 1993), which could have contributed to the observed temperature differences, is route of administration. It is likely that the time course and concentrations of pharmacologically active metabolites ((+)-methamphetamine and (+)-amphetamine) is different following i.v. and i.p. administration (Yamada et al., 1986). While it is unclear how relative concentrations of active-to-inactive drugs contribute to the observed temperature responses, different concentration histories produced by the different routes of administration may have contributed to some of the apparent differences among these studies. In addition, we recognize that even the i.v. route has weaknesses in terms of metabolic and pharmacokinetic comparisons with humans. For instance, Riviere et al. (2000) have shown that after 1.0 mg/kg i.v. administration of (+)-methamphetamine to rats, 30% of the dose in tissues (e.g., serum and brain) is (+)-amphetamine, a pharmacologically active metabolite. In humans, amphetamine is a much less significant me-

tabolite, since less than 10% of the dose in serum is due to amphetamine (Cook et al., 1993). Nevertheless, because parenteral administration is used so extensively by humans, we think the i.v. route is the most appropriate for animal studies of rapidly occurring (+)-methamphetamine effects.

In conclusion, our studies demonstrated dose-dependent effects of i.v. (+)-methamphetamine on hemodynamic and temperature responses. The duration, magnitude and time to peak effects were dependent on dose. The resulting effect vs. time curves were complex and not entirely predictable based on the increased doses. That is, increasing doses did not result in linear increases in heart rate, blood pressure and temperature. Although these and other studies show there are strengths and weaknesses in the use a rat model of human drug use, we think the magnitude, duration and complexity of (+)-methamphetamine-induced effects in the rat will be useful for assessing future medications for the treatment of (+)-methamphetamine-induced hemodynamic and temperature effects, especially since these experiments cannot be safely performed in humans.

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