Pharmacology Biochemistry and Behavior, Vol. 42, pp. 791-796, 1992

0091-3057/92 $5.00 + .00

Pharmacological Mechanisms in the Cardiovascular Effects of Methamphetamine in Conscious Squirrel Monkeys

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Received 8 January 1992

SCHINDLER, C. W., J.-W. ZHENG, S. R. TELLA AND S. R. GOLDBERG. *Pharmacological mechanisms in the cardiovascular effects of methamphetamine in conscious squirrel monkeys.* PHARMACOL BIOCHEM BEHAV 42(4) 791-796, 1992. – The effects of methamphetamine were studied on cardiovascular function in conscious squirrel monkeys. Methamphetamine (0.1-3.0 mg/kg,IV) produced a dose-dependent increase in blood pressure. Its effects on heart rate were more complex, with lower doses (0.1-0.3 mg/kg) producing increases in heart rate and higher doses (1.0-3.0 mg/kg) producing decreases. To determine the pharmacological mechanisms involved in methamphetamine's effects, a number of drugs were tested as pretreatments to an injection of 0.2 mg/kg methamphetamine. This dose produced the maximal heart rate increase. The α_1-antagonist prazosin completely antagonized the effects of methamphetamine on blood pressure, while the nonselective β-antagonist propranolol and β_1-selective antagonist atenolol completely antagonized the tachycardiac effect of methamphetamine. The dopaminergic antagonists SCH 23390 and haloperidol antagonized some of the cardiovascular effects of methamphetamine. These results indicate that the pressor and tachycardiac effects of methamphetamine are mediated via α_1- and β_1-adrenoceptor mechanisms, respectively. Dopaminergic mechanisms are also involved in methamphetamine's cardiovascular effects.

Methamphetamine Cardiovascular effects α-Adrenoceptors β-Adrenoceptors Dopamine receptors Squirrel monkeys

THE recent increase in the abuse of a smokable form of methamphetamine, known as "ice," has led to concerns that this drug may pose substantial public health problems in years to come (3). In fact, clinical reports of both psychiatric (13,22) and cardiovascular (6,11) toxicity have been recently published. Despite the long-term abuse of methamphetamine and amphetamine, the mechanisms by which these drugs produce their cardiotoxic effects are not completely understood. Both drugs are potent releasers and uptake blockers for norepinephrine, and it has been reported that these adrenergic mechanisms are important to the cardiovascular effects of methamphetamine (10). However, the amphetamines are also potent blockers of dopamine uptake, as well as strong CNS stimulants. Further, many previous studies on the cardiovascular effects of the amphetamines have been performed in anesthetized animals (2,21). As previous research with cocaine has shown that anesthesia can blunt its cardiovascular effects (24,27), it is reasonable to assume that similar effects may also occur with methamphetamine. Therefore, the purpose of the current experiment was to study the pharmacological mechanisms involved in the cardiovascular effects of methamphetamine in conscious squirrel monkeys.

Methamphetamine and cocaine are both potent sympathomimetics and share many common effects. Despite their strong similarities, methamphetamine and cocaine are distinguishable in their mechanisms of action (17). For example, methamphetamine is a potent releaser of norepinephrine (18), while cocaine is not (1). Further, cocaine has potent local anesthetic properties that may contribute to its affects. As a result of these similarities and differences, it is desirable to study the cardiovascular effects of methamphetamine in a manner in which they can be easily compared with cocaine. Therefore, the cardiovascular effects of methamphetamine were studied using the squirrel monkey primate model, which has been used extensively to study cardiovascular effects of cocaine (20,24).

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In the present study, following the determination of the dose-effect function for methamphetamine various pretreatments, including α- and β-adrenoceptor agents and dopamine receptor antagonists, were used to determine the pharmacological mechanisms of action for methamphetamine. The doses of pretreatment agents were generally comparable to those previously used in studies with cocaine. Previous research has shown that the pressor effect of cocaine is mediated primarily via α_1-adrenoceptor mechanisms while the tachycardiac effect is mediated primarily via β_1-adrenoceptor mechanisms (19,24). Dopaminergic mechanisms do not appear to strongly influence the cardiovascular effects of cocaine (20) in this species.

METHOD

Subjects

Subjects were eight adult male squirrel monkeys (*Saimiri sciureus*) housed in individual cages in rooms in which light, temperature, and humidity were controlled. Fresh water was continuously available. The monkeys' daily food intake was restricted to maintain their body weights between 800–1000g.

Subjects were first implanted with both a venous catheter (internal iliac vein) for the delivery of drug and an arterial catheter (internal iliac artery) for the measurement of blood pressure. The catheters were implanted during a single sterile surgery. The general surgical procedure has been described in detail elsewhere (9). In brief, polyvinyl chloride catheters (i.d., 0.38 mm; o.d., 0.76mm) were implanted under anesthesia with halothane-oxygen mixtures. The distal ends of the catheters were passed SC out through the skin in the middle of the back. Monkeys wore nylon jackets at all times to protect the catheters. Following a 2-week recovery period, experiments were begun. Catheters were flushed with heparinized saline (20 units/ml) at least twice weekly and sealed with stainless steel obturators when not in use.

Apparatus

During experimental sessions, monkeys sat in Plexiglas chairs similar to the one described by Hake and Azrin (8) and were loosely restrained in the seated position by a waist lock. The chairs were enclosed in ventilated, sound-attenuating chambers (model AC-3; Industrial Acoustics Co., Bronx, NY) that were provided with continuous white noise to mask extraneous sounds. The distal end of the arterial catheter was connected via polyethylene tubing to a blood pressure transducer (no. T42-20, Coulbourn Instruments, Lehigh Valley, PA). The arterial catheter was continuously flushed with heparinized saline at a rate of 0.03 ml/min. The transducer was connected to an associated amplifier (no. S72-25, Coulbourn Instruments) and blood pressure processor (no. S77-34, Coulbourn Instruments) outside the experimental chamber. The blood pressure processor analyzed the raw transducer signal, giving analog outputs of systolic (SP), diastolic (DP), and mean pressure $\{DP + [(SP - DP)/3]\}$ at the end of each cardiac cycle. The signal for the end of the cardiac cycle was fed into an Apple IIe computer. For each cycle, the computer measured the time between cycles with a resolution of 1 ms and read the analog signals for pressure from the blood pressure processor with a resolution of 1 mm Hg. These values were summed and averaged over periods of 30 s for subsequent analysis. Only mean pressure and heart rate were used for statistical analysis. The distal end of the venous catheter was passed outside the experimental chamber via polyethylene tubing and connected to a syringe for the injection of drug.

Procedure

Subjects were placed in the chamber every weekday. Animals were allowed at least 2 weeks to adapt to the experimental situation prior to any drug testing. Thereafter, injections of drugs were typically given on Tuesdays and Fridays and saline was given on Thursdays. The order of doses and drugs was nonsystematic. For all sessions, subjects were placed in the chamber for a period of 90 min, with an IV injection of methamphetamine or saline given, if scheduled, 30 min after initiation of the session. For IV pretreatment experiments, an injection of saline or one of the pretreatment agents was given 5 min prior to IV injection of 0.2 mg/kg methamphetamine (i.e., 25 min after initiation of the session), except for erythro-*dl*-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol (ICI-118,551), which was given 15 min prior to methamphetamine. For IM pretreatment experiments, an injection of saline or one of the pretreatment agents was given immediately prior to the start of the session (i.e., 30 min prior to methamphetamine injection). As the effects of 0.2 mg/kg methamphetamine were similar for both the IV and IM saline pretreatment conditions, those conditions were combined for analysis. There were multiple determinations of saline and 0.2 mg/kg methamphetamine control values throughout the experiment.

Drugs

Methamphetamine hydrochloride, prazosin hydrochloride, yohimbine hydrochloride, propranolol hydrochloride, atenolol, and clonidine hydrochloride (Sigma Chemical Co., St. Louis, MO) were dissolved in sterile saline. ICI-118,551 (ICI Pharmaceuticals, Macclesfield, Chershire, UK) was dissolved in sterile water. Haloperidol and SCH 23390 (Research Biochemicals, Inc., Natick, MA) were dissolved in sterile water with a small amount of tartaric acid added as needed for solubility. All doses are expressed as the salt except atenolol, ICI-118,551, and haloperidol, which are the base.

Data analysis

Heart rate and blood pressure data were averaged over 5-min periods from the 30-s periods averaged by the computer. Change scores were calculated using the 5-min period prior to pretreatment (saline or antagonist) as the baseline when determining the effects of pretreatments alone. The 5-min period prior to methamphetamine or saline injection at 30 min was used as the control when determining the effects of methamphetamine alone or in combination with pretreatments. In addition, maximum increases from baseline were also determined following IV injection. For the analysis of maximum increases from baseline, the first 30 min following saline or methamphetamine injection was used, as previous research has shown this interval to be appropriate when analyzing drug interactions (19). These maximums were derived from the 5-min means. Data were subjected to analysis of variance (ANOVA), with follow-up contrasts to determine differences among groups (28).

RESULTS

Figure 1 presents the time course for the effects of saline and 0.03–3.0 mg/kg methamphetamine. The saline injection produced little variation from either baseline blood pressure

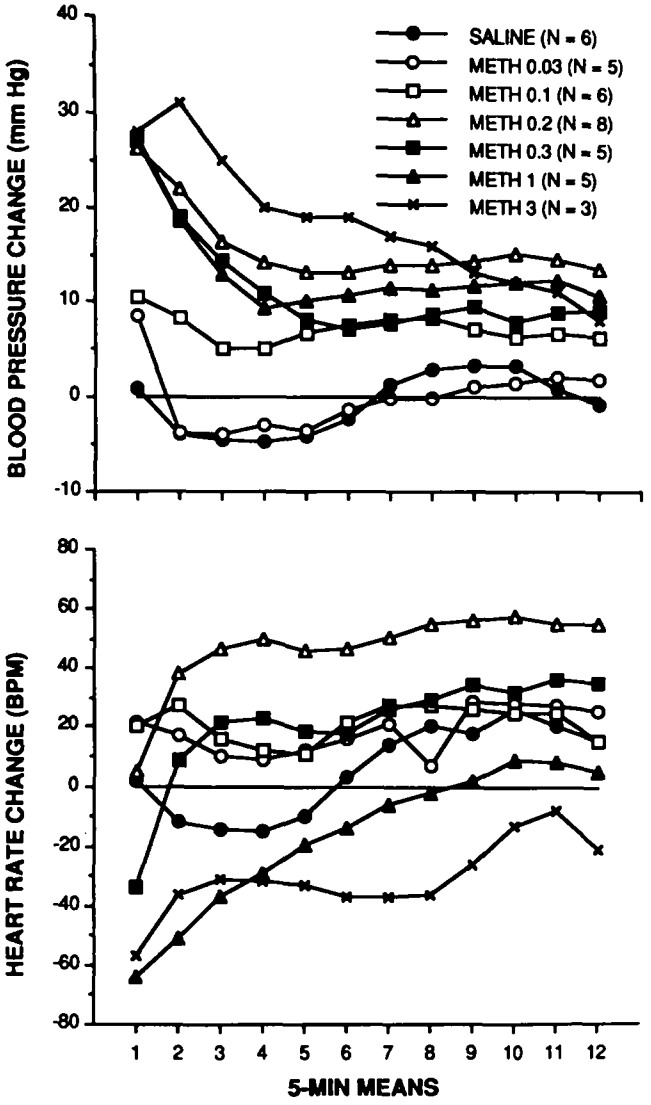

FIG. 1. Time course for the effects of methamphetamine (METH) on blood pressure and heart rate in conscious squirrel monkeys. The measure presented is the change score for 5-min periods following injection of drug. The 5-min period prior to injection was used as the control. Doses are in mg/kg. BPM, beats/min.

or heart rate, although there was a tendency for heart rate to increase toward the end of the session. This is a typical response in anticipation of being removed from the chamber. There was a fairly direct relationship between methamphetamine dose and blood pressure, with larger doses producing larger and longer-lasting effects (Fig. 2). The peak blood pressure effect typically occurred immediately following injection. The effects of methamphetamine on heart rate were more complicated (Fig. 1 and 2). As dose increased up to 0.2 mg/kg methamphetamine, heart rate also increased; at higher doses, an initial bradycardia was observed, with a delayed increase in heart rate (0.2–0.3 mg/kg) or a return to baseline at the highest doses tested (1.0 and 3.0 mg/kg). The peak reductions in heart rate were significantly different from saline ($p < 0.05$) for the 1.0- and 3.0-mg/kg doses. Monkeys did not tolerate 3.0 mg/kg methamphetamine well; therefore, this dose was given only once to three subjects. As the 0.2-mg/kg dose of methamphetamine produced the peak tachycardiac effect and a reliable pressor effect, this dose was chosen for the drug interaction studies.

Table 1 presents the results for the various drug interaction experiments. Presented in the table are the initial baseline values prior to the drug pretreatment (for haloperidol and SCH 23390, this value was for the first 5 min of the session, i.e., for the first 5 min following IM injection of haloperidol or SCH 23390), the change from baseline following pretreatment (5 min prior to the 0.2-mg/kg methamphetamine injection), and the maximal effect of 0.2 mg/kg methamphetamine (using as a baseline the 5 min period prior to injection). Saline pretreatment produced little change in either baseline heart rate or blood pressure. Following saline, 0.2 mg/kg methamphetamine produced increases in both blood pressure and heart

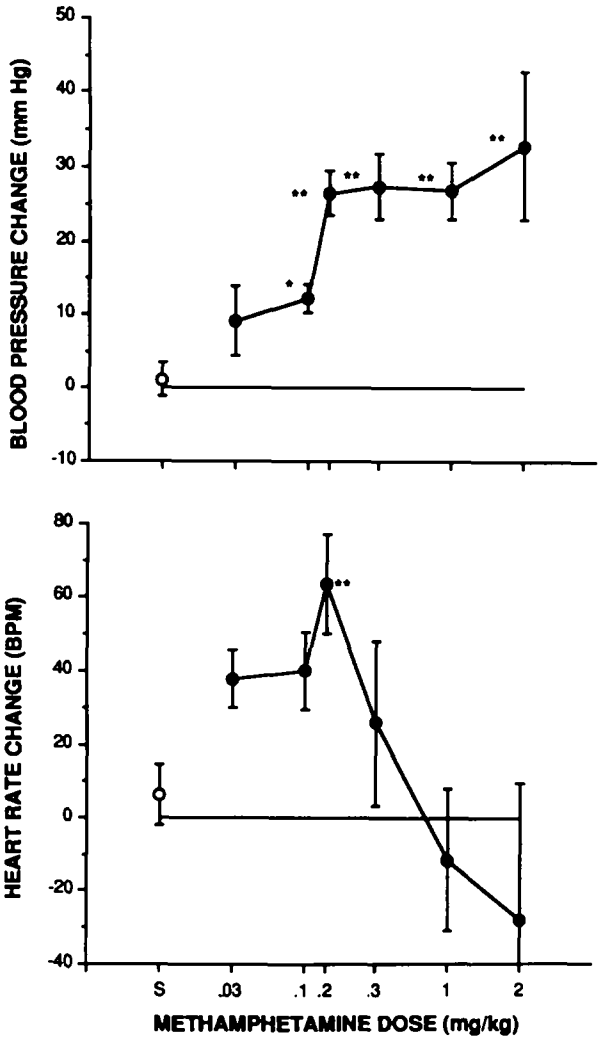

FIG. 2. Dose-effect functions for the effects of methamphetamine on blood pressure and heart rate in conscious squirrel monkeys. For both blood pressure and heart rate, the peak 5-min change score for the 30 min following injection was used. The 5-min period prior to injection was used as the control. Each curve is the mean of three to eight subjects. Error bars are ±SE. $*p < 0.05$, $**p < 0.01$ from saline control. BPM, beats/min.

TABLE 1

EFFECTS OF VARIOUS PRETREATMENTS ON THE CARDIOVASCULAR EFFECT OF 0.2 mg/kg METHAMPHETAMINE (Meth)

		Blood Pressure			Heart Rate		
Pretreatment (mg/kg)	*n*	Baseline	Baseline Change	Meth 0.2	Baseline	Baseline Change	Meth 0.2
Saline	8	94.6 ± 8.3	1.5 ± 0.7	26.5 ± 3.0	246.8 ± 13.6	1.8 ± 2.4	63.6 ± 13.3
Prazosin 0.1	6	115.0 ± 5.8	−19.0 ± 4.7*	1.2 ± 5.0*	252.5 ± 15.8	55.0 ± 12.3*	27.5 ± 11.6
Yohimbine 0.3	6	98.5 ± 3.8	17.8 ± 2.5*	9.8 ± 2.1*	241.7 ± 13.0	72.8 ± 9.9*	13.0 ± 7.8†
Clonidine 0.01	5	92.4 ± 2.7	4.4 ± 6.9	16.4 ± 7.1	238.4 ± 19.8	−15.4 ± 21.5	39.0 ± 24.3
Clonidine 0.03	5	90.8 ± 5.7	−3.2 ± 4.6	21.4 ± 2.1	245.8 ± 19.2	−67.4 ± 16.6*	24.4 ± 14.3
Propranolol 3.0	6	104.2 ± 5.9	1.0 ± 1.3	22.7 ± 2.0	265.8 ± 12.9	−59.3 ± 12.7*	5.0 ± 7.0*
Atenolol 3.0	5	89.6 ± 2.7	3.2 ± 3.0	20.0 ± 9.2	247.4 ± 29.3	−51.2 ± 14.5*	−16.6 ± 5.6*
ICI-118,551 0.3	4	101.8 ± 5.4	6.3 ± 2.4	34.0 ± 6.7	245.8 ± 11.1	−51.5 ± 10.5*	65.5 ± 17.9
Haloperidol 0.01	5	106.1 ± 7.8	−4.9 ± 4.4	28.5 ± 3.5	234.5 ± 17.2	−9.9 ± 6.6	81.5 ± 17.2
Haloperidol 0.03	5	104.6 ± 4.9	8.6 ± 3.5	13.4 ± 6.5†	229.6 ± 19.2	4.4 ± 11.8	40.0 ± 16.7
SCH 23390 0.01	5	99.6 ± 5.5	−0.8 ± 3.6	27.8 ± 6.0	247.4 ± 8.0	4.0 ± 5.0	72.2 ± 19.0
SCH 23390 0.03	5	99.8 ± 9.3	7.0 ± 11.9	9.0 ± 6.9†	226.8 ± 32.3	11.8 ± 26.8	0.0 ± 17.4†

Error bars at ±SE.
*$p < 0.01$.
†$p < 0.05$.

rate. Various drugs that interact with α-adrenoceptors, β-adrenoceptors, and dopaminergic receptors were tested for their ability to antagonize the effects of methamphetamine. Doses were chosen on the basis of previous research on the cardiovascular effects of cocaine (19,20,24). There were no significant differences in baseline blood pressure or heart rate prior to administration of any of the pretreatment drugs.

Prazosin produced a significant decrease in blood pressure and an increase in heart rate. Prazosin also completely antagonized the pressor effect of methamphetamine. While prazosin also decreased the maximal tachycardiac effect of methamphetamine, this effect was not significant due to the relatively large standard error. Yohimbine increased both blood pressure and heart rate and at least partially antagonized the pressor and tachycardiac effect of methamphetamine. As yohimbine increased both baseline blood pressure and heart rate, it is unclear whether the antagonism of methamphetamine's effects is due to a true pharmacological antagonism or simply due to a ceiling effect. Clonidine lowered heart rate at the highest dose tested, but did not significantly alter either the pressor or tachycardiac effect of 0.2 mg/kg methamphetamine.

All three β-adrenoceptor antagonists significantly lowered baseline heart rate without affecting blood pressure. Atenolol and propranolol also completely antagonized the tachycardiac effect of 0.2 mg/kg methamphetamine, while ICI-118,551 was without effect. None of the β-adrenoceptor antagonists significantly altered the pressor effect of methamphetamine. Neither SCH 23390 nor haloperidol significantly altered baseline blood pressure or heart rate. At the highest doses tested, both SCH 23390 and haloperidol did attenuate the pressor effect of methamphetamine. The 0.03-mg/kg dose of SCH 23390 also completely antagonized the tachycardiac effect of 0.2 mg/kg methamphetamine.

DISCUSSION

Methamphetamine produced a dose-dependent increase in blood pressure that was fairly linear over the entire dose range, although there was a tendency for the peak pressure increase to plateau at higher doses. In contrast, methamphetamine produced a biphasic effect on heart rate, with peak heart rate increasing up to 0.2 mg/kg. Even at 0.2 mg/kg, however, the peak increase in heart rate was delayed following injection. Above 0.2 mg/kg, methamphetamine produced a pronounced bradycardia immediately following injection that was sustained at higher doses. This bradycardia may be mediated via the baroreceptor reflex in response to the increase in blood pressure.

These results are not in complete agreement with a number of previous results showing that methamphetamine produces a potent depressor effect. Previous research with vertebral artery administration (12,15) has shown that methamphetamine produces a centrally mediated depressor response. However, both these studies used anesthetized animals and thus the influence of anesthesia may account for the differences observed with the current experiment. In fact, a hypotensive response to methamphetamine is often observed under anesthesia (2,21). It is possible that methamphetamine produces both a pressor and depressor effect, with the depressor effect predominating in anesthetized animals. Further, it is well known that methamphetamine can produce a depressor effect in hypertensive animals (25,26). The relationship of this effect to the current results is unclear.

In general, all pretreatment agents produced their expected effect on baseline blood pressure and heart rate (7). Prazosin decreased baseline blood pressure and reflexively increased heart rate. Yohimbine increased both baseline blood pressure and heart rate, as would be expected via an action at central α_2-adrenoceptors (10). Clonidine did not produce a large change in baseline blood pressure, but did reduce baseline heart rate. None of the β-adrenoceptor antagonists affected baseline blood pressure, but all decreased heart rate, indicating an action specific to β-adrenoceptors. Finally, neither haloperidol nor SCH 23390 affected baseline cardiovascular function, in agreement with previous observations (20).

The role of α_1-adrenoceptors in mediating the pressor response to methamphetamine was confirmed by the finding

that the α_1-selective antagonist prazosin completely abolished the increase in blood pressure following 0.2 mg/kg methamphetamine. The α_2-selective antagonist yohimbine also decreased the pressor effect of methamphetamine, but only at doses that significantly increased baseline blood pressure. The α_2-selective agonist clonidine did not significantly affect the blood pressure response to 0.2 mg/kg methamphetamine. Neither clonidine nor prazosin affected the tachycardiac response to methamphetamine. Yohimbine also decreased the tachycardiac response to methamphetamine, but again yohimbine also significantly increased baseline heart rate, which may have blunted the tachycardiac effect of methamphetamine due to a ceiling effect.

The role of β_1-receptors in mediating the tachycardiac effect of methamphetamine was confirmed by the finding that both the nonselective antagonist propranolol and the β_1-selective antagonist atenolol abolished the tachycardiac effect of 0.2 mg/kg methamphetamine. The β_2-selective antagonist ICI-118,551 was without effect. As this dose of ICI-118,551 has been previously shown to be effective as a β_2-selective antagonist in squirrel monkeys (19), these results support a role of β_1-receptors in tachycardiac response to methamphetamine.

Both the dopamine D_1 antagonist SCH 23390 and the D_2 antagonist haloperidol attenuated the pressor response to 0.2 mg/kg methamphetamine. SCH 23390 also completely abolished the tachycardiac response to this dose of methamphetamine. These results indicate that dopaminergic mechanisms are also involved in mediating the cardiovascular effect of methamphetamine. In this regard, it appears that D_1 mechanisms may be more important for the tachycardiac effect than are D_2 mechanisms, as only SCH 23390 attenuated the tachycardiac effect of methamphetamine.

While both methamphetamine and cocaine are potent sympathomimetics, clear similarities and differences are evident in comparisons between the drugs. α_1-Adrenoceptors are important in mediating the pressor effect of both cocaine and methamphetamine (19,24). Likewise, β_1-adrenoceptors are important in mediating the tachycardiac effect of both drugs (21,24). However, the pressor effect of cocaine is potentiated by the nonselective β-antagonist propranolol (14,16,19), while that of methamphetamine was not. In this regard, it should be noted that this effect of propranolol does not appear to be mediated by an action at β-adrenoceptors but through some unknown mechanisms (19,23). Dopaminergic mechanisms have only minimal effectiveness against the cardiovascular effects of cocaine (20) while they do appear to contribute substantially to the cardiovascular response to methamphetamine. When tested against cocaine, only 0.01 mg/kg haloperidol, but not 0.03 mg/kg, slightly attenuated the tachycardiac effect of cocaine but not the pressor effect. In contrast, 0.03 mg/kg SCH 23390 antagonized both the pressor and tachycardiac effects of methamphetamine. Finally, reflex bradycardia resulting from the increase in pressure following drug administration appears to be a more important factor in mediating methamphetamine's response than for cocaine. While some bradycardia is observed at higher doses of cocaine, this result is not consistent across animals and is not consistently antagonized by ganglionic blockade (24).

The relationship of the current results to the potential acute lethal effects of methamphetamine are not clear. In studies with rats, no significant protection of methamphetamine-induced lethality has been observed following treatment with either haloperidol or SCH 23390 (4,5). The D_1 antagonist SCH 23390 will protect against cocaine-induced lethality (4,29). While these studies and the present study involve different species and routes of administration, the finding that SCH 23390 will antagonize the cardiovascular but not the acute lethal effects of methamphetamine suggests that these two processes may be medicated by different mechanisms.

In summary, the results of the present study indicate that methamphetamine produces potent pressor and tachycardiac effects in conscious squirrel monkeys. At higher doses, methamphetamine also produces a pronounced bradycardiac response. The pressor effect of methamphetamine is mediated via α_1-adrenoceptors, while the tachycardiac effect of methamphetamine is mediated via β_1-adrenoceptors. Finally, both D_1 and D_2 dopamine receptors are involved in the cardiovascular effect of methamphetamine.

ACKNOWLEDGEMENTS

The authors thank Debra Boan for technical assistance and ICI Pharmaceuticals (Macclesfield, Chershire, UK) for the supply of ICI-118,551. A preliminary report appeared in Soc. Neurosci. Abstr. 17: 1432; 1991.

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