Pharmacology Biochemistry & Behavior, Vol. 40, pp. 157–162. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Dopamine Receptors Mediate Cocaine-Induced Temperature Responses in Spontaneously Hypertensive and Wistar-Kyoto Rats

R. W. ROCKHOLD, E. S. CARVER, Y. ISHIZUKA, B. HOSKINS AND I. K. HO

Department of Pharmacology and Toxicology, University of Mississippi Medical Center
2500 N. State St., Jackson, MS 39216-4505

Received 10 December 1990

ROCKHOLD, R. W., E. S. CARVER, Y. ISHIZUKA, B. HOSKINS AND I. K. HO. *Dopamine receptors mediate cocaine-induced temperature responses in spontaneously hypertensive and Wistar-Kyoto rats.* PHARMACOL BIOCHEM BEHAV **40**(1) 157–162, 1991.—The involvement of dopaminergic receptors in the responses of conscious, restrained spontaneously hypertensive (SHR) and Wistar-Kyoto (WKY) rats to cocaine was examined using antagonists selective for DA-1 (SCH 23390) or DA-2 (sulpiride) dopamine receptors. Following pretreatment with saline vehicle, SCH 23390 (50 mg/kg, SC), sulpiride (50 mg/kg, IP) or SCH 23390 and sulpiride, cocaine was infused (1.25 mg/kg·min, IV) until death. Cocaine caused an initial pressor and tachycardic response, which was followed by a progressively developing secondary pressor response. Combined (DA-1 and DA-2) antagonist pretreatment abolished the initial tachycardic response to cocaine. Rectal temperature during cocaine infusion increased in 38.5% of vehicle-treated SHR (designated SHR_H), but decreased in the remaining SHR (SHR_L) and all vehicle-treated WKY. The time-to-onset of cocaine-induced convulsions (T_c) was reduced in vehicle-treated SHR_H compared to vehicle-treated SHR_L and WKY. Sulpiride elevated rectal temperature in response to cocaine in SHR and WKY but reduced T_c only in SHR. SCH 23390 abolished hyperthermic responses to cocaine in SHR without altering toxicity in SHR or WKY. Combined pretreatment virtually abolished temperature responses to cocaine in SHR and WKY, but increased the T_c only in WKY. Dopamine receptors, particularly the DA-1 subtype, are involved in cocaine-induced hyperthermia.

SHR Dopaminergic receptors Sulpiride SCH 23390 Cardiovascular responses Body temperature Cocaine Convulsions

INTERACTIONS between cocaine and dopaminergic neurons are widely postulated as being pivotal to mediation of the behavioral effects of cocaine (9,12). However, the roles played by dopaminergic systems in the physiological and toxic effects of cocaine are less well established.

We have proposed the use of the genetic model of experimental hypertension, the spontaneously hypertensive rat (SHR), and its normotensive control, the Wistar-Kyoto rat (WKY), as an experimental model with which to study dopaminergic neuronal involvement in the actions of cocaine. Differences between dopaminergic neuronal systems between SHR and WKY have been well described, by our laboratory (19–21, 35) and others (1, 2, 5, 17, 18, 31). Moreover, data from our laboratory indicate that restraint stress expresses differential sensitivity, in the SHR, to the convulsive and lethal effects of cocaine (14). The demonstration that environmental factors (i.e., restraint stress) can influence the toxicity of cocaine is significant and suggests that the SHR and WKY may prove to be valuable as a model for expression of cocaine toxicity in man, which is often unpredictable. The mechanism(s) which underlie this exaggerated sensitivity is/are unresolved. However, participation of central dopaminergic mechanisms is a potential factor in mediation of exaggerated toxicity to cocaine in the SHR.

Effects on body temperature, pressor responses and tachycardia as well as precipitation of convulsions and sudden cardiac death are prominent features of the action of cocaine, both in man and in experimental animals. Of these, body temperature regulation has been most closely correlated with central dopaminergic receptor activity. Apomorphine, a nonselective dopamine receptor agonist, commonly produces hypothermia (3,11), an effect which has been reported to be greater in magnitude in the SHR than in the WKY (1,23). Cocaine itself has been shown to cause both hypothermic (10) and hyperthermic (7,32) actions. Little evidence has been reported to link the cardiovascular actions of cocaine with dopaminergic activity, although dopamine has been implicated in the regulation of arterial blood pressure and heart rate by a number of investigators (22,27). Pimozide, a dopamine receptor antagonist, was ineffective in inhibiting cocaine lethality in anesthetized dogs (4), although the results of a recent study suggest that pretreatment with the selective dopamine DA-1 receptor antagonist, SCH 23390, protects against cocaine-induced sudden death in the rat (34).

The objective of the present experiment was to utilize pretreatment of SHR and WKY with selective DA-1 and DA-2 receptor antagonists to test the relative participation of these receptors in the body temperature, cardiovascular and lethal effects of cocaine.

METHOD

Young adult, male SHR and WKY were purchased at 11 weeks of age from a commercial breeder (Taconic Farms, Inc.). Upon receipt, animals were housed in plastic group cages (3–4/cage) in a university-approved animal room under controlled conditions of lighting (12:12 h, light:dark), temperature (22–24°C) and humidity (50%).

Animals were anesthetized with halothane (2–4% in medical grade oxygen) 48–72 h prior to experimental use. Polyethylene catheters were implanted, via femoral vessels, for recording of arterial blood pressure (PE-50) and intravenous drug infusion (PE-10). Catheters were filled with heparinized (10 U/ml) saline and exteriorized at the nape of the neck. Wounds were closed and anesthesia discontinued. Each rat received 60,000 U of procaine penicillin (Pfizerpen®), SC following surgery. Rats were housed individually in plastic cages following surgery.

Arterial blood pressure and heart rate were recorded using Cobe® disposable pressure transducers. Signals were amplified by means of and displayed on a Grass Model 7D polygraph. Heart rate was calculated electronically from the pulse interval and mean arterial blood pressure was obtained by electronic damping of the pulsatile pressure signal. Rectal temperature was measured using a Sensortek Model TH-5 electronic thermometer and a probe inserted 5 cm into the rectum.

Four experimental treatment groups were utilized. The SHR and WKY were randomly assigned to one of four pretreatment regimens. Pretreatment was followed by initiation of an intravenous infusion (50 μl/kg·min of cocaine hydrochloride (25 mg/ml; Sigma) at a dose-rate of 1.25 mg/kg·min using a Sage Model 355 infusion pump. The pretreatment regimens consisted of administration of either the selective DA-1 dopamine receptor antagonist, SCH 23390 (SC, 50 μg/kg, 15 min prior to cocaine administration; Research Biochemicals, Inc.); the selective DA-2 dopamine receptor antagonist, sulpiride (IP, 50 mg/kg, 90 min prior to cocaine administration; Research Biochemicals, Inc.); a combination of both SCH 23390 and sulpiride; or vehicle (0.9% saline, pH 7.4, 0.5 ml/kg/injection, 2 injections, as per the combined treatment regimen). Dosages for dopamine receptor antagonists were chosen from literature which documented selective blockade of dopamine-mediated thermoregulatory responses (3). Rectal temperature was measured in each rat's home cage immediately prior to injection of each agent or vehicle. Thirty min prior to initiation of cocaine infusion, each rat was placed into a Plexiglas restraining tube (length = 25 cm; diameter = 6.5 cm) and a rectal probe placed into the rectum. Rectal temperature, arterial blood pressure and heart rate were monitored continuously thereafter. The total period of restraint ranged from roughly 45–60 min, depending on the duration of the cocaine infusion in different groups. Studies were performed while rats were fully conscious and recovered from acute surgical stress (48–72 h following surgery). Infusions were performed between 10:00 a.m. and 2:00 p.m. in a room with an ambient temperature of 23 ± 1°C.

Once initiated, cocaine infusions were continued until convulsions and death ensued. The time-to-onset of convulsions was recorded. Data for blood pressure and heart rate were normalized between individual rats by recording the time-to-onset of convulsions and determining pressure and rate values at decimal fractions of that time.

Data are expressed as mean values ± 1 S.E.M. Statistical comparisons between experimental groups were performed using analysis of variance (one- or two-way as indicated) followed by a posteriori Newman-Keuls tests.

TABLE 1

MAXIMAL COCAINE-INDUCED CHANGES IN CIRCULATORY VARIABLES

Treatment Group	SHR MABP (mmHg)	SHR HR (beats/min)	WKY MABP (mmHg)	WKY HR (beats/min)
Saline	30 ± 4 (11)	22 ± 3	27 ± 2 (7)	17 ± 4
Sulpiride	31 ± 2 (7)	17 ± 4	24 ± 4 (5)	22 ± 8
SCH 23390	27 ± 2 (8)	18 ± 2	21 ± 5 (6)	5 ± 6
Sulpiride/ SCH 23390	23 ± 5 (5)	6 ± 3*†	25 ± 5 (5)	−10 ± 2‡§

Maximum percent (%) changes in mean arterial blood pressure (MABP) and heart rate (HR) immediately (within 2 min; Spike) following initiation of intravenous cocaine infusion. Values of MABP immediately prior to cocaine infusion were, in SHR, 165 ± 6 (n = 11, saline), 165 ± 2 (n = 7, sulpiride), 159 ± 4 (n = 8, SCH 23390), 163 ± 6 mmHg (n = 5, combined blockade) and, in WKY, 115 ± 3 (n = 7, saline), 105 ± 6 (n = 5, sulpiride), 111 ± 2 (n = 6, SCH 23390) and 117 ± 2 (n = 5, combined blockade). Corresponding values of HR were, in SHR, 411 ± 6 (saline), 431 ± 12 (sulpiride), 417 ± 7 (SCH 23390), 448 ± 12 beats/min (combined blockade) and, in WKY, 402 ± 21 (saline), 398 ± 10 (sulpiride), 394 ± 12 (SCH 23390) and 414 ± 26 beats/min (combined blockade). Mean values ± 1 S.E.M. are given. Numbers in parentheses indicate numbers of animals from which accurate cardiovascular measurements were obtained. *$p<0.01$ compared with saline-treated SHR; †$p<0.05$ compared with sulpiride- or SCH 23390-treated SHR; ‡$p<0.01$ compared with saline- or sulpiride-treated WKY; §$p<0.05$ compared with SCH 23390-treated WKY.

RESULTS

Resting values for mean arterial blood pressure and heart rate in SHR and WKY did not differ, within a strain, between treatment groups immediately prior to initiation of cocaine infusion (Table 1). Arterial blood pressure was significantly higher ($p<0.01$) in SHR than in WKY in all four treatment groups. Values for heart rate averaged near 400 beats/min in all groups (reflecting confinement in restraining tubes) and did not differ between SHR and WKY.

Intravenous infusion of cocaine (1.25 mg/kg·min) was characterized by an immediate increase in blood pressure and heart rate (Fig. 1). This response occurred within the first 30 seconds following entry of cocaine into the venous circulation and invariably subsided within 2 min of its onset. The maximum increases (as % of control) in mean arterial blood pressure and heart rate during this phase of the response are detailed in Table 1. This response was followed by a rapid return to near preinfusion levels of blood pressure in all groups of SHR and WKY. Thereafter, the blood pressure response was characterized by a gradual, progressive increase which continued until the onset of convulsions. The time-of-onset of convulsions differed between individual rats, treatment groups and strains. Graphic representation of the patterns of cardiovascular response was facilitated by noting the time of initiation of cocaine infusion and determining the time-of-onset of convulsions in each rat. Values for mean arterial blood pressure and heart rate were then obtained at decimal fractions of the elapsed time during cocaine infusion. No significant differences between treatment groups were noted in the blood pressure response pattern. A further, rapid increase in blood pressure occurred with the onset of convulsions, an in-

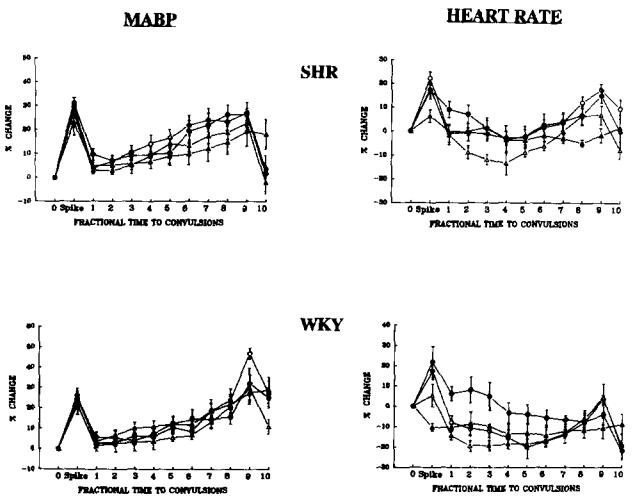


FIG. 1. Percent (%) change in mean arterial blood pressure (mmHg, left panels) and heart rate (beats/min, right panels) in SHR (upper panels) and WKY (lower panels) from the initiation of intravenous cocaine infusion (Time 0) to the onset of convulsions (Time 10). Because of the differences between groups and individual animals in the time-to-onset of convulsions, time periods were normalized to fractions (0–10) of the time-to-onset of convulsions in each animal. Spike refers to an initial (within 2 min) increase in blood pressure and heart rate which occurred following initiation of cocaine infusion. Saline-treated animals are denoted by open circles, sulpiride-treated by closed circles, SCH 23390-treated by open triangles and sulpiride/SCH 23390-treated by closed triangles. Mean values ± 1 S.E.M. are given.

crease which was sustained until abrupt cardiovascular collapse and death were noted (data not shown). Convulsions presented as increasingly severe clonic seizures. A terminal tonic-clonic seizure was always noted and episodes of tonic-clonic seizures were often observed following an initial clonic event. The duration of the period of convulsions was generally 10–15% of the interval between initiation of cocaine infusion and the time-to-onset of convulsions.

The response of heart rate differed slightly from the pattern for mean arterial blood pressure (Fig. 1), particularly in WKY. Combined pretreatment with both sulpiride and SCH 23390 essentially abolished the early increase in heart rate in both SHR and WKY (Table 1). Moreover, in contrast to the blood pressure response, heart rate returned toward and remained near preinfusion levels until the onset of convulsions in both SHR and WKY. During the period following the early spike and prior to the onset of convulsions, sulpiride pretreatment appeared to prevent this return of heart rate to preinfusion levels in both WKY and SHR, while SCH 23390 pretreatment resulted in a relative bradycardia. However, because of the complex time-course of these responses, statistical evaluation of differences between groups was not attempted, except for maximum values obtained during the initial spike.

Differences in resting rectal temperature between treatment groups were not evident at the time-of-onset of cocaine infusion. Vehicle-pretreated rats averaged 38.8 ± 0.1 (SHR_H, n = 8), 38.8 ± 0.1 (SHR_L, n = 5) and 38.2 ± 0.2°C (WKY, n = 7). Dopamine receptor antagonist pretreated SHR averaged 38.6 ± 0.1 (n = 8, sulpiride), 38.7 ± 0.2 (n = 8, SCH 23390) and 38.7 ± 0.1°C (n = 7, combined blockade). Values for WKY averaged 37.9 ± 0.2 (n = 5, sulpiride), 38.5 ± 0.2 (n = 6, SCH 23390) and 38.0 ± 0.2°C (n = 7, combined blockade). Rectal temperature was observed to undergo progressive changes during the infusion of cocaine, the magnitude and direction of which differed between strains and between treatment groups. An abrupt rise in rectal temperature occurred following the onset of convulsions in all animals, however. Cocaine infusion, in vehicle-pretreated WKY, lowered rectal temperature in all animals. However, in vehicle-pretreated SHR, both increases and decreases in rectal temperature were noted, in different animals, during cocaine infusion. In a fraction (38.5%, 5/13) of SHR, the infusion of cocaine was observed to cause a hyperthermia prior to the onset of convulsions, while in the remaining 8 SHR rectal temperature was lowered prior to the onset of convulsions. Based upon the direction of the maximal cocaine-induced change in rectal temperature (prior to convulsions), SHR were arbitrarily divided into two groups. Those SHR in which the maximal change in rectal temperature was positive (i.e., a hyperthermia) were designated SHR_H, while the remaining SHR (designated SHR_L) demonstrated decreases in rectal temperature (Fig. 2). When the time-to-onset of convulsions was compared between these two groups of SHR, a significant reduction was observed in those SHR in which rectal temperature increased (Table 2). The correlation between cocaine-induced temperature change and sensitivity to cocaine-induced convulsions and the designation of SHR_H and SHR_L have been reported previously (14). The maximal change in rectal temperature did not differ between vehicle-treated WKY and those vehicle-treated SHR in which rectal temperature fell. Again, no differences were noted in the time-to-onset of convulsions between vehicle-treated WKY and vehicle-treated SHR demonstrating cocaine-induced reductions in maximal rectal temperature responses.

Pretreatment with the selective DA-1 receptor antagonist, SCH 23390, did not significantly alter cocaine-induced reductions in rectal temperature in WKY. Such pretreatment did, however, abolish cocaine-induced hyperthermic responses in SHR. No SHR treated with SCH 23390 demonstrated an increase in rectal temperature prior to the onset of convulsions and the average change in rectal temperature was not significantly different from either saline-treated WKY or SHR_L groups (Fig. 3).

Pretreatment with the selective DA-2 receptor antagonist,

TABLE 2

TIME-TO-ONSET OF COCAINE-INDUCED CONVULSIONS

Treatment Group	SHR	WKY
Saline	14.64 ± 1.48* (H, 8) 21.33 ± 1.20 (L, 5)	22.27 ± 1.09 (7)
Sulpiride	15.85 ± 0.51*§ (8)	18.83 ± 0.95 (5)
SCH 23390	24.01 ± 1.94†‡ (8)	21.29 ± 1.36 (6)
Sulpiride/ SCH 23390	18.81 ± 0.87 (7)	30.71 ± 2.96*‡§¶ (7)

Effects of drug pretreatment on the time-to-onset of convulsions (in min) following intravenous cocaine infusion. Mean values ± 1 S.E.M. are presented. Numbers in parentheses indicate numbers of animals in which accurate measurements of elapsed time were made. L = SHR assigned to the hypothermic groups, H = SHR assigned to the hyperthermic group. *$p<0.01$ compared with saline-treated SHR_L; †$p<0.01$ compared with saline-treated SHR_H; ‡$p<0.01$ compared with sulpiride-treated SHR; §$p<0.01$ compared with saline-treated WKY; ¶$p< 0.01$ compared with SCH 23390-treated WKY.

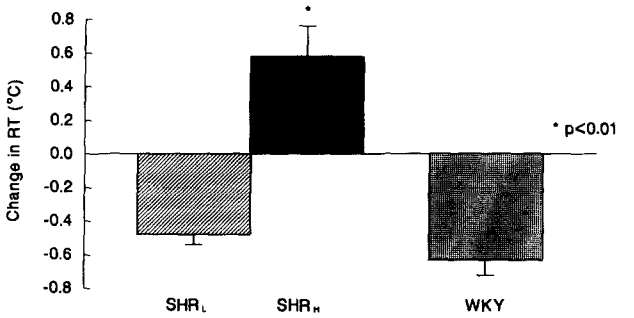
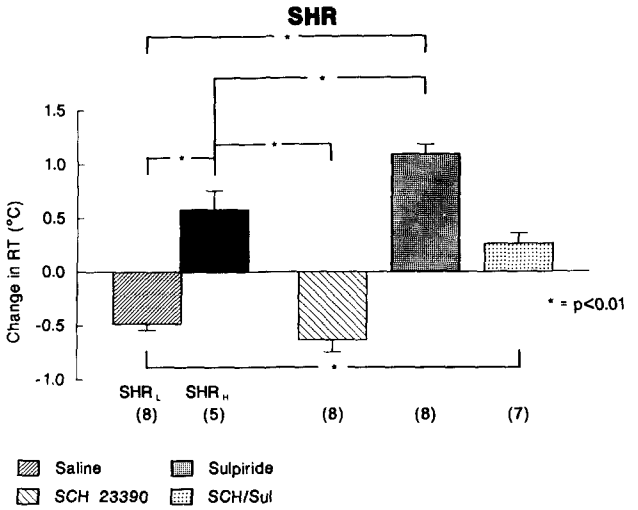


FIG. 2. Maximum changes in rectal temperature (RT) following intravenous cocaine infusion in saline-pretreated SHR and WKY. The notation SHR_L refers to those SHR in which the maximum, cocaine-induced, change in RT, prior to onset of convulsions, was positive (i.e., an increase in RT); SHR_H refers to those SHR in which RT fell following cocaine infusion. Mean values ± 1 S.E.M. are presented. *$p<0.01$ compared to values of either SHR_L or WKY.



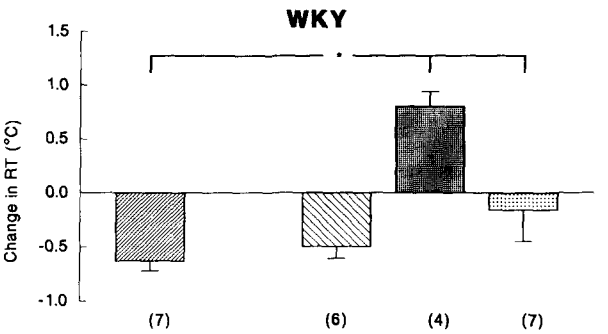


FIG. 3. (upper panel) Effects of pretreatment regimens on the maximum changes in rectal temperature (RT) produced following intravenous cocaine infusion in SHR. The notation SHR_L refers to those SHR in which the maximum, cocaine-induced, change in RT, prior to onset of convulsions, was positive (i.e., an increase in RT); SHR_H refers to those SHR in which RT fell following cocaine infusion. Numbers in parentheses indicate the numbers of animals in each group. Mean values ± 1 S.E.M. are presented. *$p<0.01$ between indicated groups. Symbols denoting the various pretreatment regimens are indicated between the upper and lower panels. (lower panel) Effects of pretreatment regimens on the maximum changes in rectal temperature (RT) produced following intravenous cocaine infusion in WKY. Numbers in parentheses indicate the numbers of animals in each group. Mean values ± 1 S.E.M. are presented. *$p<0.01$ between indicated groups.

sulpiride, abolished cocaine-induced reductions in rectal temperature in all WKY and SHR tested. Maximal increases in rectal temperature were significantly higher in sulpiride-treated SHR than in either vehicle-treated SHR_H or SHR_L and in sulpiride-treated WKY when compared to vehicle-treated WKY (Fig. 3). Combined treatment with SCH 23390 and sulpiride virtually abolished cocaine-induced changes in rectal temperature in both SHR and WKY (Fig. 3).

The effects of pretreatment regimens on the time-to-onset of convulsions are presented in Table 2. Despite alterations in cocaine-induced rectal temperature responses, dopamine receptor antagonists exerted only modest effects on sensitivity to cocaine-induced convulsions. Pretreatment with SCH 23390 significantly increased the time-to-onset of convulsions when compared to vehicle-treated SHR_H and sulpiride-treated SHR, but not when compared with vehicle-treated SHR_L or WKY. Combined treatment with SCH 23390 and sulpiride did significantly increase the time-to-onset of convulsions in WKY when compared with vehicle-, sulpiride- and SCH 23390-treated WKY. A similar protective effect was not observed in SHR following combined treatment.

DISCUSSION

The results of the present series of experiments indicate that dopaminergic systems exert significant regulatory influences over the body temperature responses to cocaine administration. Responses of the cardiovascular system and sensitivity to the convulsive actions of cocaine are influenced to a much lesser degree by modification of dopaminergic neurotransmission. However, particularly in the SHR, alterations in the regulation of body temperature play a significant role in determination of the sensitivity to cocaine-induced convulsions.

We have previously reported that continuous intravenous infusions of cocaine produce biphasic increases in arterial blood pressure and heart rate in conscious SHR and WKY (14). In general, a similar pattern of response to cocaine infusion was observed in saline-pretreated SHR and WKY in the present study.

Pressor responses to cocaine infusion were not significantly altered by any pretreatment regimen in either SHR or in WKY. These results are consistent with recognized mechanisms for cocaine-induced pressor responses (6, 28, 33). Catravas and Waters (4) could not alter the pressor and tachycardic responses to intravenous cocaine infusion in conscious dogs by pretreatment with the nonselective dopamine receptor antagonist, pimozide. In contrast, pretreatment with chlorpromazine, which possesses both dopamine receptor and alpha-adrenoceptor blocking actions, blunted cocaine-induced tachycardic and pressor responses; lethality was reduced as well. The present data indicate that dopaminergic mechanisms do not contribute significantly to such pressor responses. It should be noted that peripheral administration of dopamine receptor agonists consistently lowers blood pressure and heart rate in the SHR, due in part to centrally mediated inhibition of sympathetic neuronal activity (22,27). The cardiovascular effects of cocaine must, therefore, be mediated by factors other than, or in addition to, alterations in dopami-

nergic neuronal activity.

A different pattern of response was evident with respect to cocaine-induced tachycardia. In particular, dopaminergic receptor blockade altered the early, transient tachycardic response to cocaine infusions. Combined DA-1 and DA-2 receptor blockade abolished the early tachycardia, indicating mediation of this phase of the response by dopaminergic receptors. Following this initial response, heart rate returned toward preinfusion levels, with a tendency to increase once again shortly before convulsions began. Pretreatment regimens produced only minor alterations in secondary chronotropic responses and the significance of these effects remains to be determined. There has been no indication from previous reports that dopaminergic receptors are essential to cocaine-induced tachycardia. Indeed, Jones and Tackett (15) recently noted a dose-dependent, phentolamine-sensitive, tachycardia following intracerebroventricular cocaine injection in conscious, unrestrained WKY rats, which indicates central mechanisms in the development of cocaine-induced tachycardia. The present data, however, would suggest that dopamine release does play a role in cocaine-induced tachycardia.

An earlier report from this laboratory noted heterogeneity in SHR, with respect to cocaine-induced temperature responses, under conditions of restraint stress (14). Thus cocaine infusion is accompanied (prior to the onset of convulsions) by hypothermia in WKY and roughly 50% of SHR (SHR_L) tested. The remaining SHR (SHR_H) demonstrated hyperthermic responses to cocaine. In the present study, similar results were noted in SHR and WKY receiving saline pretreatment. The etiology of the heterogeneity in SHR is not certain. However, Morley et al. (25) have recently examined the relationship of stress to body temperature regulation in SHR and WKY using remote biotelemetry. Their data indicated that true resting body temperature does not differ between SHR and WKY. However, even mild handling stress increased core temperature in both SHR and WKY. Clearly, restraint stress can modify body temperature responses in SHR and WKY.

The effects of pretreatment with selective dopamine receptor blocking agents were most clearly evident when responses of rectal temperature to cocaine infusion were examined. The involvement of dopamine in thermoregulation is well documented (8, 16, 22) and cocaine is known to exert significant alterations in thermoregulatory responses, particularly at toxic doses (4, 10, 32). To our knowledge, the effects of selective dopaminergic receptor blockade on body temperature responses to cocaine in the rat have not been reported previously.

The present results are consistent with DA-2 dopaminergic receptor mediation of cocaine-induced hypothermic responses. Others have demonstrated that injection of the nonselective dopamine receptor agonist, apomorphine, will produce hypothermia in the rat (3, 11, 23). This effect appears to be mediated selectively by DA-2 receptors (3,11). Acute cocaine injection has been shown to lower body temperature in conscious rats, an effect which could be blocked by pretreatment with either 6-hydroxydopamine, the tyrosine hydroxylase inhibitor, alpha-methyl-m-tyrosine, or haloperidol, which suggests dopaminergic mediation of the hypothermia (10).

The hyperthermic responses observed in some SHR following cocaine infusion were completely abolished by pretreatment with SCH 23390, indicating mediation of cocaine-induced hyperthermia by DA-1 dopamine receptors. Hyperthermic responses to cocaine have been documented in the rat, although a role for dopamine receptors was not examined (7,32). Body temperature responses to administration of SCH 23390 alone can be complex, depending on dose employed (3,11), on the pretreatment interval (11) and the route of administration (3). No significant alteration in resting body temperature between pretreatment groups was observed at the time of onset of cocaine infusion in the present study, which agrees with the results of Carboni et al. (3). Faunt and Crocker (11) noted biphasic effects of SCH 23390 on resting body temperature, with an initial increase and a subsequent fall in temperature. However, the magnitude of both of these effects was dose-dependent. Catalepsy has been reported following SCH 23390 administration in the rat, an effect attributed to specific DA-2 receptor antagonism (24). Although animals in the present study were restrained, it is possible that cocaine-induced hyperthermic responses are related to increases in cocaine-induced muscle tone, since cocaine produces locomotor stimulation (29). The cataleptic action of SCH 23390 may have acted to minimize this increased muscle tone, thereby limiting hyperthermic responses. This interaction has not been specifically examined. However, obvious sedation was not noted in our animals following SCH 23390 treatment.

The ability of dopamine receptor blockade to alter sensitivity to cocaine-induced convulsions remains to be considered. We have shown previously that the time-to-onset of convulsions, and, therefore, the dose of cocaine needed to induce convulsions, is linearly correlated with cocaine-induced changes in rectal temperature in the restrained SHR (14). Thus animals in which cocaine raises, rather than lowers body temperature, were significantly more sensitive to cocaine-induced convulsions. This phenomenon was reproduced in the present series of experiments. Catravas and Waters concluded that hyperthermia was the most significant contributor to lethality in conscious dogs following intravenous cocaine infusion (4). Furthermore, these investigators predicted the relationship between rectal temperature responses and cocaine-induced convulsions that we observed in SHR. Dopaminergic receptor blockade, regardless of the selectivity of the antagonism or the effects of cocaine-induced rectal temperature changes, did not consistently exert a significant protective influence against cocaine-induced convulsions. In fact, blockade of DA-2 receptors increased sensitivity to cocaine toxicity in SHR, but not in WKY, although such blockade resulted in hyperthermic responses to cocaine in both strains. Selective DA-1 receptor blockade did not significantly alter cocaine toxicity in either strain, although it did eliminate the presence of the SHR_H response. Witkin et al. (34) reported that pretreatment with SCH 23390, but not haloperidol, would protect against cocaine-induced sudden death in the rat. Our data do not support a similar protective action of SCH 23390 using cocaine infusion and the end-point of convulsions. Combined DA-1 and DA-2 receptor blockade did increase, modestly, the dose of cocaine required to produce convulsions in WKY. This effect was not evident in the SHR, despite the fact that cocaine-induced rectal temperature changes were virtually abolished in both strains. Thus the clear demonstration of an association between hyperthermia and sensitivity to cocaine-induced convulsions in untreated or vehicle-treated animals is not observable in rats pretreated with DA receptor antagonists. It is probable that the involvement of dopaminergic systems in thermoregulation is largely distinct from those systems which directly influence sensitivity to cocaine-induced convulsions.

It is difficult, at the present time, to attribute the differential cocaine-induced responses of SHR and WKY to specific alterations in dopaminergic neurochemistry. Dopaminergic receptors (both DA-1 and DA-2) (1, 2, 5, 19, 20), levels of dopamine itself (35) or its metabolites (13,35), and dopamine uptake (20,30) either differ between SHR and WKY or are differentially altered in SHR and WKY by cocaine treatment. Moreover, analysis of these effects can be further complicated by regional brain or age-associated variations in dopaminergic neurochemistry.

It would appear that changes in rectal temperature may be a

significant indicator of sensitivity to the toxic effects of cocaine, in at least some groups of animals or in specific situations. Many factors must modify this association, however, and it is not possible to explain the effects which pretreatment with selective dopamine antagonists exerts on cocaine toxicity by such a mechanism. Dopaminergic receptor blockade does significantly alter specific responses to cocaine in the rat, which supports dopaminergic mediation of cocaine-induced responses. Nevertheless, dopamine receptor antagonists, regardless of their selectivity, do not appear to be useful antagonists of cocaine toxicity in the rat.

ACKNOWLEDGEMENTS

These investigations were supported in part by NIDA (DA 04264) and by the American Heart Association, Mississippi Affiliate (R.W.R.). The authors gratefully acknowledge the support of the Vice-Chancellor of the University of Mississippi Medical Center, who provided support for E.S.C. in the form of a Summer Medical Student Research Fellowship.

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