Pharmacology Biochemistry & Behavior, Vol. 36, pp. 889–892. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

Cocaine and Body Temperature in the Rat: Effect of Exercise

PETER LOMAX[1] AND KERI A. DANIEL

Department of Pharmacology, School of Medicine and the Brain Research Institute
University of California, Los Angeles, CA 90024-1735

Received 5 December 1989

LOMAX, P. AND K. A. DANIEL. *Cocaine and body temperature in the rat: Effect of exercise.* PHARMACOL BIOCHEM BEHAV **36**(4) 889–892, 1990.—The laboratory rat is being studied as a model to determine if abuse of cocaine constitutes a risk factor in the pathogenesis of stress or exertion induced heatstroke. During running on a treadmill for 60 min under thermoneutral conditions (T_a 22°C) a rise in core temperature of ~1°C was recorded. Injection of cocaine (10 or 20 mg/kg IP) or its vehicle (0.9% NaCl solution) did not modify the running behavior or the core temperature change. Cocaine (30 mg/kg IP) led to a significant increase in the core temperature (compared to animals treated with saline or the lower doses of cocaine) at 45 and 60 min. The rats recovered rapidly following cessation of exercise. Repeated (3) injections of cocaine (30 mg/kg) at 7-day intervals did not alter the magnitude of the final hyperthermia, i.e., neither tolerance nor potentiation were in evidence.

Cocaine Body temperature Hyperthermia Ambient temperature Exercise Rats

THE number of emergency room admissions because of cocaine toxicity continues to rise with the increasingly widespread abuse of the drug by all strata of society, particularly in major cities in the United States. There were over 580 cocaine associated deaths (excluding gang related homicides) in Los Angeles in 1988. Frequently the patients present with marked hyperthermia, and indications of " . . . terminal hyperpyrexia in a number of cases . . . " were mentioned in a review of street deaths following recreational use of cocaine (9). Intravenous injection of cocaine does not alter oral temperature in humans at rest under normal ambient conditions (2) but Loghmanee and Tobak (6) reported the death of a young (20-year-old) white male with a rectal temperature of 109°F (42.8°C) following an evening of cocaine and ethanol abuse. A previously healthy 23-year-old woman (in late April in Queensland, Australia, which has a hot, humid summer climate) developed hyperpyrexia (rectal temperature >42°C) after intravenous self-administration of cocaine. Subsequent fatal complications included status epilepticus, rhabdomyolysis, hypotension, disseminated intravascular coagulation and hepatic dysfunction (1). Over the past two years there have been continual reports of the occurrence of rhabdomyolysis associated with ingestion of cocaine (particularly "crack") (11,12). Death from cocaine overdose is frequently ascribed to "acute cardiac failure"; it should be noted that this is usually the initial, and often the final, recorded cause of death in heatstroke victims. To what extent these toxic effects are due to primary actions of cocaine on the organ systems (brain, heart, liver, muscles, etc.), or are secondary to induced thermoregulatory changes, is unclear; certainly the clinical pictures of severe cocaine toxicity and terminal heatstroke are almost identical.

We are using the laboratory rat as a model to determine if abuse of cocaine constitutes a risk factor in the pathogenesis of exertion induced heatstroke. In previous reports (7,8) we have demonstrated that the core temperature changes after injection of cocaine (10–40 mg/kg IP) in the rat are dose dependent and are a function of the ambient temperature (T_a). At normal laboratory temperature (T_a 22°C) a fall in core temperature occurs which is accompanied by vasodilation in the tail during the early period when the temperature is falling (suggesting a downward shift in the thermoregulatory set point). When T_a is above 30°C cocaine causes hyperthermia. At the highest dose (40 mg/kg) increased motor activity and seizures are common and the animals have to be cooled with ice packs due to life-threatening hyperpyrexia. There was no evidence of tolerance to these effects with repeated injection of cocaine.

The mortality rate from stress induced heatstroke is very high, exceeding 80% unless expeditious and skilled emergency treatment is available (4), so it is important to determine the nature of the thermoregulatory changes in cocaine toxicity. The present study was undertaken to determine the effect of exercise, at normal T_a, on the core temperature of rats treated with cocaine.

METHOD

Sprague-Dawley rats, with an initial body weight of ~150 g, were housed at 22 ± 1°C and ambient humidity (30–60% under normal weather conditions) on a standard 12-hr light/dark cycle. The animals were observed for any signs of disease for at least 7

[1]Requests for reprints should be addressed to Dr. Peter Lomax, Department of Pharmacology, UCLA School of Medicine, Los Angeles, CA 90024-1735.

days prior to the experiments and during this period they were handled and allowed to adapt and stabilize to the laboratory environment. All experimental sessions were started at 0800 hr to control for circadian variations. Food and water were freely available up to the start of each recording cycle.

Deep body temperature was measured with a small animal thermistor probe, inserted through the rectum for at least 6 cm, and connected to a telethermometer. The readings were generally taken at 15-min intervals with at least a 30-min stabilization period prior to treatment.

The rats were trained to exercise on a dual small animal treadmill (Columbus Instruments) with a running space 38 cm long × 14 cm wide × 12 cm high. Each lane was enclosed in a Plexiglas chamber of ~15 liters capacity provided with an air mixing fan. The temperature in the chamber was monitored with a thermistor transducer taped to an interior wall and remained constant at 22 ± 1°C (ambient room temperature) during the exercise period. The animals were encouraged to run on the belt by gentle pushing so that it was unnecessary to utilize the electrical stimulus grid built into each treadmill. The animals were trained to run on the belt for 5 days each week for 7 weeks with the following schedule:

Week	Belt Speed (m/sec)	Grade (deg)	Duration (min)
1	0.12	0	20
2	0.12	0	30
3	0.16	0	40
4	0.16	2.5	45
5	0.22*	2.5	50
6	0.22	2.5	60
7	0.22	2.5	60

*0.5 mph.

This level of exercise consistently led to a significant rise in core temperature.

The experiments were conducted from the 8th week. The animal was placed in the chamber of the treadmill and one or more core temperature readings were made at 15-min intervals prior to the onset of running and at 15-min intervals during the 60-min exercise period. Drugs were administered by intraperitoneal injection 15 min after running commenced (the start of exercise is indicated as "0" time in the figures).

Cocaine hydrochloride was dissolved in pyrogen free NaCl (0.9%) solution to the appropriate concentration to allow an injection volume of 0.1 ml/100 g body weight. Doses are the weight of the salt.

The research protocols were approved by the institutional animal research committee.

Data were analyzed using a microcomputer statistical program which calculates exact probability levels.

RESULTS

Six rats were trained to run on the treadmill and the core temperature was recorded at the start and end of 60 min of exercise at T_a 22°C. Similarly, a second group of 6 was exercised for 60 min and each animal was treated, in random order on 2 separate days, 15 min after the start of running, with 0.9% NaCl (0.1 ml/100 g IP) and cocaine (10 mg/kg IP). The mean core temperatures at the start, and after 60 min, of exercise are presented in Table 1. In each case the temperature increased significantly during running. The time course of the temperature changes in these animals is illustrated in Fig. 1. A slight fall in temperature, which arrests the initial rate of rise, is seen following injection of cocaine and the time course of this corresponds to that which occurs when the same dose is injected into nonexercising rats (8) (inset Fig. 1). The final core temperature was not significantly different in each of the three groups.

TABLE 1

MEAN CORE TEMPERATURE CHANGES DURING 60 MIN RUNNING

Treatment (dose)*	Number of Animals	Initial Temperature (mean ± SEM)	Final Temperature (mean ± SEM)
None	6	37.60 ± 0.25	38.73 ± 0.07†
0.9% NaCl (0.1 ml/100 g)	6	37.89 ± 0.06	38.99 ± 0.17‡
Cocaine (10 mg/kg)	6	37.80 ± 0.17	39.10 ± 0.17§

*Administered 15 min after start of running.

†Significantly different from initial temperature ($p<0.0014$; Students t-test).

‡Significantly different from initial temperature ($p<0.0001$; Students t-test).

§Significantly different from initial temperature ($p<0.0003$; Students t-test).

Four groups of animals were exercised at T_a 22°C and injected after 15 min with 0.9% NaCl (0.1 ml/100 g IP) or cocaine (10, 20 or 30 mg/kg IP). The starting temperatures were the same for each group and, after 60 min exercise, all had increased significantly. However, at the highest dose of cocaine (30 mg/kg), the final temperature was significantly elevated over those in the other treatment groups (Table 2). Figure 2 compares the time course of the temperature change in the cocaine (30 mg/kg) animals with the saline controls.

A further group of 6 rats was treated with cocaine (30 mg/kg IP) during exercise at T_a 22°C three times at 7-day intervals. On each occasion the final temperatures (39.9 ± 0.28°C; 39.4 ± 0.21°C; 39.3 ± 0.12°C) were essentially the same (Fig. 3).

DISCUSSION

In previous studies (7,8) in the rat under thermoneutral (22°C) ambient conditions cocaine (10–40 mg/kg) caused a fall in body temperature over a period of 30 min with recovery to the control level within the following 45 min, as illustrated in the inset to Fig. 1. With none of these doses did the core temperature rise above the resting level, even though some of the animals developed marked hyperactivity at the highest dose tested (40 mg/kg). This hypothermic action appears to be manifest in the exercising animals by the interruption of the rise in temperature for 15 min following injection of cocaine.

During moderately strenuous exercise at the ambient temperature to which the animals were acclimated there was a progressive rise in core temperature of about 1°C over 20–30 min, at which level it appeared to have stabilized (see Figs. 2 and 3). This probably represents the physiological response to the increase in the thermoregulatory set point triggered by proprioceptive input from the working muscles. It did not cause any unusual behavioral manifestations and the animals rapidly recovered (within 30 min) when they were removed from the treadmill. Injection of cocaine (10 and 20 mg/kg) did not modify this increase (compare final

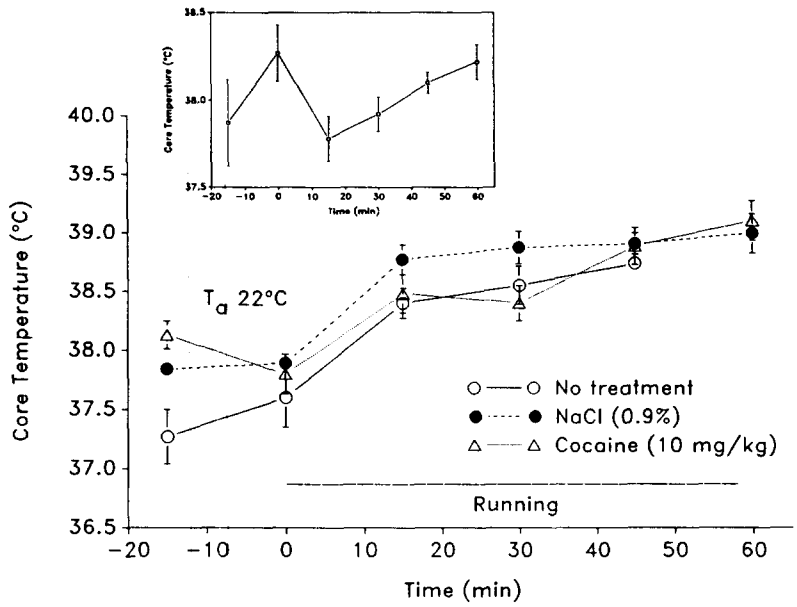

FIG. 1. Time course of the core temperature changes in groups of 6 rats during exercise from time 0 to 60 min at T_a 22°C. Saline or cocaine were injected 15 min after the start of the running. Inset figure illustrates the fall in body temperature following injection of cocaine (10 mg/kg IP) at time 0 in 6 rats at rest.

temperatures in Table 2) nor did it interfere with the animals' running behavior.

At the highest dose of cocaine (30 mg/kg), after the initial period of temperature stabilization from 15 to 30 min, the temperature increased further and at 45 and 60 min was significantly greater than in the saline controls and the 10 and 20 mg/kg groups (Table 2; Fig. 2).

The exercise to which the rats were subjected is much less severe than that used in studies "to exhaustion." However, in order to allow for the time course of the drug effect, it was necessary to select a level of running (belt speed and gradient) which the animals could maintain over a period of at least 60 min.

Even so, it is apparent that this imposed a thermal stress of a degree such that the animals were unable to regulate the core temperature at the exercise induced elevated set point in the face of the high dose of cocaine. The initial fall in core temperature following injection of cocaine to rats at rest under thermoneutral conditions may be due to a lowering of the set point (8). However, when cocaine is administered to rats exposed to a high ambient temperature (30°C) an increase in body temperature occurs which is accompanied by heat loss behavior (sprawling, saliva spreading) indicating that the thermoregulatory set point is below the core temperature. Thus, it would appear that cocaine has a dual effect on thermoregulation. The ambient temperature and exercise induced heat production seem to be the major determinants of the

TABLE 2

MEAN CORE TEMPERATURE IN GROUPS OF RATS RECORDED 60 MIN AFTER START OF EXERCISE

Treatment (dose)*	Number of Animals	Core Temperature (mean ± SEM)
0.9% NaCl (0.1 ml/100 g)	6	39.08 ± 0.07
Cocaine (10 mg/kg)	6	39.10 ± 0.17
Cocaine (20 mg/kg)	10	39.06 ± 0.11
Cocaine (30 mg/kg)	6	39.87 ± 0.28†‡

*Administered 15 min after start of running.

†Significantly different from saline control and cocaine (10 mg/kg) ($p<0.05$; Students t-test).

‡Significantly different from cocaine (20 mg/kg) ($p<0.01$; Students t-test).

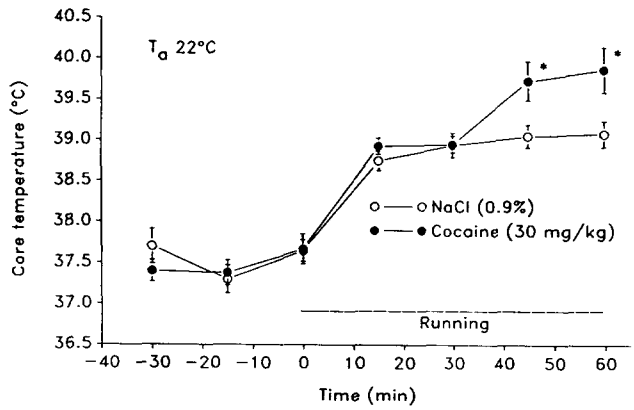

FIG. 2. Body temperature changes in two groups of 6 rats during exercise from 0 to 60 min at T_a 22°C. Saline or cocaine were injected 15 min after the start of running. *Significantly different from saline control ($p<0.03$; Students t-test).

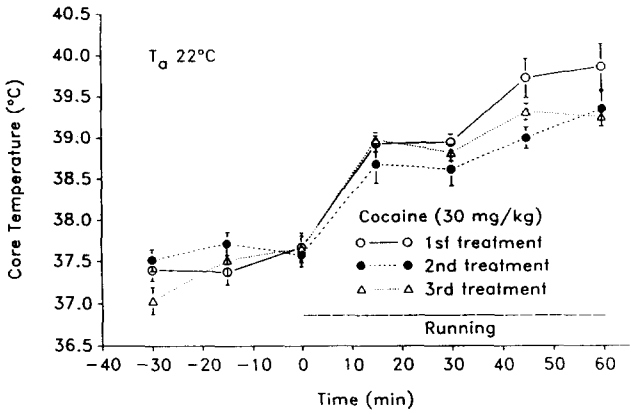

FIG. 3. Body temperature changes in a group of 6 rats during exercise from 0 to 60 min at T_a 22°C treated with cocaine at weekly intervals. Cocaine was injected 15 min after the start of running. The group mean temperatures did not differ significantly at any time point.

direction of the change in core temperature.

In dogs acclimated to a laboratory temperature of 20–22°C for 1 hr cocaine (1 mg/kg/min) was infused intravenously until a generalized motor seizure occurred (3). The mean total dose in 8 animals was 17.9 ± 1.63 mg/kg. A progressive rise in core temperature occurred, up to 30 min after the infusion was discontinued, so that the animals became hyperpyrexic (maximum temperatures 43.4–44.8°C) and developed life threatening cardiac arrhythmias unless cooled by cold water immersion. Panting was absent during the period of hyperpyrexia; whether this suppression of the major effector for heat loss in the canine species is due to a direct effect of the cocaine, or is a reflection of a drug induced elevation of the thermoregulatory set point, is unclear. The major avenue for heat loss in the rat is by radiation from the skin of the tail (10) which mechanism appears to be able to prevent any dangerous rise in core temperature, even after high doses of cocaine, provided the ambient temperature is within the animal's thermoneutral range. In this respect the rat is probably a more appropriate model for investigating the effects in man.

Neither tolerance to, nor potentiation of, cocaine induced hyperthermia were in evidence with repeated weekly injections (Fig. 3). It is difficult to determine if tolerance occurs to the subjective effects of cocaine in man, although there is some indication that the initial "rush" decreases in intensity during continuous infusion of cocaine into volunteers (5). The present study does not lend any assurance that repeated abuse of cocaine lends any protection to its adverse effects. In the present study the effects of weekly injections were compared to assure that tolerance would not be a complicating factor in the research protocol. Previously it was shown that daily injections did not lead to tolerance or potentiation (7,8). Shorter time intervals, which might be more likely to demonstrate an effect from the repeated injections, could not be used since, although the temperature response is relatively short lived, cumulative toxicity occurs over several hours so that even after six hours the second dose frequently induced seizures and death.

One possible approach to counteracting cocaine dependence is the development of drugs which will antagonize its euphoric effect (13). Blockade, or reversal, of the temperature changes during exercise in the rat might constitute a convenient primary screen for such potential therapeutic compounds.

ACKNOWLEDGEMENT

This research is supported by a grant from the National Institute on Drug Abuse No. DA 04904.

REFERENCES

1. Campbell, B. G. Cocaine abuse with hyperthermia, seizures and fatal complications. Med. J. Aust. 149:387–389; 1988.
2. Clark, W. G.; Lipton, J. M. Changes in body temperature after administration of adrenergic and serotonergic agents and related drugs including antidepressants: II. Neurosci. Biobehav. Rev. 10:153–220; 1986.
3. Gold, M. S.; Ehrenkranz, J. R. L.; Ehrhart, W.; D'Ver, A. S. Treatment of acute cocaine toxicity. Soc. Neurosci. Abstr. 14:661; 1988.
4. Khogali, M.; El-Sayed. H.; Amar, M.; El-Sayed, S.; Al Habashi, S.; Mutwali, A. Management and therapy regimen during cooling and in the recovery room at diffferent heat stroke treatment centres. In: Khogali, M.; Hales, J. R. S., eds. Heat stroke and temperature regulation. Sydney: Academic Press; 1983:149–156.
5. Kumor, K. M.; Sherer, M. A.; Gomez, J.; Cone, E.; Jaffe, J. H. Subjective response during continuous infusion of cocaine. Pharmacol. Biochem. Behav. 33:443–452; 1989.
6. Loghmanee, F.; Tobak, M. Fatal malignant hyperthermia associated with recreational cocaine and ethanol abuse. Am. J. Forensic Med. Pathol. 7:246–248; 1986.
7. Lomax, P.; Daniel, K. A. Body temperature changes induced by cocaine in the rat. Proc. Thermal Physiol. Symp. Tromsø 1989. Amsterdam: Elsevier; in press.
8. Lomax, P.; Daniel, K. A. Cocaine and body temperature in the rat: effects of ambient temperature. Pharmacology; in press.
9. Mittleman, R. E.; Wetli, C. V. Death caused by recreational cocaine use. JAMA 252:1889–1893; 1984.
10. Rand, R. P.; Burton, A. C.; Ing, T. The tail of the rat in temperature regulation and acclimatization. Can J. Physiol. Pharmacol. 43:257–267; 1965.
11. Reinhart, W. H.; Stricker, H. Rhabdomyolysis after intravenous cocaine. Am. J. Med. 85:579; 1988.
12. Roth, D.; Alarcón, F. J.; Fernandez, J. A.; Preston, R. A.; Bourgoignie, J. J. Acute rhabdomyolysis associated with cocaine intoxication. N. Engl. J. Med. 319:673–677; 1988.
13. Waldrop, M. M. NIDA aims to fight drugs with drugs. Science 245:1443–1444; 1989.