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BRIEF COMMUNICATION

Comparative Pharmacology of Norcocaine in *M. Mulatta* and *M. Fascicularis*[1]

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WILSON, M. C., J. A. BEDFORD, A. H. KIBBE AND J. A. SAM. *Comparative pharmacology of norcocaine in M. mulatta and M. fascicularis*. PHARMAC. BIOCHEM. BEHAV. 9(1) 141–145, 1978.—Norcocaine was administered intravenously (0.05, 0.5, 5.0 mg/kg) to three chaired unanesthetized male rhesus monkeys and to three chaired male cynomolgus monkeys. Respiration rate, heart rate and rectal temperature were monitored. In the rhesus monkeys tachycardia and hyperventilation resulted. However, similar qualitative and quantitative changes were not observed in the cynomolgus species. There was a statistically significant difference in the response to norcocaine across species. These results indicate that cynomolgus monkeys are either less sensitive or respond differently than rhesus monkeys to some of the pharmacological effects of norcocaine. Furthermore, these data confirm that norcocaine is an active derivative of cocaine in both rhesus and cynomolgus monkeys.

Norcocaine Cardiovascular Rhesus Cynomolgus Species difference

IT HAS BEEN reported that following the parenteral administration of cocaine, N-demethylation results in the formation of norcocaine. This metabolite has been detected in the brain of rats [5], dogs [7] and monkeys [2]. There have been little data reported concerning the pharmacological activity of this metabolite. It has been reported that the intravenous administration of norcocaine to rats resulted in tachycardia and convulsions and resembled cocaine with respect to potency, onset and duration of activity and pharmacological spectrum [6]. Other investigators also presented evidence that norcocaine is an active metabolite of cocaine [2]. These investigators reported that norcocaine was equipotent to cocaine as an inhibitor of the uptake of tritiated norepinephrine by synaptosomes while other metabolites of cocaine demonstrated little activity.

An improved synthetic pathway for norcocaine [1] was recently reported. Furthermore, preliminary data on the activity of this compound in a rhesus monkey suggested that norcocaine possessed convulsive, mydriatic, hypothermic and respiratory stimulant actions. The present study was conducted to ascertain in greater detail the pharmacological profile of norcocaine in two species of macaque: *M. mulatta* (Rhesus) and *M. fascicularis* (Cynomolgus). Because the rhesus monkey is becoming less available for use in the laboratory, the less expensive cynomolgus species is achieving widespread popularity as a laboratory animal and was therefore included in this study.

METHOD

Animals and Surgery

The animals for this experiment were three juvenile male rhesus monkeys and three juvenile male cynomolgus monkeys weighing 3.0–4.0 kg. All animals had been drug free for at least 90 days prior to this study. Animals were anesthetized with 50 mg of ketamine hydrochloride (Ketalar®, Parke Davis) and a polyethylene catheter (PE50-Intramedic, Clay Adams) was inserted into the saphenous vein. Animals were then positioned in primate restraining chairs (Plas Labs). At this time, rectal temperature probes (Yellow Springs Instruments) were inserted and subcutaneous stainless steel needle electrodes attached over the thorax for later monitoring of colonic temperature (Yellow Springs Instruments, Telethermometer) and heart rate (Narco-Biosystems, Physiograph) respectively. The restraining chairs were placed in sound attenuated experimental cubicles in a room where the temperature was maintained at 23° ± 2°C. The saphenous catheter was attached to a saline (Baxter Laboratories) drip to maintain catheter patency. While chaired, animals had ad lib access to water and were fed Purina Monkey Chow® in the morning and evening. Food was withheld on the morning of drug testing. Approximately one hr prior to drug administration, a pneumatic cuff (Narco-Biosystems) was placed around each animal's abdomen in order to monitor respiration rate (Narco-Biosystems, Physiograph).

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Procedure

The day following placement in the chairs, the animals were treated with either saline or a saline solution of norcocaine. Norcocaine was prepared and analyzed according to the method of Borne *et al.* [1]. Solutions were prepared on the day of use and were administered intravenously as a bolus via the saphenous vein. Administration of drug was followed with an injection of saline. All drugs were administered from outside the experimental chamber with the chamber door closed so that the animal would not be excited by the presence of the observer.

On a given treatment day each animal received three 1.0 ml injections of either saline or a saline solution of norcocaine. The initial injection consisted of either 0.05 mg/kg of norcocaine or the equivalent volume of saline. Thirty min later a second dose of 0.5 mg/kg norcocaine was administered. Two hr following administration of the second dose, 5.0 mg/kg of norcocaine was injected. These time intervals were chosen based on preliminary data which indicated that behavioral or physiological changes induced by these dosages of norcocaine had completely dissipated by the time that the succeeding injection was to be administered. The other treatment was administered 3 days following the initial treatment. Treatments were administered to each animal in a randomized sequence. The technician charged with administering the treatments was unaware of their identity.

Thirty min prior to the initial injection, recording of respiration rate, heart rate and body temperature was initiated and continued for 8 hr. The percentage change from control (value immediately preceding the first injection of the session) for each parameter at various post-treatment intervals, was calculated for each animal following both the saline and norcocaine treatments. These values were then averaged within a species. Within a species the effects of norcocaine on these parameters were statistically compared to those of saline using a matched-pairs t test. The effects of norcocaine were compared across species using the Student's t.

RESULTS

The administration of norcocaine did not result in any statistically significant changes in colonic temperature in either animal species. However, a 2°C elevation in temperature was observed in one rhesus monkey after dosing with 5.0 mg/kg. Saline did not alter temperature in this animal. This same dose of norcocaine produced a decrease in body temperature of a similar magnitude in one cynomolgus animal. Saline treatment did not alter temperature in this animal.

The effects of treatment with norcocaine on heart rate and respiration rate in both species are illustrated in Fig. 1 and Fig. 2 respectively. As compared to saline in the rhesus monkeys, norcocaine produced a statistically significant increase in heart rate at 20, 30 and 60 min following administration of 5.0 mg/kg. The duration of this tachycardia varied greatly across animals as reflected in the large variability in response at 120 and 180 min post-treatment. At lower dosages interanimal variability in sensitivity to this effect was prominent. Norcocaine likewise significantly elevated respiratory rate as compared to saline following administration of 5.0 mg/kg in this species. Whereas there was a mean increase of 40% in heart rate, respiratory rate essentially doubled. Within an animal the duration of the tachycardia and hyperventilation following this dose were very similar but the duration of these effects varied greatly across animals. Nonsignificant increases in respiration rate were observed in some animals immediately after treatment with 0.5 and 0.05 mg/kg.

In the cynomolgus species a different spectrum of action resulted from the administration of norcocaine. Compared to saline, norcocaine produced a statistically significant bradycardia rather than a tachycardia in these animals. This effect was produced by both 0.05 and 0.5 mg/kg and consisted of a moderate 10–15% decrease in rate. The variability in this response was small. The bradycardia was not significant following treatment with the highest dose, however the rates were comparable to those following treatment with the lower dosages. Furthermore, unlike the rhesus, there were no increases in heart rate exceeding 4% noted in any animal of this species following any of the dosages of norcocaine. This species difference could not be attributed to a different baseline heart rate since this value was comparable for both species. This difference in effect on heart rate across species was statistically significant following treatment with 5.0 mg/kg but not after treatment with 0.05 or 0.5 mg/kg.

Norcocaine did not significantly affect respiration in the cynomolgus monkeys. However, the 5.0 mg/kg dose decreased this parameter 10–60 min postinjection. Mean respiratory rate decreased by 10–20% with little intraspecies variability in this response. This effect was in sharp contrast to the statistically significant elevation in rate produced by the same dose of norcocaine in the rhesus monkeys. A statistically significant difference in effect occurred across species with respect to this parameter following this dosage.

In summary, whereas norcocaine resulted in an increase in heart rate, respiration rate and body temperature (one animal) in the rhesus monkey; bradycardia, no increase in respiration rate and hypothermia (one animal) occurred in the cynomolgus species.

DISCUSSION

The results of the present study demonstrate that norcocaine is pharmacologically active in nonhuman primates. Such activity had been suggested by a previous report [1]. These authors reported that 4.5 mg/kg of norcocaine administered intravenously as a bolus to a rhesus monkey induced convulsions, hypothermia, and an initial increase followed by a decrease in respiration rate. Convulsions were not observed in either species in the present study. Furthermore, no significant change in body temperature was recorded. These results suggest that the hypothermia reported in the earlier study may have been related to the convulsive activity of norcocaine.

The effects of 5.0 mg/kg of norcocaine in the rhesus monkey in this study closely resemble those reported with cocaine in the same species [8]. In the latter study 5.0 mg/kg of cocaine produced a statistically significant increase in heart rate, respiration rate and body temperature. Lower dosages (0.5 and 0.05 mg/kg) also increased these parameters but not significantly. Similar results have been reported with cocaine in rhesus monkeys [4].

Kibbe *et al.* [3] reported that 0.03, 0.3 and 3.0 mg/kg of cocaine administered intravenously to unanesthetized cynomolgus monkeys failed to increase heart rate. However, the largest dose did produce a doubling in respiration rate. From these data, then, it would appear that the cynomolgus species is less sensitive than the rhesus with respect to the cardiovascular actions of cocaine. Based on the present data

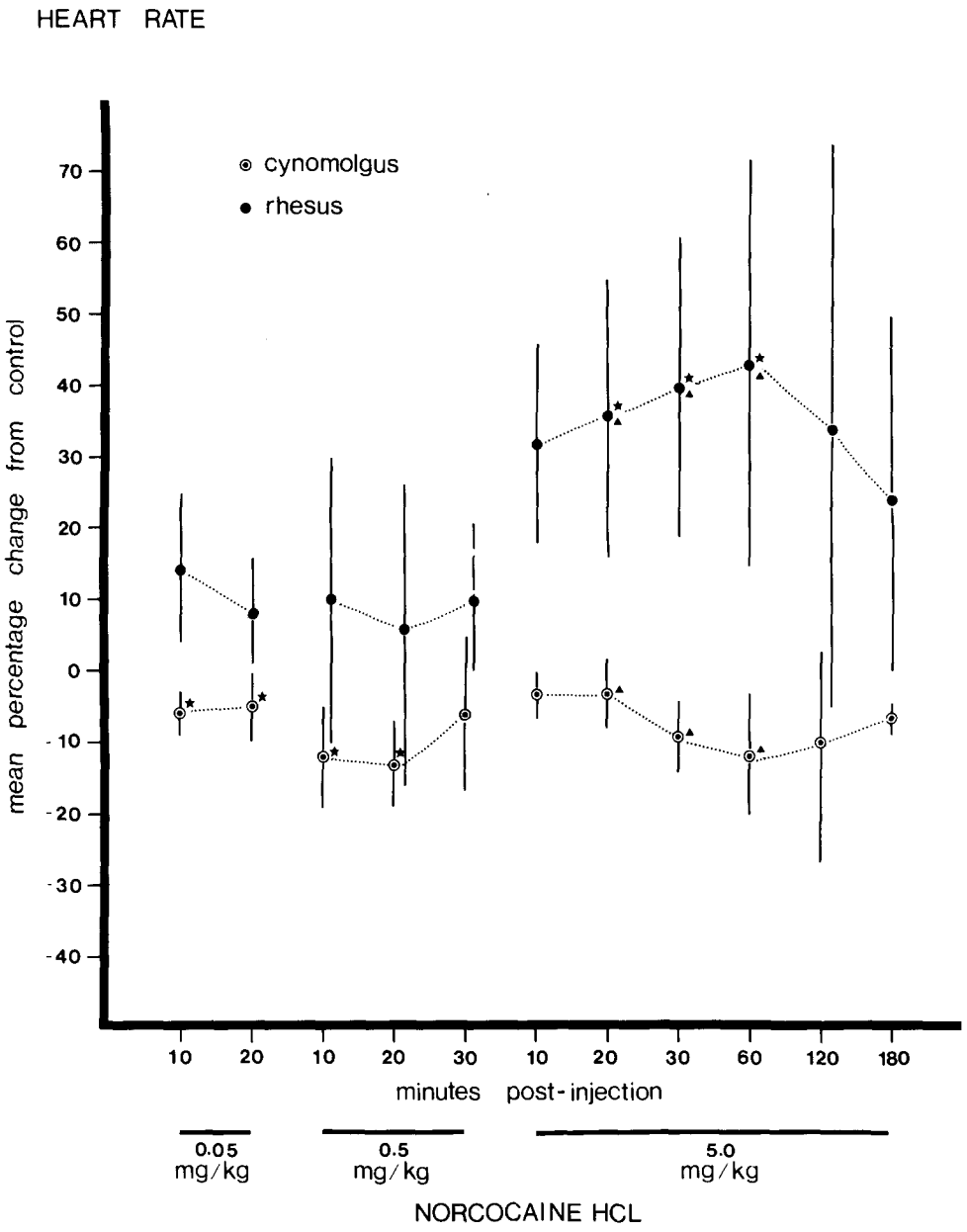

FIG. 1. Mean (N=3) percentage change in heart rate as a function of norcocaine dose, post-treatment time and species of macaque. A single asterisk denotes a significant difference ($p<0.05$) from saline at the corresponding post-treatment time. Vetical lines represent the SEM. A triangle indicates a significant species difference ($p<0.05$) in norcocaine effect at a given dose and post-treatment time.

this species difference in response also extends to the cardiovascular response to norcocaine. Whether this species difference in cardiorespiratory sensitivity to these agents is a manifestation of a differential behavioral response (increased hyperreactivity) remains to be ascertained.

Since the cynomolgus species is largely replacing the rhesus monkey as a laboratory species due to cost and availability, investigators should be cautious about extrapolating behavioral pharmacological data between the two species until such extrapolation can be validated.

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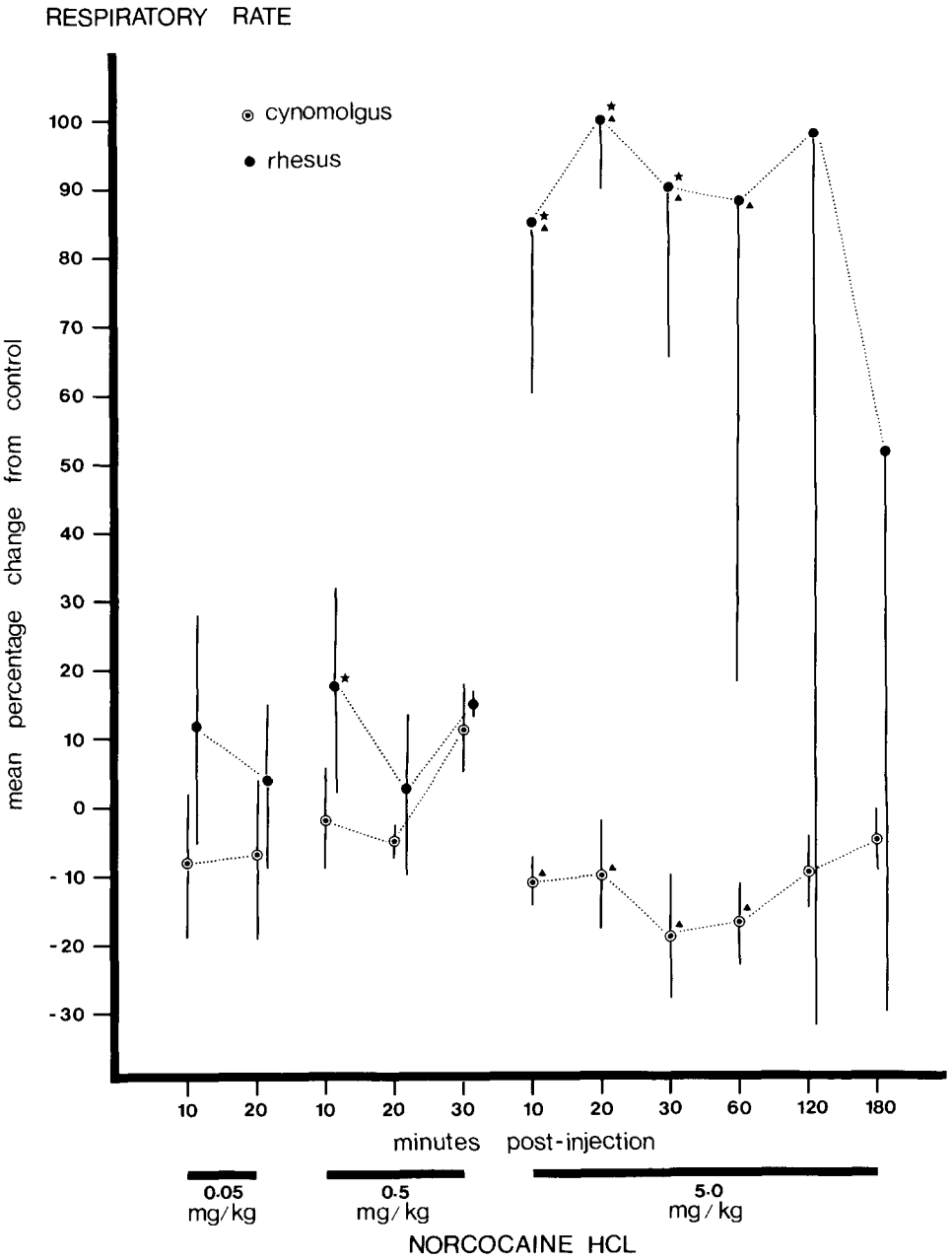

FIG. 2. Mean (N=3) percentage change in respiration rate as a function of norcocaine dose, post-treatment time and species of macaque. A single asterisk denotes a significant difference ($p<0.05$) from saline at the corresponding post-treatment time. Vertical lines represent the SEM. A triangle indicates a significant species difference ($p<0.05$) in norcocaine effect at a given dose and post-treatment time.

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