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PCA: Effects on Ejaculation, Thermoregulation, Salivation, and Irritability in Rats[1]

C. R. HUMPHRIES, M. O'BRIEN AND G. PAXINOS[2]

School of Psychology, The University of New South Wales, P. O. Box 1, Kensington, New South Wales, Australia, 2033

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HUMPHRIES, C. R., M. O'BRIEN AND G. PAXINOS. *PCA: Effects on ejaculation, thermoregulation, salivation, and irritability in rats.* PHARMAC. BIOCHEM. BEHAV. 12(6) 851–854, 1980.—The short term monoamine releaser *p*-chloroamphetamine (PCA) was injected intraperitoneally in male rats housed at 20°C. Within 2 hr of PCA injections (2.5, 5.0, 8.0 or 10.0 mg/kg), rats showed ejaculation, decreased colonic temperature, increased salivation, and increased irritability. Ejaculation and salivation scores were considerably lower in the 2.5 mg/kg than in the higher dose groups, but otherwise were not dose dependent at the doses used. Hypothermia was of similar magnitude in all groups, but lasted longer in the higher dose groups. Irritability increased with dose size. In order to study the role of ambient temperature in PCA-induced behavioral changes, observations were made on an additional group or rats housed at the higher ambient temperature of 25°C. In these rats an increase, rather than a decrease, in mean colonic temperature was observed following PCA injection (5 mg/kg). Ejaculation and irritability scores were similar to those observed at the lower ambient temperature, but salivation was enhanced. It is suggested that PCA induces ejaculation, salivation, irritability and, depending on the ambient temperature, either hypothermia or hyperthermia.

p-Chloroamphetamine Ejaculation Thermoregulation Salivation Irritability Ambient temperature

p-CHLOROAMPHETAMINE (PCA) injections produce a number of behavioral and pharmacological changes in rats. Within a few minutes of PCA injection a behavioral syndrome consisting of tremor, rigidity, straub tail, hindlimb abduction, lateral head weaving, and reciprocal forepaw treading appears [21]. Within an hour of injection an increase in colonic temperature usually occurs [4, 8, 9, 17]. However, in one study a decrease in colonic temperature was reported [10]. Pharmacologically, PCA's main effects appear to be short-term elevation of central monoamine levels [11] followed by long-term depletion of central 5-hydroxytryptamine (5-HT) [16]. The short-term behavioral effects are generally attributed to the initial release of central monoamines [6, 19, 20, 21]. In pilot work in this laboratory, it was observed that PCA induced spontaneous ejaculation, excessive salivation (appearing as underbody wetness), and irritability, as well as the frequently reported temperature changes. In the first experiment an examination was made of the dose dependency of these effects of PCA at an ambient temperature of 20 ± 1°C. In a second experiment the effect of change of ambient temperature to 25 ± 1°C was examined.

EXPERIMENT 1: AMBIENT TEMPERATURE 20 ± 1°C

METHOD

Animals

Thirty-two male Wistar rats with a body weight of 300 ± 80 (SD) g at the time of injection were used. They were given ad lib access to food and water and were individually housed in wire mesh cages which were kept in a room maintained at 20 ± 1°C and on a 12:12 hr light/dark cycle.

Procedure

The rats were randomly allocated to five groups. Eight rats were placed in the PCA 5 mg/kg group, and six in each of the 2.5, 8.0, 10.0 mg/kg and control groups. DL-PCA HCl (Regis Chemical Co.) was dissolved in saline as a 2.5, 5.0, 8.0 or 10.0 mg/ml solution and injected intraperitoneally in doses of 2.5, 5.0, 8.0 and 10.0 mg/kg approximately 7 hr after the onset of the light cycle. Control rats received saline injections.

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[2]Send reprint requests to: G. Paxinos, School of Psychology, The University of New South Wales, P. O. Box 1, Kensington, New South Wales, Australia, 2033.

Measurements of temperature and irritability were taken twice in the hour prior to the PCA injection, and the second measurement was used as the pre-injection baseline. After injection, measurements of ejaculation, temperature, salivation, and irritability were taken once an hour for a minimum of 3 hr on a "blind" basis, with the observer unaware of the prior treatment of the rats.

Ejaculation was scored by counting the pieces of seminal material collected each hour from paper towelling placed beneath the cages. A fully formed gelatinous plug was taken as evidence of one ejaculation and scored 1, while fragments were each scored 0.5 or 0.25 depending on their size. The number of rats exhibiting ejaculation was also recorded.

To measure temperature, an STC F23 thermistor probe was inserted 3–4 cm into the rat's rectum and held there until the dial reading stabilised.

Salivation was scored according to the extent of wetness under the body: 0 (dry), 1 (wet under the chin), 2 (wet under the chin and abdomen).

Irritability scores were obtained using the following three category scale: (a) biting reaction to a gloved hand that intruded into the cage and pushed the rat against the cage wall; (b) resistance to capture; (c) vocalization during the preceding two tests. Ratings of 0 (no response), 1 (weak response), or 2 (intense response) were given for each category.

Three days after PCA injections (5 mg/kg) forebrain 5-HT levels were assayed in eight rats (matched with experimental rats and kept in similar conditions) according to procedures described elsewhere [1, 13, 18].

RESULTS AND DISCUSSION

Ejaculation

The mean ejaculation scores in the four PCA-injected groups (the 2.5, 5.0, 8.0 and 10.0 mg/kg groups) were 0.8, 4.9, 3.0, and 2.6, respectively. No control rat ejaculated. In all PCA-injected groups ejaculation scores were highest during the first hour after the injection (Fig. 1). It does not appear from these results that the ejaculatory response was dose dependent at the doses used except that the lowest PCA dose (2.5 mg/kg) was less effective than the higher doses.

Temperature

At the ambient temperature of 20°C each PCA-injected group showed a mean decrease in temperature of approximately 1.8°C. There was less variability in the temperature scores of rats in the two lower than in the two higher dose groups. In the 2.5, 5.0, and 8 mg/kg dose groups the maximum decrease in mean temperature occurred 1 hr after PCA injection, but in the 10.0 mg/kg group it occurred 2 hr after injection. In the two higher dose groups the hypothermia also lasted longer. The vehicle-injected control group showed no change in temperature. (The pre-injection mean was 37.8°C and the post-injection mean was 37.5°C.)

In the present experiment, rectal temperature decreased following PCA injection and this agrees with the results of Messing *et al.* [10]. The magnitude of hypothermia observed here in 300 g Wistar rats was less than that observed by Messing *et al.* in 150 g Sprague-Dawley rats (1.8°C as compared to 3.0°C) and this may be partly due to strain and/or age differences.

Salivation and Irritability

All PCA doses induced increased salivation and irritability and the increases were smallest in the 2.5 mg/kg dose group. Irritability increased consistently with dose size.

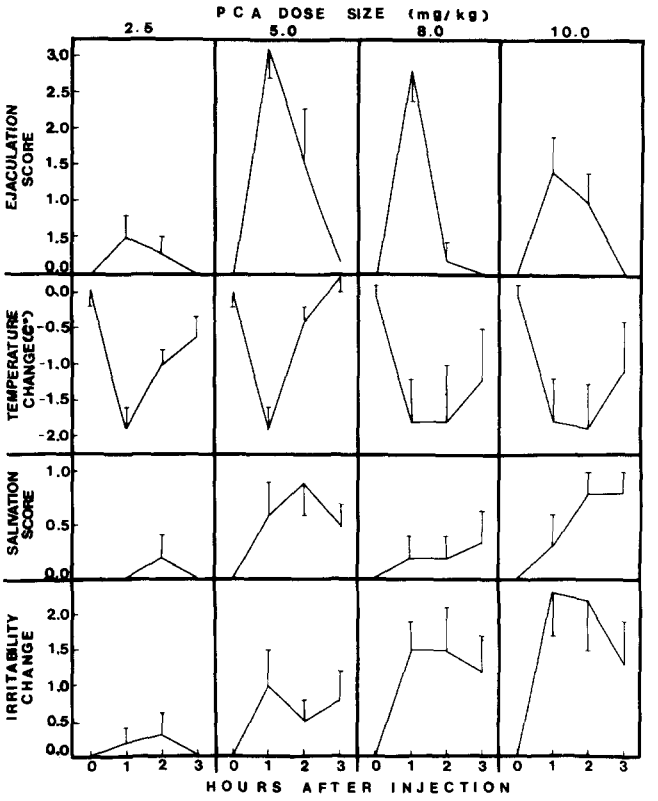

FIG. 1. The mean irritability change, salivation, temperature change, and ejaculation score for the four PCA dose groups prior to and after injection at the ambient temperature of 20 ± 1°C. Vertical lines indicate SE.

Factor analysis showed that ejaculation, hypothermia, salivation, and irritability were moderately correlated with one factor which accounted for 40% of the variance. The duration of these effects appeared to be related to dose size, but not in a simple monotonic manner. PCA may be less specific at higher doses than at lower doses [7] and this may account for the absence of a strong dose/response relationship.

Assays showed that forebrain 5-HT was depleted by approximately 60% at the time of decapitation (3 days after PCA injection). This is consistent with PCA-induced 5-HT depletion reported elsewhere [11, 14, 16]. While the assays do not reflect 5-HT levels present when the rats were being tested they do indicate that PCA had the expected effect.

EXPERIMENT 2: AMBIENT TEMPERATURE 25 ± 1°C

Messing *et al.* [10] housed their rats at an ambient temperature of 22 ± 1°C and, as in Experiment 1 here, observed hypothermia following PCA injection. However, most other workers [4, 8, 9] housed their rats at approximately 25°C and observed hyperthermia following PCA injections [4, 8, 9]. It therefore seemed possible that environmental temperature might influence the direction of PCA-induced temperature change. In Experiment 2 the ambient temperature was accordingly raised to 25 ± 1°C.

METHOD

Animals and Procedure

Eighteen male Wistar rats with a body weight of 258 ± 30 (SD) g at the time of injection were used. The procedure was the same as used in Experiment 1 except that the rats were housed for the 2 days prior to and during the experiment in a room maintained at 25 ± 1°C. Approximately 7 hr after the onset of the light cycle, PCA (5 mg/kg) was injected intraperitoneally into 12 rats and saline into the remaining 6.

RESULTS AND DISCUSSION

Temperature

All 12 PCA-injected rats showed hyperthermia. The mean rise in temperature was maximal 4 hr after the injection (Fig. 2), and temperatures were still substantially elevated 6 hr after the injection (additional observations). Vehicle-injected control rats showed no change in mean colonic temperature. Thus, in the present experiment rectal temperatures increased following PCA injection and this agrees with the results of other workers using an ambient temperature of approximately 25°C [4, 8, 9].

Ejaculation

All 12 PCA-injected rats ejaculated. The mean ejaculation score was 2.6, and, as in Experiment 1, the greatest number of vaginal plugs was emitted during the first hour after injection.

Salivation

All PCA-injected rats showed salivation, and the mean salivation score was 1.5. (This was more than twice the score obtained by rats kept at the lower ambient temperature in Experiment 1).

Irritability

Half of the PCA-injected rats exhibited increased irritability with a mean change score of 0.5.

Since ejaculation, salivation and irritability occurred in this experiment as well as in Experiment 1, it is evident that the direction of temperature change is not causally related to the occurrence of the other effects.

GENERAL DISCUSSION

In these two experiments it has been shown that PCA injections in male rats induce (a) spontaneous ejaculation, (b) decreases in temperature at an ambient temperature of 20°C, (c) increases in temperature at an ambient temperature of 25°C, (d) excessive salivation, and (e) dose related irritability.

The mechanisms of drug-induced ejaculation have not been well defined. "Massive erections and some ejaculation" have been reported to follow intraperitoneal injection of amantadine in male rats [2]. Amantadine is a drug which releases central stores of catecholamines and inhibits their uptake. The involvement of central monoamines in amantadine-induced ejaculation was therefore postulated [2]. It is possible that the mechanism subserving PCA-induced ejaculation is similar to that subserving amantadine's effect, since PCA's short term pharmacological effect is also a potentiation of central monoamine function.

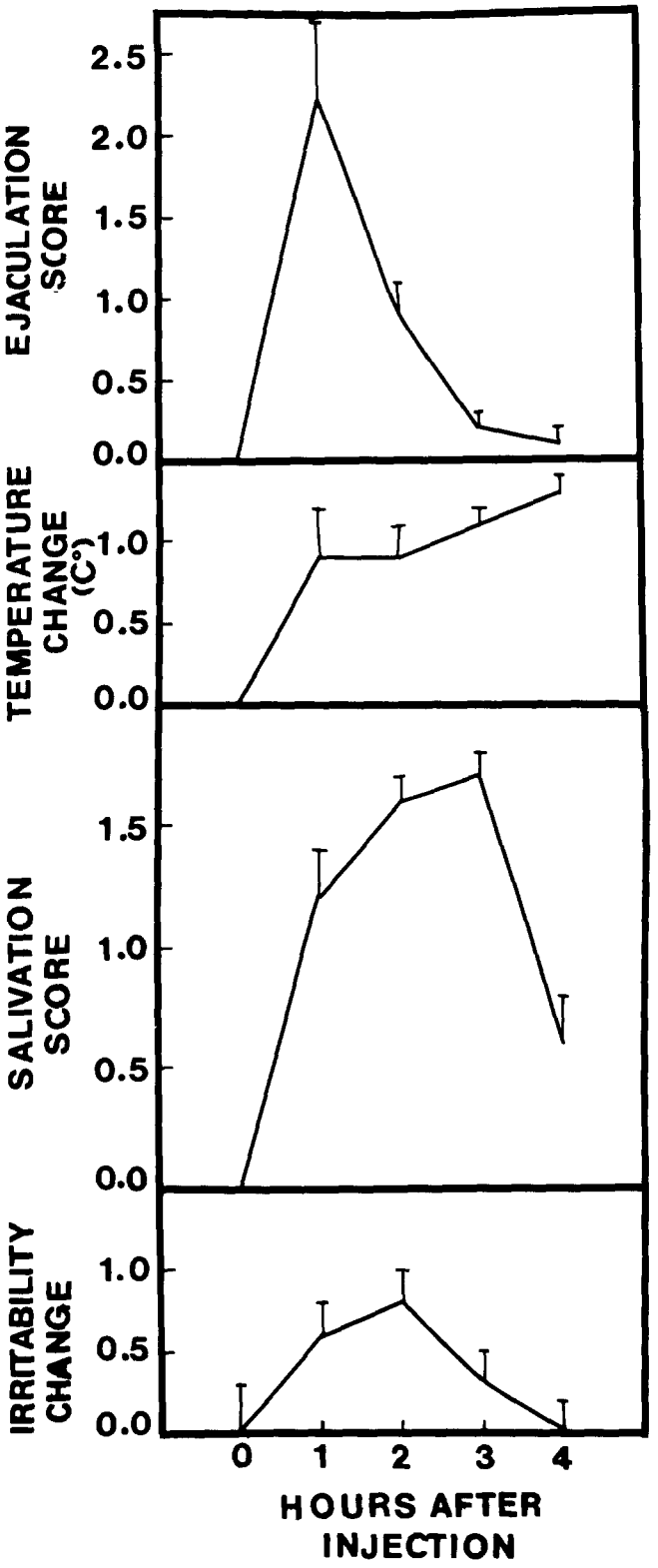

FIG. 2. The mean irritability change, salivation, temperature change, and ejaculation score for the PCA group prior to and after injection at the ambient temperature of 25 ± 1°C. Vertical lines indicate SE.

The finding that ambient temperature can influence the direction of PCA-induced temperature change may account for the fact that some experimenters obtained hypothermia and some hyperthermia following PCA injections. PCA is an analogue of amphetamine, and the finding of the influence of ambient temperature on PCA-induced temperature change is consistent with observations on the influence of ambient temperature on the amphetamine-induced temperature change [22].

The underbody wetness induced by PCA is apparently produced mainly by saliva which leaks from the mouth but is not actively spread by the rat. A small amount of wetting was also observed in the anal region apparently originating in the anus. Excessive salivation was more pronounced in rats exhibiting PCA-induced hyperthermia than in those showing hypothermia, but the fact that it also occurs in hypothermic rats suggests that it is not just a simple heat-loss mechanism.

Irritability was the only PCA-induced response which increased consistently with dose size. Irritability has sometimes been reported to follow injection of drugs that primarily act on central 5-HT [13], but this has been after injection of depletors rather than potentiators as at present. PCA has short-term potentiating effects not only on 5-HT but also on dopamine and noradrenalin and it is possible that irritability was produced by disturbances in the functioning of more than one neurotransmitter.

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