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Increased Urination Following p-Chloroamphetamine[1]

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STEIN, J. M., M. J. WAYNER AND K. M. KANTAK. *Increased urination following p-chloroamphetamine*. PHARMAC. BIOCHEM. BEHAV. 15(2) 297–301, 1981.—Para-chloroamphetamine (PCA) is a drug whose long-term and short-term neurochemical and behavioral effects have received considerable attention. The purpose of the present study was to determine whether PCA produces acute urination, defecation, and body weight changes similar to that seen following various amphetamine derivatives. Following baseline test sessions, rats were administered either 0.5, 1.0, 2.0, 5.0 or 10.0 mg/kg of PCA or saline. Results indicated increased urination at some doses tested. Increased defecation, salivation, locomotor activities, and body weight losses were also observed. These data are discussed in terms of possible CNS or peripheral mechanisms of action.

Para-chloroamphetamine (PCA) Urination Defecation Body weight

THE administration of amphetamine, the halogenated amphetamine analogue fenfluramine, or various amphetamine derivatives has been shown to produce changes in fluid and electrolyte balance. Rats, acutely or chronically treated with amphetamine, increase their water consumption [26,34] and acute administration of amphetamine, fenfluramine, phentermine or chlorphentermine produces a diuresis and a natriuresis [11, 18, 25, 26, 32]. In humans, amphetamine induced increases in urine and sodium excretion has been effectively used in the treatment of idiopathic edema [27]. Since these diuretic effects have been observed in hydrated rats tested in metabolism cages with no food or water present, the increases in urine and sodium output can not be attributed to changes in food or water consumption [18]. In addition, the anorectic properties of these drugs [13, 14, 19] might suggest that a decrease rather than an increase in water intake and urine output could be predicted if the observed effects on fluid balance were attributable to changes in food intake.

Para-chloroamphetamine (PCA) is an amphetamine derivative which has been used with increased frequency in experiments during the last several years. While initial reports concentrated on the anorectic properties of PCA [4, 13, 14, 18], recent studies have examined the physiological and behavioral consequences of PCA induced decreases in central nervous system (CNS) serotonin (5-HT) concentrations [5, 10, 16, 17, 24, 35]. Whether or not PCA also increases urine excretion has not been determined. However, indirect evidence suggests that acute changes in fluid balance occur following PCA. Rats injected with PCA, 5 mg/kg, precipitously decreased their body weights, losing up to 15 g during the first hr post-drug period [30]. Although some of this weight loss might be attributable to decreases in food and water intakes [30,31], the initial body weight losses in PCA injected rats were greater than those displayed by control animals administered isotonic saline but totally deprived of food and water [28]. In addition, rats administered 1.0–10.0 mg/kg of PCA have shown large increases in water intakes during the 24–48 hr post-drug period which were not associated with increases in food intakes [29,31].

The purpose of the present experiment was to determine the effects of PCA on urine excretion in the rat. Unanesthetized rats were administered 0.5, 1.0, 2.0, 5.0, or 10.0 mg/kg of PCA or saline. Subsequent measurement of urine volumes, fecal weights, and body weights revealed dose dependent effects.

METHOD

Animals

Forty-two female hooded rats, at least 4 months old and 229–359 g in weight, were selected from our colony and placed into individual cages. A 12 hr light-dark cycle began at 0700 hr and was followed by a 12 hr dark phase. The room temperature was maintained at 20° ± 1°C.

Apparatus

Metabolism cages consisted of 24.5×17.5×19.0 cm pull-out stainless steel rat cages (Hoeltge, Inc.). Each cage floor consisted of a grid with 1.1×1.1 cm openings. An aluminum pan, 32.0×22.0 cm, equipped with a wire grid on one end

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was used for the collection of urine and feces. Each pan rested on an incline 8.0 cm below each cage. Urine was collected from each pan using 1 cc injection syringes with 26 g intradermal needles.

Drugs

PCA injection solutions, 0.5, 1.0, 2.0, 5.0, and 10.0 mg/cc calculated from the base, were prepared from d, l-para-chloroamphetamine hydrochloride (Sigma Chemical) dissolved in 0.9% NaCl in triple distilled water. Saline injections were of 0.9% NaCl. All injections were administered intraperitoneally in volumes of 1 cc per kg of body weight immediately prior to testing at 1800 hr.

Procedure

For a period of 10 days, Days 1–10, animals were adapted to their home cages. During this time and for the entire experiment, body weights and ad lib food and water consumption were measured daily between 1400 and 1600 hr. Animals were tested in individual metabolism cages during 5 experimental sessions: adaptation sessions on Days 11 and 13 during which saline was administered; baseline test sessions on Days 15 and 17 during which saline was administered; and a final test session on Day 19 during which either PCA or saline was administered. Each session began at 1800 hr. During each session, animals were weighed, given drug or saline injections and immediately placed into the metabolism cages. Following each session, animals were reweighed and returned to their home cages. No food or water was present in the metabolism cages during any test session. On Days 11 and 13, the 2 adaptation test sessions, all animals were injected with saline and placed into metabolism cages for 1-hr periods. On Days 15 and 17, the 2 baseline test sessions, all animals were similarly injected with saline but placed into metabolism cages for 3-hr periods. On Day 19, the Drug Day, animals were divided into 6 groups of 7 rats each comprising the 0.0, 0.5, 1.0, 2.0, 5.0 and 10.0 mg/kg Groups. Animals in these groups were injected, respectively, with 0.0 (saline), 0.5, 1.0, 2.0, 5.0, and 10.0 mg/kg of PCA. Urine volumes and fecal weights were measured hourly during test sessions on Days 15, 17 and 19.

RESULTS

Body Weight

Mean body weights measured prior to each test session and net body weight loss during the 3 hr test sessions were analyzed by means of 6×2 analyses of variance with repeated measures [37]. The factors for each analysis were groups and days. The 6 levels of the groups factor were the 0.0, 0.5, 1.0, 2.0, 5.0 and 10.0 mg/kg Groups. The 2 levels of the days factor were Day 19, the Drug Day, and the mean of Days 15 and 17, the 2 baseline days.

Analysis of mean body weights measured prior to each test session indicated that the days factor was significant, $F(1,36)=7.59$, $p<0.01$. Mean body weights on the Drug Day was 297.5 g and the mean of the body weights on the baseline days was 293.2 g. Neither the groups factor nor the group × days interaction was significant. Therefore, there were no differences between the mean body weights of the groups and all groups increased their body weights at the same rate.

Analysis of the net body weight loss during the 3 hr test sessions indicated significant differences between the groups, $F(5,36)=9.47$, $p<0.01$, the days, $F(1,36)=194.06$, $p<0.001$, and the group × days interaction, $F(5,36)=15.44$, $p<0.001$. Further analyses examining within group and between group differences were performed using simple main effects and Tukey A tests, respectively. Figure 1 illustrates the mean net body weight loss of each group during the 3-hr test session on Day 19, the Drug Day. Within group comparisons indicated significantly more body weight loss on the Drug Day compared to the baseline days, in the 0.5, $p<0.05$, 1.0, 2.0, 5.0 and 10.0, $p<0.01$, mg/kg Groups. There were no differences in the body weight loss between days in the 0.0 mg/kg Group. Between group comparisons indicated no significant differences between groups on the baseline test days. In contrast, on the drug day, the 1.0 mg/kg Group lost significantly more body weight compared to the 0.0 mg/kg Group, $p<0.01$; the 2.0 mg/kg Group lost significantly more body weight compared to the 0.0, 0.5 and 1.0 mg/kg Groups, $p<0.01$, the 5.0 mg/kg Group lost significantly more body weight compared to the 0.0, 0.5, 1.0, $p<0.01$, and 2.0, $p<0.05$, mg/kg Groups; and the 10.0 mg/kg Group lost significantly more body weight compared to the 0.0, 0.5 and 1.0 mg/kg Groups, $p<0.01$.

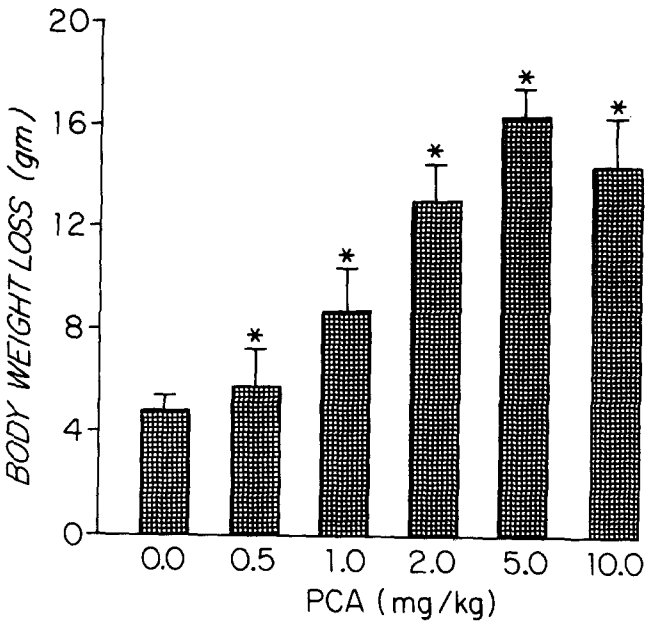

FIG. 1. Mean body weight losses ± SEM during the 3 hr test session on the Drug Day for the groups receiving 0.0, 0.5, 1.0, 2.0, 5.0 and 10.0 mg/kg of PCA. *Indicates significantly greater weight losses ($p<0.05$) within each group on the Drug Day compared to the baseline days.

In summary, rats injected with PCA lost significantly more body weight on the Drug Day than on the baseline test days. The increased body weight loss occurred at every dose level tested. A dose dependent effect, indicated by significantly different body weight losses among the 0.0, 0.5, 1.0, and 2.0 mg/kg Groups, was observed at the lower dosages. Comparisons of the body weight losses among the 2.0, 5.0 and 10.0 mg/kg Groups indicated no significant differences between groups.

Defecation

Mean fecal weights measured during the 3 hour test sessions were analyzed by means of a 6×3×2 analysis of variance with repeated measures. The factors were groups,

hours and days. The six levels of the groups factor were the 0.0, 0.5, 1.0, 2.0, 5.0 and 10.0 mg/kg Groups. The three levels of the hours factor were the 0–1, 1–2 and 2–3 hour post-injection periods. The 2 levels of the days factor were Day 19, the Drug Day, and the mean of Days 15 and 17, the 2 baseline test days.

Analysis of mean fecal weights indicated significant differences between the groups, $F(5,36)=5.83$, $p<0.001$, the hours, $F(2,72)=45.14$, $p<0.001$, and the days, $F(1,36)=28.46$, $p<0.001$. All of the interactions were significant: groups × days, $F(5,36)=4.40$, $p<0.005$, groups × hours, $F(10,72)=7.33$, $p<0.001$, hours × days, $F(2,72)=33.82$, $p<0.001$, and groups × hours × days, $F(10,72)=10.56$, $p<0.001$. Further analyses examining within group and between group differences were performed using simple main effects and Tukey A tests, respectively. Figure 2 illustrates the mean hourly fecal weights for each group on Day 19, the Drug Day. Within group comparisons indicated significantly more defecation on the Drug Day compared to the baseline test days during the 0–1 hour post-injection period in the 2.0, 5.0 and 10.0 mg/kg Groups, $p<0.001$. There were no differences within the 0.0, 0.5 and 1.0 mg/kg Groups. Between group comparisons indicated no significant differences between groups on the baseline test days. In contrast, on the Drug Day during the 0–1 hour post-injection period, there was significantly more defecation in the 2.0 mg/kg Group compared to the 0.0, 0.5 and 1.0 mg/kg Groups, $p<0.01$, significantly more defecation in the 5.0 mg/kg Group compared to the 0.0, 0.5, 1.0 mg/kg Groups, $p<0.01$, and significantly more defecation in the 10.0 mg/kg Group compared to the 0.0, 0.5, 1.0, $p<0.01$, and 2.0, $p<0.05$, mg/kg Groups. There were no significant differences between groups on the Drug Day during the 1–2 and 2–3 hour post-injection periods.

In summary, rats injected with PCA defecated significantly more on the Drug Day than on the baseline test days. Increased defecation only occurred at the higher doses tested, (2.0, 5.0 and 10.0 mg/kg of PCA) and only occurred during the 0–1 hr post-injection period. A dose dependent effect was indicated by the significant differences in the levels of defecation in the 2.0 mg/kg Group when compared to the 0.0, 0.5, 1.0, and 10.0 mg/kg Groups. There was no significant difference between the levels of defecation in the 5.0 and 10.0 mg/kg Groups. In general, the dose dependent pattern of increased defecation was an all or none effect with defecation occurring at doses of 2.0 mg/kg or greater.

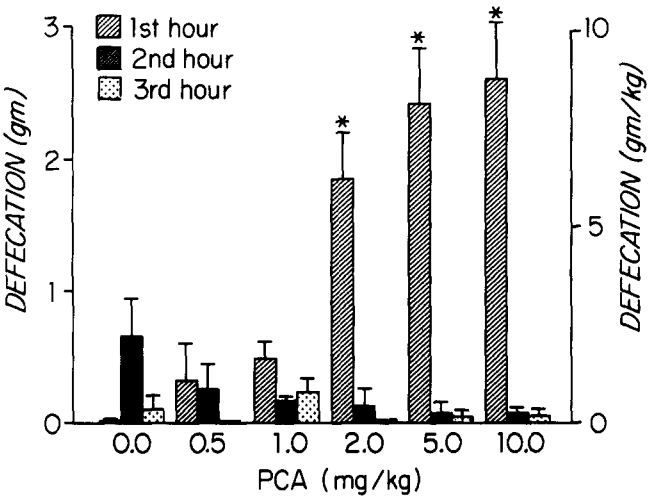

FIG. 2. Mean fecal weights ± SEM during the 0–1, 1–2, and 2–3 hr post-injection periods on the Drug Day for the groups receiving 0.0, 0.5, 1.0, 2.0, 5.0 or 10.0 mg/kg of PCA. *Indicates significantly increased defecation ($p<0.05$) within each group on the baseline days.

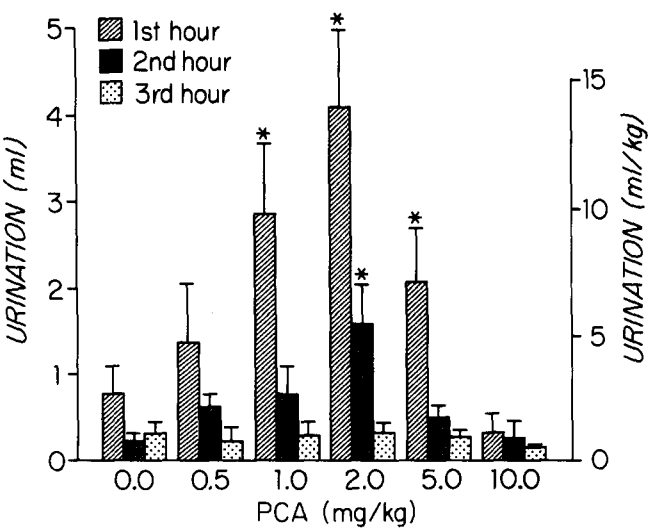

FIG. 3. Mean urine volumes ± SEM during the 0–1, 1–2, and 2–3 hr post-injection periods on the Drug Day for the groups receiving 0.0, 0.5, 1.0, 2.0, 5.0 and 10.0 mg/kg of PCA. *Indicates significantly increased urination ($p<0.05$) within each group on the Drug Day compared to the baseline days.

Urination

Mean urine volumes measured during the 3-hr test sessions were analyzed by means of a 6×3×2 analysis of variance with repeated measures. The factors were groups, hours and days. The six levels of the groups factor were the 0.0, 0.5, 1.0, 2.0, 5.0 and 10.0 mg/kg Groups. The 3 levels of the hours factor were the 0–1, 1–2 and 2–3 hr post-injection periods. The two levels of the days factor were Day 19, the Drug Day, and the mean of Days 15 and 17, the 2 baseline test days.

Analysis of urine volumes indicated significant differences between the groups, $F(5,36)=5.51$, $p<0.001$, the hours, $F(2,72)=39.00$, $p<0.001$, groups × hours, $F(10,72)=4.22$, $p<0.001$, hours × days, $F(2,82)=26.14$, $p<0.001$, and groups × hours × days, $F(10,72)=3.19$, $p<0.005$. Further analyses examining within and between group differences were performed using simple main effects and Tukey A tests, respectively. Figure 3 illustrates the mean hourly urine volumes for each group on Day 19, the Drug Day. Within group comparisons indicated significantly more urination on the Drug Day compared to the baseline test days during the 0–1 hr post-injection period in the 1.0, 2.0 and 5.0 mg/kg Groups, $p<0.005$, and during the 1–2 hr post-injection period in the 2.0 mg/kg Group, $p<0.005$. There were no differences within the 0.0, 0.5, or 10.0 mg/kg Groups. Between group comparisons indicated no significant differences between groups on the baseline test days. In contrast, on the Drug Day during the 0–1 hr post-injection period, there was significantly more urination in the 1.0 mg/kg Group compared to the 0.0, 0.5 or 10.0 mg/kg Groups, $p<0.01$; significantly more urination in the 2.0 mg/kg Group compared to the 0.0, 0.5, 5.0, 10.0,

$p<0.01$, and 1.0, $p<0.05$, mg/kg Groups; and significantly more urination in the 5.0 mg/kg Group compared to the 0.0, $p<0.05$, and 10.0, $p<0.01$, mg/kg Groups. In addition, there was significantly more urination on the Drug Day during the 1–2 hr post-injection period in the 2.0 mg/kg Group, compared to the 0.0, 10.0, $p<0.01$, and 5.0, $p<0.05$, mg/kg Groups. There were no between group differences on the Drug Day during the 2–3 hr post-injection period.

In summary, rats injected with PCA urinated significantly more on the Drug Day than on the baseline test days. Increased urination occurred at the 1.0, 2.0 and 5.0 mg/kg doses during the 0–1 hr post-injection period on the Drug Day. Increased urination also occurred during the 1–2 hr post-injection period on the Drug Day in the 2.0 mg/kg Group. While a dose dependent increase in urination seemed to be present at dosages up to 2.0 mg/kg, this pattern did not continue at the 5.0 or 10.0 mg/kg dosages. A smaller increase in urination occurred in the 5.0 mg/kg Group compared to the 2.0 mg/kg Group and there was no significant difference in the urination measured in the 10.0 mg/kg Group compared to the 0.0 mg/kg Group.

Behavioral Effects

Five to ten min following administration of PCA, changes in posture and locomotor activity were observed. Hindlimb abduction, myoclonus, forepaw treading, crouching, piloerection, and circling were seen. The magnitude of these responses was dose dependent with the 0.5 mg/kg Group showing the smallest increases in abnormal behaviors and the 10.0 mg/kg Group showing the greatest changes in behavior. The duration of this drug induced syndrome was at least 3 hr.

DISCUSSION

These results indicate that PCA increases urine excretion in the rat. In this respect, PCA appears to act similarly to amphetamine and several other amphetamine derivatives [11, 18, 26]. The large decreases in body weights which have been previously shown to occur within the first several hours following PCA are in part attributable to increased urination [30]. Increased urination occurred at doses up to 5.0 mg/kg but was most prominent in the 2.0 mg/kg Group. It was only in the 2.0 mg/kg Group that diuresis occurred both in the first and second hour post-injection. While increased urination appeared to be prominent at lower doses of PCA, increases in defecation appeared to be an all or none effect at doses of 2.0 mg/kg or greater. All of the excreted fecal matter was in the form of solid boli and was eliminated during the first hour post-injection. Diarrhea was not observed.

Although increased urination and defecation accounted for some of the body weight losses seen during testing, some weight loss can be attributed to both insensible water loss and unmeasured fluid excretion. When rats were examined during the first 3-hr post-injection period, it was observed that the fur of those that received the highest PCA doses was saturated with fluid. The animals that received 10.0 mg/kg had their entire ventral surfaces soaked with fluid. Animals that received 5.0 mg/kg of PCA were somewhat less saturated. The animals that received 2.0 mg/kg were only wet near their hindlimbs and genitals and the animals in the 1.0 mg/kg Group were nearly dry. It is unclear whether this fluid was urine or saliva. Urine might be suspected due to the increased incidences of hindlimb abduction and postural changes associated with PCA-induced stereotypy [5, 10, 35]. However, increased salivation at high doses of PCA has been reported [5]. This supports our observations concerning the location of the saturated fur. Thus, some of the discrepancy between the body weight loss data and the urination and defecation data was probably due to increased salivation. Some of this saliva remained on the fur of the animals when they were weighed at the end of the three hour test session and attenuated the increases in body weight loss. If any of the fluid were urine, evaporation undoubtedly would have affected the urination data. In order to circumvent these problems, further research directed at examining PCA-induced diuresis might require urinary bladder catheterizations.

The mechanism of action by which PCA increases defecation might involve either CNS or peripheral actions or both. The increased defecation might be attributable to increased release of 5-HT seen shortly following PCA administration [21,35]. Increases in defecation, intestinal motility, and net intestinal fluid excretion are all effects reported to occur following 5-HT or 5-hydroxytryptophan administration [3, 9, 38].

The increased urination presently reported might be associated with either increases in blood pressure which occur following PCA [14,15] or direct actions of the drug on the kidneys. While it has been shown that PCA acutely increases brain 5-HT, norepinephrine (NE), and dopamine (DA) concentrations [21,33], a CNS mediated diuresis appears unlikely. Pharmacological procedures designed to increase CNS 5-HT have produced either antidiuretic states or have been without effect on urine flow [17, 20, 36]. Similarly, cholinergic, noradrenergic, dopaminergic or histaminergic CNS chemical stimulation has produced antidiuretic responses [6, 7, 8, 17, 36].

An hypothesis explaining PCA induced diuresis which focuses on the increased blood pressure seen following the drug can be more easily accepted. Increased blood pressure, initiating the inhibition of anti-diuretic hormone (ADH) release, could account for these effects. Amphetamine is known to release NE both in the periphery and the CNS [1,2]. In addition, alpha adrenergic stimulation following systemically administered NE has been shown to inhibit ADH release via carotid sinus stimulation and produces a diuresis [12,22]. Natriuretic and diuretic effects have also been shown to occur following elevated renal artery pressure [23]. Therefore, a blood pressure hypothesis accounting for PCA induced diuresis can be well supported although a direct action of the drug on the kidney can not be discounted.

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