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Rewarding and aversive properties of IP and SC cocaine: assessment by place and taste conditioning

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Abstract. Three experiments were conducted to compare the effectiveness of intraperitoneally (IP) administered or subcutaneously (SC) administered cocaine to produce place and/or taste conditioning after four conditioning trials. In each experiment, IP (5–20 mg/kg) cocaine produced a place preference, but SC (0.5–20 mg/kg) cocaine at concentrations that prevented necrosis, did not produce a place preference. The failure of SC cocaine to produce a place preference was not a function of conditioning trial duration. On the other hand, SC cocaine (20 mg/kg) produced conditioned taste avoidance, but IP cocaine (20 mg/kg) did not produce conditioned taste avoidance. The results suggest that IP cocaine, but not SC cocaine, is rewarding.

Key words: Cocaine – Conditioned place preference – Conditioned taste aversion – Drug reinforcement – Dopamine – Subcutaneous – Intraperitoneal

Some psychoactive drugs, such as amphetamine, have been reported to be reinforcing in the place conditioning or drug self-administration paradigms, but aversive in the conditioned taste avoidance paradigm (Wise et al. 1976; Reicher and Holman 1977). Among these "paradoxical" drugs is cocaine. Cocaine is self-administered, produces a conditioned place preference, and can produce conditioned taste avoidance (for review see Hunt and Amit 1987).

The ability of cocaine to produce conditioned taste avoidance (CTA) appears to vary as a function of the route of its administration (Ferrari et al. 1991). Cocaine has been reported to produce relatively weak CTA when administered intraperitoneally (IP; Cappell and LeBlanc 1975; Goudie et al. 1977; Foltin and Schuster 1981). When administered IP, doses of 24–36 mg/kg cocaine, which produce marked increases in activity, are required to produce CTA in a single trial (Booth et al. 1977; Goudie et al. 1977). On the other hand, it has been reported that when cocaine is delivered subcutaneously (SC), stronger, more robust, CTA is produced. At a dose of 20 mg/kg, SC, cocaine produces CTA (Issac et al. 1989; Van Haaren and Hughes 1990) after a single conditioning trial (Issac et al. 1989). Ferrari et al. (1991) reported that subcutaneously (SC) administered cocaine produces CTA at doses of 32 mg/kg and 50 mg/kg, but not at 18 mg/kg. However, in this experiment, CTA was assessed with a one-bottle test, while the previously described experiments used a two-bottle choice test which is considered to be a more sensitive measure of CTA. In fact, Van Haaren and Hughes (1990) assessed cocaine-induced CTA with both one-bottle and two-bottle tests. The rats tested with the one-bottle test showed CTA after having been conditioned with a dose of 20 mg/kg, SC, of cocaine, but the rats tested with the two-bottle test showed CTA after having been conditioned with 5 mg/kg, SC, of cocaine. Subcutaneously administered cocaine, therefore, appears to produce CTA at lower doses than does intraperitoneally administered cocaine. There appears to be no evidence that cocaine has the ability to produce conditioned taste preference at any dose administered through any route.

Cocaine appears to possess aversive properties when assessed by the CTA test, yet it has also been demonstrated to possess rewarding properties in tests of place conditioning. The strength of the rewarding properties, like that of the aversive properties, appears to vary as a function of route of administration (Nomikos and Spyraki 1988). When administered intraperitoneally, cocaine has been reported to produce a conditioned place preference (Spyraki et al. 1982; Bardo et al. 1986; Morency and Beninger 1986; Lawley and Kantak 1988; Nomikos and Spyraki 1988; Houdi et al. 1989). In one of the earlier experiments, Spyraki, Fibiger and Phillips (1982) assessed the ability of several doses of IP cocaine (1.25, 2.5, 5.0, 10.0, and 20 mg/kg) to produce place preference. They found that the strength of the cocaine-induced place preference increased as the dose increased, with asymptotal conditioning occurring at 5 mg/kg, and no further in-

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crease in the strength of place conditioning at higher doses. When administered intravenously (IV), cocaine has been shown to produce a more robust conditioned place preference than when administered IP (Nomikos and Spyraki 1988). The ability of SC cocaine to produce place conditioning has received little attention in the literature; however, in a single experiment, a dose of 5 mg/kg, sc, of cocaine was shown to produce a relatively weak place preference (Issac et al. 1989) that was present after two, but not four to six conditioning trials.

The pharmacokinetics of cocaine may explain the behavioural differences produced by cocaine when administered by different routes as suggested by Ferrari et al. (1991). It is known that IP cocaine has a shorter duration of action, with peak blood levels occurring with a shorter latency, than SC cocaine (Nayak et al. 1976; Benuck et al. 1987; Yeh and Hertzen 1991). Thus, the concentration of cocaine in the blood may differ at any given time post-injection between these two routes of administration. It has therefore been suggested that the short duration of action of IP cocaine may prevent it from serving as an effective agent in producing conditioned taste avoidance (Foltin et al. 1981).

If the duration of action of cocaine predicts its hedonic properties, then it is conceivable that a short latency/short duration psychoactive effect (via IP administration) may be experienced as rewarding and a long latency, long duration effect (via SC administration) may be experienced as an aversive effect. Therefore, IP cocaine may be more effective in producing place preference than SC cocaine and SC cocaine may be more effective in producing taste avoidance than IP cocaine. The following experiments assessed the rewarding/aversive properties of SC and IP cocaine in taste and place conditioning paradigms.

Experiment 1

Reicher and Holman (1977) reported that when rats consumed a flavoured solution while in a chamber in which they experienced amphetamine, they later demonstrated avoidance of the amphetamine-paired flavour and a preference for the amphetamine-paired chamber. Experiment 1 assessed the ability of cocaine to produce flavour conditioning and place conditioning in the same animals. The groups differed on the basis of the route of administration of a dose of 20 mg/kg cocaine (SC or IP).

The three-choice place conditioning apparatus used in the experiments below, described by Parker (1992), included not only a drug-paired and a saline-paired chamber, but also a novel chamber among the choices. This test provided a conservative assessment of the rewarding properties of cocaine because in order to demonstrate a conditioned place preference, the rats must demonstrate a greater preference for the drug-paired chamber than their natural preference for the novel chamber (Bardo et al. 1990). The choice of a novel chamber was included to ensure that the demonstration of a preference for the cocaine-paired chamber was not simply the result of cocaine-induced interference with habituation to the conditioning chamber (see Scoles and Siegel 1986).

Materials and methods

Subjects. Twenty-four male Sprague-Dawley rats weighing between 201 and 232 g, from Charles River Laboratories (St Constant, Quebec) served as subjects. All rats were individually housed in stainless steel cages. The rats were trained and tested in the light phase of the 12/12 h light/dark schedule. Purina lab chow and water were continuously available to rats except as indicated.

Apparatus The place conditioning apparatus was in the shape of a T-maze with three distinctive chambers and a central choice area (25×25 cm). The wooden walls of each chamber ($35 \times 25 \times 30$ cm) were painted flat black with different floor textures used for conditioning cues. The floors of each of the three chambers differed visually and tactually: 1) P: a thick sheet of black plastic, 2) G: small grid (0.6 cm), 3) S: 5 cm strips of black sandpaper located 10 cm apart on the black wooden floor. Clear plastic lids covered each of the chambers. As analyzed by group means, rats do not significantly differ in their unconditioned preferences for these chambers (Parker 1992). On conditioning trials the rats were confined to each chamber with a divider painted flat black. The room was illuminated by two fluorescent ceiling lights.

The location of the rat during preference testing was monitored by a videotracking apparatus (Videomex V, Columbus Instruments). A camera, located in the ceiling of the testing room, monitored the movement of a white rat, defined as the location of the largest part of the rat's body at a given moment, against the black background of the maze and sent a signal of the rat's location to the videotracking apparatus. The signal was then sent to an IBM computer for later analysis. The videotracking apparatus monitored the amount of time spent in each of the chambers.

Conditioning procedure. The rats arrived in the laboratory 1 week before the first conditioning trial and were handled daily. Five days after arrival, their water bottles were removed. On the next 2 days, the rats were allowed 15 min per day to drink tap water in their home cages while 24 h water deprived.

On the following day the conditioning trials began. Every rat received four cycles of conditioning trials. Each cycle included a two-trial sequence with the first trial always being a saline trial and the second trial always being a drug trial. The trials were separated by 24 h. On the first trial of each conditioning cycle, the rats were given either a 1% NaCl or 0.02% saccharin solution to drink for 15 min before being removed from their home cages and injected either IP or SC with saline (3 ml physiological saline). The SC injections were administered in the nape of the neck. Five minutes later, the rats were placed in one chamber of the place conditioning apparatus for 15 min. On the second conditioning trial of each cycle, the rats were presented with a graduated tube containing the alternate flavoured solution to that presented on the first trial (saccharin or NaCl solution) for 15 min. Upon removal of the solution they were injected with 20 mg/kg cocaine (20 mg/kg per 3 cc saline solution) by either the IP or SC route of administration. The volume of the cocaine solution injected was 3 cc/rat. Cocaine was prepared in a solution of 20 mg/ml saline solution. Using a 3-cc syringe, 1 ml/kg of the stock solution was drawn followed by the appropriate amount of saline to provide an injection of a volume of 3 cc. When the concentration of cocaine was reduced in this manner, necrosis was not observed in the rats that received SC cocaine. Five minutes after the injection, the rats were placed in a different chamber of the place conditioning apparatus from that of the first trial. Half of the rats ($n=12$) received intraperitoneal (IP) injections and half of the rats ($n=12$) received subcutaneous (SC) injections. The flavoured solutions presented and the chambers paired with the agents were completely counterbalanced among the groups. The rats did not experience a third novel chamber during conditioning trials. This third chamber would serve as the novel chamber during testing.

During conditioning, the two-trial (saline/cocaine) conditioning cycles 1 through 4 occurred successively over 4 days, with 2 days intervening between cycles 2 and 3. During the intervening days between cycles 2 and 3, the rats received 15 min access to water in their home cage.

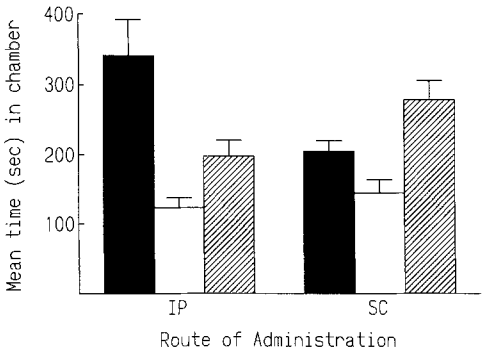

Fig. 1. Mean number of seconds (±SEM) that the rats in the IP and SC groups spent in each chamber of the T-maze after four conditioning cycles in experiment 1. (■) Cocaine; (□) saline; (▨) novel

Test procedure. The place preference test was conducted 3 days after the final conditioning trial. During the place preference test, drug free rats were placed in the central choice section of the place conditioning apparatus with the barriers to each of the chambers removed. The Videomex V apparatus recorded the movement of each rat among the chambers for 15 min to determine the amount of time spent in each side.

On the day following the place preference test, the rats were deprived of water for 24 h. For each of the following 2 days, the rats were given access to water in a graduated tube for 15 min per day. Twenty-four hours later, the rats were given a 15-min two-choice test, with one graduated tube containing the NaCl solution and the other graduated tube containing the saccharin solution. The total consumption of each solution was measured.

Results

Place Conditioning. Figure 1 presents the mean amount of time spent in each chamber during the place conditioning test. The data were analyzed as a 2×3 mixed factor ANOVA with the between-groups factor of Route of administration of cocaine (IP, SC) and the within-groups factor of Chamber (drug-paired, saline-paired, and novel). The analysis revealed a significant Chamber main effect [$F(2,44) = 8.5$; $P < 0.001$) and a significant Route by Chamber interaction [$F(2,44) = 5.3$; $P < 0.01$]. Since the interaction was significant, separate single factor within groups ANOVAs for the chamber preferences were conducted for the groups conditioned with cocaine by the IP and the SC Routes. The chamber effect was significant for both the IP conditioned group [$F(2,22) = 7.5$; $P < 0.001$], and the SC conditioned group [$F(2,22) = 5.4$; $P < 0.01$]. Subsequent Newman-Keuls analysis of the Chamber effect for the IP conditioned group revealed that the rats preferred the cocaine-paired chamber significantly more than the saline-paired chamber and the novel chamber ($Ps < 0.01$). The rats' preference for the saline-paired chamber and the novel chamber did not significantly differ from each other. Newman-Keuls analysis of the Chamber effect for the SC conditioned group revealed that the rats preferred the novel chamber to the saline-paired chamber ($Ps < 0.05$), but did not differ in their preference for the cocaine-paired and the saline-paired chambers or the novel chamber. Therefore, a cocaine-induced place preference was only established by the IP route of administration.

The mean amount of time (s) spent in the central choice section by the IP conditioned rats (238 s ± 23.7, $\bar{X} \pm$SEM) and by the SC conditioned rats (271 s ± 21.1, $\bar{X} \pm$SEM) did not differ significantly [$t(22) = 1.2$].

Taste conditioning. The taste conditioning data from the CTA test were converted into preference ratios prior to the analysis. A preference ratio was determined by the following formula: amount of cocaine-paired flavoured solution consumed divided by the total amount of cocaine-paired and saline-paired flavoured solution consumed in the 15-min test. A preference ratio of 0.5 indicates that the rat consumed equal amounts of the cocaine-paired and saline-paired solutions. A ratio less than 0.5 indicates that the rat consumed less of the cocaine-paired flavour than the saline-paired flavour and a ratio greater than 0.5 indicates that the rat consumed more of the cocaine-paired flavour than the saline-paired flavour. The preference ratio for the IP administered cocaine-paired flavour was 0.35 (±0.13) and the preference ratio for the SC administered cocaine-paired flavour was 0.10 (±0.04). These preference ratios were each compared with a value of 0.5 by *t*-tests. The analysis revealed that the SC administered cocaine produced flavour avoidance [$t(11) = 10.0$; $P < 0.001$], but the IP administered cocaine did not produce flavour avoidance [$t(11) = 1.15$].

Discussion

Experiment 1 demonstrated that 20 mg/kg cocaine effectively produced conditioned taste avoidance (CTA) when administered subcutaneously in four conditioning trials, but not when administered intraperitoneally. This finding is important because unlike previous reports of CTAs produced with SC cocaine (Issac et al. 1989; Van Haaren and Hughes 1990; Ferrari et al. 1991), the concentration of cocaine used in the present experiment was adjusted to prevent the occurrence of necrosis. By contrast, the place preference test revealed that, when administered by the IP route, cocaine produced a robust place preference; however, when administered by the SC route, cocaine did not produce a place preference.

The taste and place conditioning findings of experiment 1 suggest that unlike amphetamine (e.g. Reicher and Holman 1977), doses of cocaine that produce CTA when administered SC do not also produce a place preference. When administered subcutaneously, 20 mg/kg cocaine appears to possess primarily aversive properties as indicated by its ability to produce taste avoidance and its inability to produce a place preference. When administered intraperitoneally, 20 mg/kg cocaine appears to possess primarily rewarding properties as indicated by its inability to produce taste avoidance and its ability to produce place preference. Therefore, the hedonic properties of cocaine, unlike amphetamine, do not appear to be "paradoxical".

Experiment 2

Experiment 2a examined the ability of a lower range of doses of cocaine (5–15 mg/kg) administered either intraperitoneally or subcutaneously to produce place conditioning in the three-choice T maze apparatus used in experiment 1. Additionally, experiment 2b assessed the ability of two lower subcutaneously administered doses of cocaine (0.5 and 1.5 mg/kg) to produce place conditioning.

Materials and methods

Seventy-two male Sprague-Dawley rats weighing between 238 and 270 g in experiment 2a and 24 rats between 248 and 278 g in experiment 2b, were given place conditioning training on each of four conditioning cycles as in experiment 1, except as specified. In experiments 2a and 2b, CTA training and testing were not conducted.

In experiment 2a, 1 week after their arrival in the laboratory, the rats received the first conditioning trial. On this day, the rats were given either an IP or an SC injection of 3 ml physiological saline, 5 min prior to their placement in the appropriate side of the place conditioning apparatus for 15 min. On the second day of the first cycle, the rats received either a 3 ml IP or SC injection of 5, 10 or 15 mg/kg cocaine in a saline vehicle, 5 min prior to their placement in the appropriate side of the apparatus. There were 12 rats in each condition. This procedure continued for a total of four successive conditioning cycles according to the schedule described in experiment 1. Two days after the final conditioning trial, the rats were tested for their place preference. During the place conditioning test, the rats were placed in the centre of the T maze apparatus for 15 min while the Videomex V recorded their movement among the chambers.

In experiment 2b, the identical procedures were followed except that the rats received a 3-ml SC injection of 0.5 or 1.5 mg/kg cocaine in a saline vehicle, 5 min prior to placement in the appropriate chamber.

Results and discussion

Experiment 2a. Figure 2 presents the mean amount of time that the rats conditioned with IP or SC cocaine (at 5, 10, and 15 mg/kg) spent in each chamber of the place conditioning apparatus during preference testing. The data were analyzed as a $2 \times 3 \times 3$ mixed factor ANOVA with the between-groups variable of Route of administration (IP or SC) and Dose (5, 10, or 15 mg/kg) and the within-groups variable of Chamber (drug-paired, saline-paired, and novel). The results revealed significant main effects of Route of administration [F (1,66) = 6.71; $P < 0.01$] and Chamber [F (2,132) = 15.4; $P < 0.001$] and a significant Route by Chamber interaction [F (2, 132) = 13.7; $P < 0.001$].

Separate 3 by 3 ANOVAs were conducted for each Route of administration. The analysis of the preferences for the IP conditioned rats, depicted in the upper section of Fig. 2, revealed only a significant main effect of Chamber [$F(2,66) = 13.08$; $P < 0.001$]. Subsequent Newman-Keuls tests revealed that, pooled across the 3 doses, the rats preferred the novel and cocaine-paired chambers to the saline-paired Chamber ($Ps < 0.01$) and they preferred the cocaine-paired chamber to the novel chamber

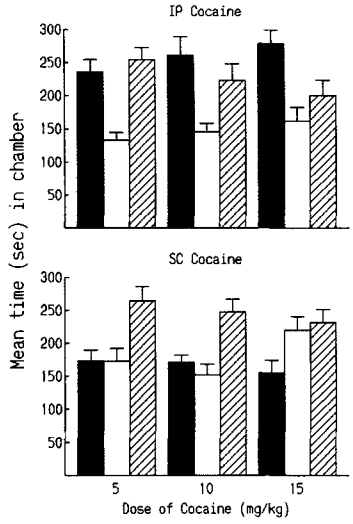

Fig. 2. Mean number of seconds (±SEM) that the rats in the various dose groups conditioned with IP or SC cocaine spent in each chamber of the T-maze after four conditioning cycles in experiment 2a. (■) Cocaine; (□) saline; (▨) novel

($P < 0.05$). The analysis of the preferences for the SC conditioned rats, depicted in the lower section of Fig. 2, revealed only a significant effect of Chamber [$F(2,66) = 11.9$; $P < 0.001$]. Subsequent Newman-Keuls analysis revealed that the rats preferred the novel chamber overall to both the saline-paired and the cocaine-paired chambers ($Ps < 0.01$). They did not differ in their preference for the saline-paired and cocaine-paired chambers; therefore, there was no evidence of the establishment of a conditioned place preference in the groups conditioned with SC cocaine.

The mean amount of time (s) that the rats spent in the central choice area during the preference test was assessed by a 2 by 3 between-groups ANOVA for the factors of Route of administration and Dose of cocaine. The only significant effect was that of Route of administration [F (1,66) = 10.0; $P < 0.01$]; the rats conditioned with SC cocaine ($\bar{X} = 288.9$ s) spent more time in the central choice area than the rats conditioned with IP cocaine ($\bar{X} = 254.9$ s).

Experiment 2b. The 2 by 3 mixed factor ANOVA for the between-groups variable of Dose (0.5 or 1.5 mg/kg) and the within-groups variable of Chamber (cocaine-paired, saline-paired and novel) revealed no significant effects [Chamber: $F(2,44) = 0.9$; Dose by Chamber: $F(2,44) = 0.2$]. There was also no significant difference among the dose conditions in the mean time spent in the central choice area [$t(22) = 1.3$]. Thus, there was no evidence of place conditioning with low doses of subcutaneously administered cocaine.

Experiment 3

In experiments 1 and 2, cocaine was only effective in conditioning a preference for a place with which it was paired when it was administered IP, but not when it was

administered SC. It is likely that the difference in the pharmacokinetics of cocaine produced by each route may be responsible for the differing effects. When administered IP, cocaine has a much shorter latency of onset and duration of action than when administered SC, with peak blood levels lasting considerably longer for SC than for IP cocaine (Nayak et al. 1976); the plasma half-life for IP cocaine is approximately 0.3 h and the plasma half-life for SC cocaine is approximately 0.8 h. Therefore, the duration of action of cocaine and/or latency to onset of action may be inversely related to its ability to produce a conditioned place preference.

Although the difference in the speed of onset of IP versus SC cocaine may produce different hedonic effects, it is also possible that the failure to establish place conditioning with SC cocaine was the result of the relative timing of the peak effects of cocaine and exposure to the conditioning chamber. During place conditioning, the peak effects of IP cocaine may have been experienced while the rats were in the conditioning chamber during the 15-min conditioning trial, but the peak effects of SC cocaine may have been experienced after the rats were returned to their home cage following the conditioning trial. Therefore, experiment 3 was designed to determine whether the conditioning trial duration would effect the ability of SC and IP cocaine to produce place conditioning.

Materials and methods

Seventy-two male Sprague-Dawley rats weighing between 258 and 405 g were given place conditioning training on each of four conditioning cycles as in experiment 2, except as specified.

One week after their arrival in the laboratory, the rats received the first conditioning trial. They were given either an IP or an SC injection of 20 mg/kg cocaine (20 mg/kg per 3 cc saline) or physiological saline (3 cc) 5 min prior to placement into the appropriate chamber on the first trial of the cycle and were injected with the alternate solution on the second trial of the cycle in a counterbalanced order. The groups differed on the basis of the duration of the conditioning trials: 30, 60 or 90 min. The various groups (route: conditioning trial duration) were as follows: IP: 30 ($n=12$), SC: 30 ($n=12$), IP: 60 ($n=12$), SC: 60 ($n=12$), IP: 90 ($n=12$), SC: 90 ($n=12$). The test trial duration was 15 min for all rats, as in experiments 1 and 2.

Results and discussion

Figure 3 presents the mean number of seconds that the rats in the various groups of experiment 3 spent in each of the chambers during the place preference test. A 2 by 3 by 3 mixed factor ANOVA revealed only a significant Route by Chamber interaction [$F(2,132)=3.7$; $P<0.025$]. Subsequent 3 by 3 mixed factor ANOVAs for each route of administration revealed a significant main effect of Chamber [$F(2, 66)=10.8$; $P<0.001$] for the IP conditioned rats, but not for the SC conditioned rats. For the IP conditioned rats, subsequent Newman-Keuls tests revealed that the rats spent more time in the cocaine-paired chamber than in either the saline-paired or novel chamber ($Ps<0.01$); no other effects were significant.

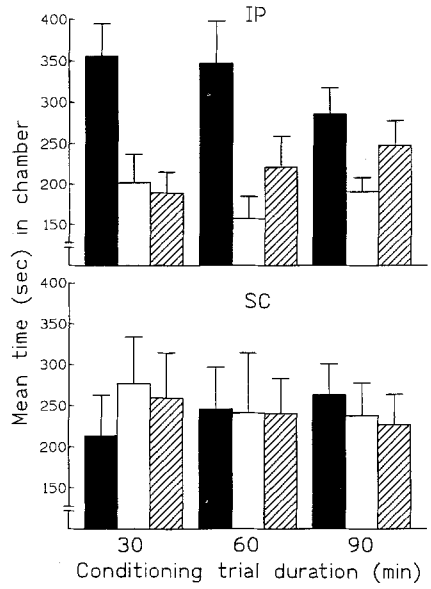

Fig. 3. Mean number of seconds (±SEM) that the rats in experiment 3 that received 30-, 60- or 90-min conditioning trials spent in each chamber of the T-maze after four conditioning cycles. The *top section* presents the rats conditioned with IP cocaine and the *bottom section* presents the rats conditioned with SC cocaine. (■) Cocaine; (□) saline; (▨) novel

Regardless of the duration of the conditioning trial, IP cocaine produced a place preference and SC cocaine did not produce a place preference. Therefore, the inability of SC cocaine to produce place conditioning in the previous experiments that employed 15 min conditioning trials was not a function of the peak effects of cocaine occurring after removal from the conditioning chambers. Such an effect would be expected to occur within the 90 min of chamber exposure in experiment 3 (Nayak et al. 1976). Instead, it is more likely that the faster speed of onset of IP cocaine is responsible for place preference conditioning.

General discussion

When administered intraperitoneally (IP), doses of 5–20 mg/kg cocaine produced a conditioned place preference, yet even a dose as high as 20 mg/kg did not produce conditioned taste avoidance. On the other hand, when administered subcutaneously (SC), doses of 0.5–20 mg/kg cocaine did not produce a conditioned place preference and a dose of 20 mg/kg, SC, produced conditioned taste avoidance. Doses as low as 5 mg/kg, SC, of cocaine are effective in producing a conditioned taste avoidance (Issac et al. 1991; Parker 1993). Therefore, cocaine, unlike amphetamine (Reicher and Holman 1977), does not produce both taste avoidance and a place preference at the same dose by the same route of administration.

Since the half-life of SC cocaine (0.8 h) is longer than that of IP cocaine (0.3 h; Nayak et al. 1976), it was considered possible that in experiments 1 and 2 the peak blood level of SC cocaine occurred after the rats were removed from the conditioning chamber when the conditioning

trial duration was 15 min. The SC cocaine, but not the IP cocaine, rats may then have experienced the rewarding properties of cocaine in their home cages rather than in the conditioning chambers. In fact, when amphetamine is used as the unconditioned stimulus in place conditioning, a place preference is produced only when the drug precedes placement in the chamber, but not when the drug follows placement in the chamber (e.g. Costello et al. 1989). In experiments 1 and 2, SC cocaine effects may have functionally followed placement in the chamber during the 15-min trials. Experiment 3, however, demonstrated that SC cocaine does not produce a place preference even when the rats are allowed to remain in the conditioning chamber for 90 min post-injection (with a 5-min injection-chamber placement interval).

Instead, it is more likely that the latency to onset of drug action is the factor that differentiates the rewarding properties of IP and SC cocaine. Other findings support this possibility. Nomikos and Spyraki (1988) reported that IV cocaine produces stronger place conditioning than IP cocaine. Furthermore, deWit, Bodker and Ambre (1992) recently reported in humans that the rate of increase of the plasma drug level is directly related to reported "liking" for the drug; the faster the increase in plasma drug level of pentobarbitone, the greater the positive hedonic rating of the drug. Our results suggest that the speed of onset of cocaine effects may also play a role in the rewarding properties of this agent.

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References

Bardo MT, Neisewander JL, Pierce RC (1990) Novelty-induced place preference behavior in rats: effects of opiate and dopaminergic drugs. Pharmacol Biochem Behav 32:683–687

Bardo MT, Neisewander JL, Miller JS (1986) Repeated testing attenuates conditioned place preference with cocaine. Psychopharmacology 89:239–243

Benuck M, Lajtha A, Reith MEA (1987) Pharmacokinetics of systemically administered cocaine and locomotor stimulation in mice. J Pharmacol Exp Ther 243:144–149

Booth DA, Pilcher GD, D'Mello GD, Stolerman IP (1977) Comparative potencies of amphetamine, fenfluramine and related compounds in taste aversion experiments in rats. Br J Pharmacol 61:669–677

Cappell H, LeBlanc AE (1975) Conditioned aversion by psychoactive drugs: does it have significance for an understanding of drug dependence? Addict Behav 1:55–64

Costello NL, Carlson JN, Glick SD, Bryda M (1989) Dose-dependent and baseline-dependent conditioning with *d*-amphetamine in the place conditioning paradigm. Psychopharmacology 99:244–247

deWit H, Bodker B, Ambre J (1992) Rate of increase of plasma drug level influences subjective response in humans. Psychopharmacology 107:352–358

Ferrari CM, O'Connor DA, Riley AL (1991) Cocaine-induced taste aversions: effect of route of administration. Pharmacol Biochem Behav 38:267–271

Foltin RW, Schuster CR (1982) The effects of cocaine in a gustatory avoidance paradigm: a procedural analysis. Pharmacol Biochem Behav 16:347–352

Foltin RW, Preston KL, Wagner GC, Schuster CR (1981) The aversive stimulus properties of repeated infusions of cocaine. Pharmacol Biochem Behav 15:71–74

Goudie AJ, Dickins DW, Thornton EW (1977) Cocaine-induced conditioned taste aversion in rats. Pharmacol Biochem Behav 8:757–761

Houdi AA, Bardo MT, Van Loon GR (1989) Opioid mediation of cocaine-induced hyperactivity and reinforcement. Brain Res 497:195–198

Hunt T, Amit Z (1987) Conditioned taste aversion induced by self-administered drugs: Paradox revisited. Neurosci Biobehav Rev 11:107–130

Issac WL, Nonneman AJ, Neisewander J, Landers T, Bardo MT (1989) Prefrontal cortex lesions differentially disrupt cocaine-reinforced conditioned place preference but not conditioned taste aversion. Behav Neurosci 103:345–355

Lawley SI, Kantak KM (1990) Post-conditioning effects of magnesium on cocaine conditioned place preference in mice. Pharmacol Biochem Behav 36:531–538

Morency MA, Beninger RJ (1986) Dopaminergic substrates of cocaine-induced place conditioning. Brain Res 399:33–41

Nayak PK, Misra AL, Mule SJ (1976) Physiological disposition and biotransformation of [3H] cocaine in acutely and chronically treated rats. J Pharmacol Exp Ther 196:556–569

Nomikos GG, Spyraki C (1988) Cocaine-induced place conditioning: Importance of route of administration and other variables. Psychopharmacology 94:119–125

Parker LA (1992) Place conditioning in a three or four choice apparatus: role of stimulus novelty in drug-induced place conditioning. Behav Neurosci 106:1–13

Parker LA (1993) Taste reactivity responses elicited by cocaine-paired, phencyclidine-paired, and methamphetamine-paired sucrose solutions. Behav Neurosci 107:118–129

Reicher MA, Holman EW (1977) Location preference and flavour aversion reinforced by amphetamine in rats. Anim Learn Behav 5:343–346

Scoles MT, Siegel S (1986) A potential role of saline trials in morphine-induced place preference conditioning. Pharmacol Biochem Behav 35:583–587

Spyraki C, Fibiger HC, Phillips AG (1982) Cocaine-induced place preference conditioning: lack of effects of neuroleptics and 6-hydroxydopamine lesions. Brain Res 253:195–203

Van Haaren F, Hughes CE (1990) Cocaine-induced conditioned taste aversions in male and female wistar rats. Pharmacol Biochem Behav 37:693–696

Wise RA, Yokel P, Dewitt H (1976) Both positive reinforcement and conditioned aversion from amphetamine and from apomorphine in rats. Science 191:1273–1274

Yeh SY, Haertzen CA (1991) Cocaine-induced locomotor activity in rats. Pharmacol Biochem Behav 39:723–727