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The Effects of Nicotine and Nicotine Withdrawal on Taste Reactivity

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PARKER, L. A. AND K. DOUCET. *The effects of nicotine and nicotine withdrawal on taste reactivity.* PHARMACOL BIOCHEM BEHAV **52**(1) 125–129, 1995.—The effect of nicotine pretreatment on the palatability of flavored solutions was assessed using the taste reactivity test. In Experiment 1, low doses of nicotine [0.2–0.4 mg/kg, subcutaneously (SC)] suppressed the aversive taste properties of quinine and quinine–sucrose mixture and enhanced the hedonic taste properties of sucrose (0.4 mg/kg, SC) in rats that were nicotine naive. In Experiment 2, rats were chronically preexposed to nicotine or saline over a period of 21 pretreatment days. Tolerance developed to the ability of nicotine to enhance the palatability of sucrose. Furthermore, rats that were chronically preexposed to nicotine displayed enhanced hedonic evaluation of sucrose 24 h after nicotine was withdrawn. These results confirm human self-reports that withdrawal from nicotine dependency enhances the palatability of sweet-tasting foods.

Nicotine Taste reactivity Sucrose Quinine Withdrawal Feeding Reward Ingestion Addiction

HUMAN self-reports reveal that tobacco smoking suppresses appetite and cessation of smoking enhances appetite [e.g., (9,21)]. Grunberg (9) reported that chronic exposure to nicotine selectively suppresses the intake of sweet foods and withdrawal from nicotine selectively enhances the intake of sweet foods in both rats and humans. Therefore, he suggested that the modification of appetite by nicotine and nicotine withdrawal is caused by a hedonic shift in the palatability of sweet foods. Rodin (21) verified that in humans cessation of smoking enhances the hedonic evaluation of sweet foods independently of changes in body weight. In subsequent animal studies, some investigators reported that chronic nicotine pretreatment selectively suppresses the intake of sweet foods (9–11,22); others reported that it enhances the intake of sweet foods (13). However, withdrawal from nicotine in chronically nicotine-pretreated rats has consistently been reported to enhance sweet food consumption (9,13). It is therefore conceivable that these effects are the result of a shift in the palatability of the tastant.

The palatability of tastants can be directly assessed by the taste reactivity (TR) test devised by Grill and Norgren (8). When rats are intraorally infused with a sweet, highly palatable flavor such as sucrose, they display a characteristic set of ingestive reactions that include tongue protrusions, paw licks, and mouth movements. On the other hand, when they are intraorally infused with a bitter, highly unpalatable flavor such as quinine solution, they display a characteristic set of aversive reactions that include chin rubs, gapes, paw treads, head shakes, and forelimb flails. These reactions have been extensively employed to assess the palatability of tastants.

The following experiments employed the TR test to assess the ability of nicotine to modify the palatability of palatable (sucrose) and unpalatable (quinine) tastants. Furthermore, the effect of nicotine and nicotine withdrawal on taste reactivity was assessed in rats that received 21 days (two times per day) of preexposure to nicotine.

EXPERIMENT 1

The ability of nicotine to modify the palatability of sucrose, quinine, and sucrose–quinine mixture solutions in rats with no previous experience with the drug or with the tastants was assessed using the TR test.

Method

Subjects. The subjects were 47 male Sprague–Dawley rats weighing between 290 and 349 g on the test day. They were maintained on ad lib water and Lab Diet (PMI Feed, Inc., St.

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Louis, MO) in individual wire mesh cages. The room was illuminated on a 12L : 12D schedule.

Procedure.

Surgery. One week after arriving in the laboratory, the rats were implanted with intraoral cannulae as previously described by Parker (16). After being deprived of water for 12 h, the rats were initially injected with atropine [0.5 mg/kg, intraperitoneally (IP)] 15 min before an injection of ketamine (100 mg/kg, IP) and xylazine (3 mg/kg, IP).

Once the rats were anesthesized, a 15-ga thin-walled, stainless-steel subcutaneous (SC) needle was inserted through their skin in the midneck region and exited through the inside of the cheek behind the first molar. The skin around each punctured site was swabbed with iodine. With the needle in place, a 10.2-cm length of polyethylene (PE 90) tubing was inserted through the barrel. The needle was then removed and the tubing was secured at the neck by a 20-ga intramedic adapter and in the mouth by a 5-mm plastic washer.

TR testing. One week after the surgery, the rats received the first of three TR adaptation trials. On each of 3 consecutive days, the rat was placed in the glass taste reactivity (TR) test chamber (22.5 × 26 × 20 cm). The room was illuminated by three 100-W lightbulbs with one placed on either side of the chamber and one aimed at the mirror below the chamber. Once the animal was placed in the chamber, its cannula was connected to the infusion pump (Harvard Model 20) by a 35-cm-long tube. The rat received a 5-ml introral infusion of water 1 min later, at the rate of 1 ml/min for 5 min.

The rats received the taste reactivity test trial 24 h after the final adaptation trial. Thirty minutes before the TR test trial, the rats were injected SC with saline (n = 17), 0.2 mg/kg nicotine (n = 15), or 0.4 mg/kg nicotine (n = 15). The nicotine ([−]-Nicotine, free base; Sigma Chemicals, St. Louis, MO) was prepared in a solution of 0.4 mg nicotine/ml saline. The test trial was conducted identically to the adaptation trials, except that the solution infused was sucrose solution (20%, w/v), sucrose-quinine solution (20% sucrose, w/v, and 0.05% quinine, w/v) or quinine solution (0.05%, w/v). All rats were tested with each solution on consecutive days; the order of solution presentation was counterbalanced for each group. During the infusion, the orofacial and somatic reactions of the rat were videorecorded by a Panasonic videocamera from a mirror that was placed at an angle below the TR chamber to facilitate viewing of the ventral surface of the rat.

Behavioral categories. The videotapes of the TR test were scored by an observer blind to the experimental conditions in real time by means of an event recorder package for the IBM computer ("The Observer"; Noldus, Inc., The Netherlands). The behavioral categories that were measured included the ingestive reactions, aversive reactions, and passive drips. The ingestive reactions included tongue protrusions (extensions of the tongue either to the side or the front of the mouth), mouth movements (movement of the lower mandible without opening the mouth), and paw licking (licking the solution by catching it with the paws). These measures were combined to produce a composite ingestive reaction score. The aversive reactions included gaping (large amplitude, rapid opening of the mandible with concomitant retraction of the corners of the mouth), chin rubbing (mouth in direct contact with the floor or a wall and projecting the body forward), paw treading (sequential extension of one forelimb forward against the floor while the other forelimb is being retracted), head shaking (rapid horizontal movements of the head) and forelimb flailing (rapidly shaking both forelimbs with a high frequency response); these behaviors were combined to produce a composite aversive reaction score. In addition, the mildly aversive or neutral (3) reaction of passive dripping (number of drops of the test solution that drip from the rat's mouth to the floor when the rat is not actively ejecting the solution by an aversive response) was scored separately. This method of scoring has been shown to be significantly correlated with a slow-motion method of scoring (17).

Results and Discussion

Figure 1 presents the mean frequency or duration of each taste reaction displayed by the rats injected with 0.2 mg/kg saline or 0.4 mg/kg nicotine 30 min before an intraoral infusion of sucrose, sucrose-quinine, or quinine solution. The ability of the various doses of nicotine to modify each category of reaction during the infusion of each test solution was assessed as a single-factor, between-groups analysis of variance (ANOVA).

The ANOVAs revealed a significant dose effect for aver-

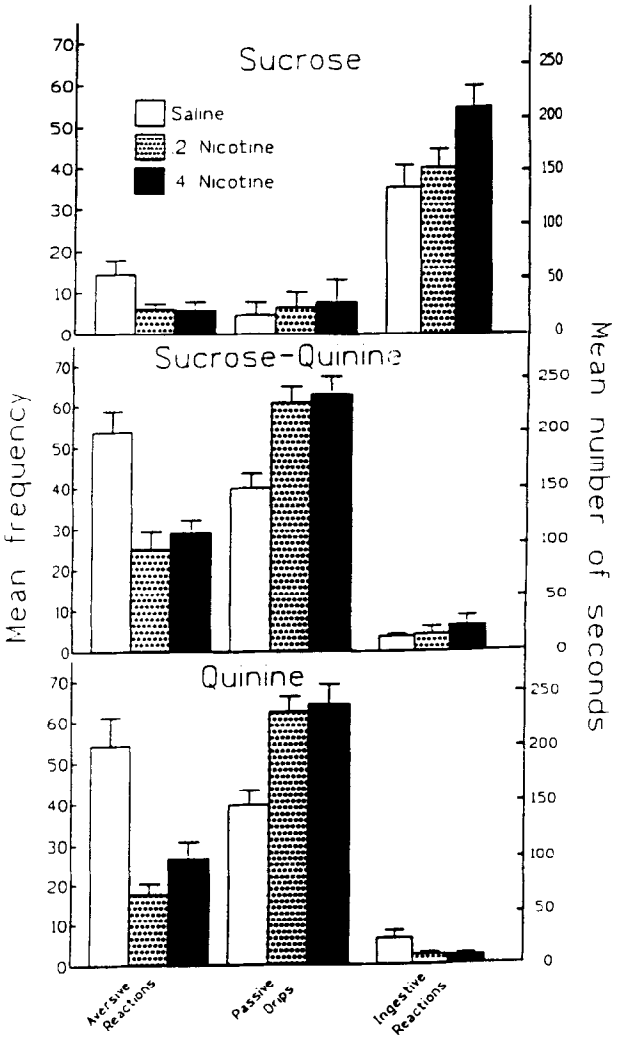

FIG. 1. Mean frequency of aversive reactions and passive drips or duration (s) of ingestive reactions elicited during the 5-min intraoral infusion of 20% sucrose, 20% sucrose-0.05% quinine mixture, or 0.05% quinine solutions, following an injection of 0.0, 0.2, or 0.4 mg/kg nicotine in Experiment 1.

sive reactions regardless of the solution infused [$F > (2, 44) = 3.8; p < 0.05$; by subsequent Newman-Keuls tests for each test solution, the saline group displayed more aversive reactions than did the 0.2 or 0.4 nicotine groups ($p < 0.05$). During the sucrose-quinine [$F(2, 44) = 10.2; p < 0.01$] and quinine [$F(2, 44) = 10.9; p < 0.01$] infusions, there was also a significant dose effect for the reaction of passive drips; Newman-Keuls tests revealed that for both solutions, the saline group displayed fewer passive drips than did either the 0.2 or 0.4 nicotine groups ($p < 0.05$). For these two aversive solutions, nicotine appeared to shift the palatability from aversive to mildly aversive or neutral.

Finally, the dose effect was significant for the ingestive reactions displayed during the infusion of sucrose [$F(2, 44) = 4.3; p < 0.025$] and during the infusion of quinine [$F(2, 44) = 4.6; p < 0.025$]. By subsequent Newman-Keuls tests, the 0.4 nicotine group displayed more ingestive reactions during an intraoral infusion of 20% sucrose solution than did either the saline or 0.2 nicotine groups ($p < 0.05$); however, the saline group displayed more ingestive reactions than either the 0.2 group or 0.4 nicotine group during an intraoral infusion of 0.05% quinine solution ($p < 0.05$). Nicotine enhanced ingestive reactions elicited by a highly palatable solution, but suppressed ingestive reactions elicited by a highly unpalatable solution.

The mean frequency or duration of each taste reaction displayed during the 1st min of testing was also analyzed; this is the interval of time most commonly employed with the taste reactivity test [e.g., (3)]. During the 1st min of the intraoral infusion of 20% sucrose solution, a dose effect was evident for ingestive reactions only [$F(2, 44) = 4.7; p < 0.025$]; as in the complete 5-min test, the 0.4 nicotine group displayed more ingestive reactions than did the saline group ($p < 0.05$). During the infusion of the sucrose-quinine mixture, a dose effect was also significant for passive drips during the 1st min [$F(2, 44) = 3.8; p < 0.05$]; as in the 5-min test, the saline group displayed fewer passive drips than either nicotine-injected group during the 1st min ($p < 0.05$). No other effects were significant during the 1st min of the test.

Discussion

Low doses of nicotine suppressed aversive reactions elicited by both palatable and unpalatable solutions and enhanced the mildly aversive passive drip reactions elicited by unpalatable solutions. Furthermore, a dose of 0.4 mg/kg nicotine enhanced the ingestive reactions elicited by sucrose solution during the entire 5-min TR test and during the 1st min of the TR test. This pattern of results suggests that low doses of nicotine enhance the palatability of tastants, as suggested by Jias and Ellison (13). The only finding contrary to this conclusion was the tendency for nicotine to suppress ingestive reactions displayed during an intraoral infusion of quinine solution; however, the extremely low baseline of the reaction in the saline-pretreated group questions the significance of further suppression by nicotine pretreatment.

EXPERIMENT 2

Experiment 1 demonstrated that an injection of nicotine enhances the palatability of novel sucrose solution in nicotine-naive rats. Experiment 2 assessed the ability of nicotine and withdrawal from nicotine to modify the palatability of novel sucrose solution in nicotine-experienced rats. Rats were repeatedly injected (twice a day) with nicotine or saline on each of 21 days. On the test day (24 h after the final nicotine preexposure injection), half of the rats in each group were injected with nicotine and half were injected with saline before a TR test with sucrose. Those rats pretreated with nicotine and tested with saline assessed the effects of withdrawal from nicotine on the palatability of sucrose. Those rats pretreated with nicotine and tested with nicotine assessed the effects of experience with nicotine on nicotine enhancement of palatability evident in Experiment 1.

Method

Subjects. The subjects were 31 naive male Sprague-Dawley rats weighing between 343 and 424 g. They were maintained under similar conditions as in Experiment 1.

Procedure. The procedure was similar to that of Experiment 1 except as indicated. One week following the intraoral cannulation procedure the rats were randomly assigned to either the nicotine preexposure group ($n = 15$) or the saline preexposure group ($n = 16$). For a period of 21 consecutive days, all rats received an SC injection of either nicotine or saline every 12 h. The nicotine was prepared at a concentration of 1 mg/ml saline. On the 1st preexposure day, rats in the nicotine preexposure group were injected with 0.4 mg/kg of nicotine at 800 and 2000 h; on each of the following preexposure days, the nicotine injections were increased by 0.05 mg/kg to a maximum dose of 0.8 mg/kg, which was the dose employed until the final preexposure trial on preexposure day 21. The saline preexposure group received an equivolume SC injection of saline at each of the 12-h intervals for the 21-day period.

The TR test procedure was conducted 24 h after the final preexposure injection (day 22). On the test trial, the rats were injected SC with either 0.8 mg/kg nicotine or physiological saline at a volume of 1 ml/kg. The groups are presented as preexposure drug-test drug: nicotine-nicotine ($n = 8$), nicotine-saline ($n = 7$), saline-nicotine ($n = 8$), and saline-saline ($n = 8$).

Each rat was placed in the TR chamber 20 min after the injection. For a 10-min period, the rat was habituated to the TR chamber and to the sound of the infusion pump. After the habituation period, the rat's cannula was attached to the infusion pump and 1 min later, 20% sucrose solution was infused through the cannula at the rate of 1 ml/min for 5 min. The rats' ingestive reactions were videorecorded and scored as in Experiment 1.

Results

During the preexposure phase, the saline-pretreated rats gained more weight than the nicotine-pretreated rats as previously reported [e.g., (22)]. This difference was assessed by comparing the body weights of the rats on preexposure day 1 with the body weights of the rats on preexposure day 21 by a 2×2 mixed-factor ANOVA with the factors of preexposure group (nicotine or saline) and preexposure day (1 or 21). The analysis revealed a significant interaction [$F(1, 27) = 32.74; p < 0.001$]. Although the groups did not differ on preexposure day 1, the nicotine-pretreated group weighed less than the saline-pretreated group on preexposure day 21 ($p < 0.01$).

Figure 2 presents the mean number of seconds that the rats in the saline and nicotine preexposure groups displayed ingestive reactions during the 5-min infusion of 20% sucrose solution following an injection of either nicotine or saline in Experiment 2. A 2×2 between-group analysis of variance (ANOVA) with the factors of preexposure drug (nicotine, saline) and test drug (nicotine, saline) revealed a significant pre-

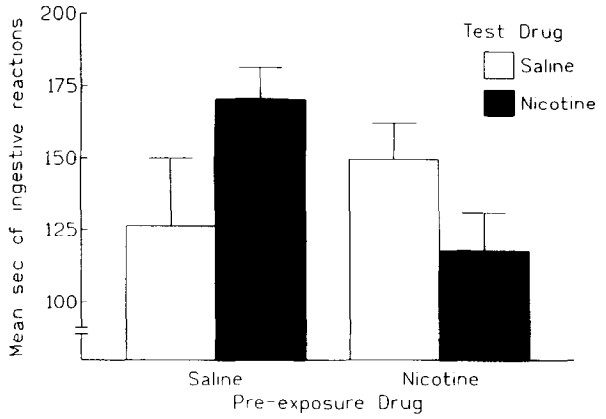

FIG. 2. Mean duration (s) of ingestive reactions during the 5-min intraoral infusion of 20% sucrose solution following an injection of nicotine or saline in the nicotine- or saline-preexposed groups of Experiment 2.

exposure drug × test drug interaction [$F(1, 27) = 5.6$; $p < 0.05$]. By subsequent Newman-Keuls pairwise comparison tests, the saline-nicotine group spent more time displaying ingestive reactions than did the saline-saline group ($p < 0.05$) or the nicotine-nicotine group ($p < 0.05$); however, the nicotine-saline group did not significantly differ from any group during the entire 5-min test trial.

Figure 3 presents the mean duration of ingestive reactions displayed by the various groups during the 1st min of testing in Experiment 2. A 2 × 2 between-group ANOVA revealed a significant pretreatment condition × test drug interaction [$F(1, 27) = 12.4$; $p < 0.01$]. Subsequent Newman-Keuls pairwise comparison tests revealed that the saline-nicotine and nicotine-saline groups spent more time displaying ingestive reactions than did the saline-saline or nicotine-nicotine groups ($p < 0.05$).

Discussion

Even at a dose as high as 0.8 mg/kg, nicotine enhanced sucrose palatability (as in Experment 1 at a dose of 0.4 mg/kg) in nicotine-naive rats. However, repeated pretreatment with nicotine eliminated its ability to enhance sucrose palatability, suggesting that tolerance developed to nicotine's modulation of palatability.

The group that had been chronically preexposed to nicotine but was tested with saline (24 h after the final nicotine injection) served to assess the ability of nicotine withdrawal to modify sucrose palatability. During the 1st min of testing, but not throughout the 5-min test, this group spent more time displaying ingestive reactions than did the group pretreated with saline and tested with saline. Therefore, the present results provide support for Grunberg's (9) suggestion that withdrawal from nicotine is accompanied by an increase in the hedonic evaluation of sweet tastes in rats [e.g., (9,13)].

GENERAL DISCUSSION

During nicotine withdrawal, humans report an increased preference for sweets (9,21). On the basis of such self-reports, Grunberg (9) suggested that the hedonics of sweet tastes are modified during nicotine withdrawal. The present findings support this assertion, using a direct measure to assess taste hedonics, the taste reactivity test. During the 1st min of the TR test [which is the typical TR test duration [e.g., (3,8)] employed to unambiguously assess palatability independent of postingestive factors], the saline-tested rats that were withdrawn for 24 h from repeated nicotine exposure displayed more ingestive reactions than did the saline-tested rats that had been preexposed to saline. Furthermore, preexposure to nicotine eliminated the enhancement of sucrose palatability that nicotine produced in naive rats, suggesting that tolerance developed over the period of 21 days of nicotine exposure to the ability of nicotine to enhance sucrose palatability.

Nicotine consistently enhanced the hedonic evaluation of sweet sucrose solution in naive rats [as previously reported (13)]. This effect was apparent at doses of 0.4 and 0.8 mg/kg, SC. Furthermore, nicotine suppressed the display of aversive reactions elicited by quinine, quinine-sucrose, and sucrose solutions, and enhanced the display of neutral or mildly aversive passive drips elicited by quinine and quinine-sucrose solutions. This pattern of results suggests that nicotine enhances the palatability of novel flavored solutions in nicotine-naive rats. Although previous evidence from consumption tests suggests that nicotine suppresses the consumption of sweet food (9–11), the suppression is apparent during chronic treatment with nicotine, unlike the present procedure. In fact, in Experiment 2, when rats that had been chronically exposed to nicotine were injected with nicotine before sucrose exposure, they did not display enhanced ingestive reactions (although they also did not display suppressed ingestive reactions) relative to rats that had been chronically exposed to saline and tested with saline.

Because nicotine effectively establishes a conditioned aversion to the flavored solution with which it is paired (12), it is conceivable that the suppression of feeding by chronic nicotine pretreatment (8–10) may in part be mediated by a conditioned aversion to the food. Conditioned aversions have been reported during chronic exposure to lithium (2).

The dose of nicotine may also determine whether it enhances or suppresses palatability. At the doses employed in the present experiments, nicotine has been shown to produce a conditioned place preference (1,4,9) and to enhance responding for electrical brain stimulation reward (23); there-

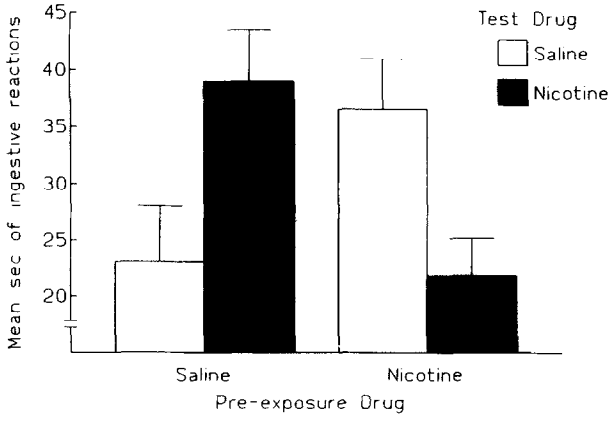

FIG. 3. Mean duration (s) of ingestive reactions elicited during the 1st min of the infusion in Experiment 2.

fore, these doses of nicotine appear to be rewarding to rats. The pattern of TR reactions produced by nicotine is similar to that produced by morphine and amphetamine, two other rewarding drugs. In fact, like morphine and amphetamine [e.g., (23)], nicotine enhances dopamine within the nucleus accumbens (14). Morphine (2 mg/kg, SC) also produces enhancement of sucrose palatability (6,20) and suppression of quinine aversiveness (5,19), and amphetamine also produces suppression of quinine aversiveness (18). It is therefore conceivable that drugs that are rewarding produce a shift in palatability of flavored solutions in a manner that reflects increased hedonic evaluation of the solutions.

The flavors that were intraorally delivered in the present experiment were novel. Therefore, the rats' reactions to the flavor may be influenced by the effects of nicotine and nicotine withdrawal on neophobia rather than simply on palatability. This suggestion, however, is unlikely, because previous work that specificially manipulated the novelty of the test solution revealed that drug-induced modification of palatability does not vary as a function of the novelty of the test solution (15,19).

In summary, nicotine suppressed aversive taste properties of unpalatable flavored solutions and enhanced hedonic taste properties of sucrose solution in rats that were nicotine naive. Tolerance developed to the ability of nicotine to enhance the palatability of sucrose across 21 pretreatment days. Finally, when nicotine-preexposed rats were tested with saline (24 h after the final nicotine exposure), they displayed enhanced hedonic evaluation of sucrose solution, suggesting that the palatability of sucrose was enhanced during withdrawal from nicotine.

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REFERENCES

1. Acquas, E.; Carboni, E.; Leone, P.; DiChiara, G. SCH 23390 blocks drug-conditioned place-preference and place-aversion: Anhedonia (lack of reward) or apathy (lack of motivation) after dopamine-receptor blockade? Psychopharmacology 99:151–155; 1989.
2. Bernstein, I. L.; Goehler, L. E. Chronic lithium chloride infusions: Conditioned suppression of food intake and preference. Behav. Neurosci. 97:290–98; 1983.
3. Berridge, K. C.; Grill, H. J. Alternating ingestive and aversive consummatory responses suggest a two-dimensional analysis of palatability in rats. Behav. Neurosci. 97:563–573; 1983.
4. Carboni, E.; Acquas, E.; Leone, P.; Di Chiara, G. 5-HT_3 receptor antagonists block morphine- and nicotine- but not amphetamine-induced reward. Psychopharmacology 97:175–178.
5. Clarke, S.; Parker, L. A. Morphine-induced modification of quinine palatability: Effects of multiple morphine-quinine trials. Pharmacol. Biochem. Behav. (in press).
6. Doyle, T. G.; Berridge, K. C.; Gosnell, B. A. Morphine enhances hedonic taste palatability in rats. Pharmacol. Biochem. Behav. 46:745–749; 1993.
7. Fudala, P. J.; Teoh, K. W.; Iwamoto, E. T. Pharmacologic characterization of nicotine-induced conditioned place preference. Pharmacol. Biochem. Behav. 22:237–241; 1985.
8. Grill, H. J.; Norgren, R. The taste reactivity test: I. Mimetic responses to gustatory stimuli in neurologically normal rats. Brain Res. 143:263–279; 1978.
9. Grunberg, N. E. The effects of nicotine and cigarette smoking on food consumption and taste preferences. Addict. Behav. 7:317–331; 1982.
10. Grunberg, N. E.; Bowen, D. J.; Maycock, V. A.; Nespor, S. M. The importance of sweet taste and caloric content in the effects of nicotine on specific food consumption. Psychopharmacology 87: 198–203; 1985.
11. Grunberg, N. E.; Popp, K. A.; Winders, S. E. Effects of nicotine on body weight in rats with access to "junk" foods. Psychopharmacology 94:536–539; 1988.
12. Kumar, R.; Pratt, J. A.; Stolerman, I. P. Characteristics of conditioned taste aversion produced by nicotine in rats. Br. J. Pharmacol. 79:245–253; 1983.
13. Jias, L. M.; Ellison, G. Chronic nicotine induces a specific appetite for sucrose in rats. Pharmacol. Biochem. Behav. 35:489–91; 1990.
14. Imperato, A.; Mulas, A.; DiChiara, G. Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. Eur. J. Pharmacol. 132:337–338; 1986.
15. Leeb, K.; Parker, L.; Eikelboom, R. Effects of pimozide on the hedonic properties of sucrose: Analysis by the taste reactivity test. Pharmacol. Biochem. Behav. 39:895–901; 1991.
16. Parker, L. A. Conditioned suppression of drinking: A measure of the CR elicited by a lithium conditioned flavor. Learn. Motiv. 11:538–559; 1980.
17. Parker, L. A. Rewarding drugs produce taste avoidance, but taste aversion. Neurosci. Biobehav. Rev. (in press).
18. Parker, L. A.; Leeb, K. Amphetamine-induced modification of quinine palatability: Analysis by the taste reactivity test. Pharmacol. Biochem. Behav. 47:413–420; 1994.
19. Parker, L. A.; Maier, S.; Rennie, M.; Crebolder, J. Morphine- and naltrexone-induced modification of palatability: Analysis by the taste reactivity test. Behav. Neurosci. 106:999–1010; 1992.
20. Rideout, H. J.; Parker, L. A. Morphine-induced enhancement of sucrose palatability: Analysis by the taste reactivity test. Pharmacol. Biochem. Behav. (in press).
21. Rodin, J. Weight change following smoking cessation: The role of food intake and exercise. Addict. Behav. 12:303–17; 1987.
22. Winders, S. E.; Grunberg, N. E. Nicotine, tobacco smoke, and body weight: A review of the animal literature. Ann. Behav. Med. 11:125–133; 1989.
23. Wise, R. A. The brain and reward. In: Liebman, J. M.; Cooper, S. J., eds. The neuropharmacological basis of reward. Clarendon Press: Oxford; 1989:23–28.