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Selective Inhibition by Nicotine of Shock-Induced Fighting in the Rat[1]

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DRISCOLL, P. AND K. BAETTIG. *Selective inhibition by nicotine of shock-induced fighting in the rat.* PHARMAC. BIOCHEM. BEHAV. **14**(2) 175–179, 1981.—The frequency of shock-induced fighting, posturing and "no reaction" (running/jumping or freezing), after acute SC injections of 0, 0.1, 0.2 and 0.4 mg/kg nicotine, was measured in 38 pairs of male and 12 pairs of female rats. Sensitivity to footshock was also measured, at the same nicotine doses, in males. Nicotine inhibited shock-induced fighting in 32 pairs of high-frequency fighting males in a dose-dependent fashion, with fighting being gradually replaced by posturing at the 0.1 and 0.2 mg/kg doses. There was a significant increase in the "no reaction" category (especially freezing behavior) only at 0.4 mg/kg, indicating that reduced activity may have been partly responsible for the reduction in fighting seen at that dose. None of the doses had a significant effect on sensitivity to footshock. Nicotine had no effect on shock-induced fighting in the six low-frequency fighting male pairs, and affected the female pairs only at the 0.4 mg/kg level, where fighting was also decreased due to an increase in the "no reaction" category. It could be concluded that small doses of nicotine, under favorable conditions, were capable of inhibiting shock-induced fighting in rats without altering shock sensitivity or depressing activity.

Shock-induced fighting in rats Shock thresholds Nicotine

IT has been suggested that a frequent precondition for the smoking of tobacco is stress as perceived by the individual, either due to his or her susceptibility to over-arousal, or due to being placed in stressful situations [11]. Not only do smokers appear to smoke more when exposed to a stressful situation, but it is now generally believed that the reinforcement that maintains smoking behavior appears to be a nicotine-mediated reduction in the impact of aversive stimuli, protecting the coping ability of the smoker from the disruptive effects of excessive arousal [14, 21, 24], the most important of these being displays of aggressive behavior and/or a reduction in efficiency.

A main impediment to the acceptance of studies with rats which have investigated the behavioral actions of nicotine, as an animal model for human behavior, has been the inability to demonstrate with rats another vital facet of human smoking behavior, that being the addiction to nicotine [2,21]. This problem has recently been resolved through the first fully successful demonstration of nicotine self-administration by rats [23], at a wide range of doses considered to be comparable to "smoking doses" in humans. That accomplishment has helped to rationalize the many studies involving the effects of nicotine on rat behavior.

At about the same time that the preliminary report of this present study appeared in abstract form [12], a separate investigation reported a dose-dependent inhibition of shock-induced fighting in rats by parentally-administered nicotine [33], and subsequent experiments have also shown similar results through the intracerebraventricular application of nicotine [44]. Certain important differences, other than the method of injection, exist among these studies, however. For example, one of the other studies [33] did not record the frequency of posturing behavior, a parameter whose importance cannot be overestimated in this test [9,26]. The recording of posturing behavior (when the two rats face each other in an upright position, without actually fighting), has proven to be critical in this present analysis of the effects of nicotine on shock-induced fighting in rats.

The present study investigated the effects of various doses of nicotine on shock-induced fighting in male and female rats. The males were subsequently divided into high- and low-frequency fighting pairs for separate statistical analysis. To determine the effects of the dosage levels of nicotine used on the sensitivity to footshock per se, a second experiment measured shock thresholds after injection with nicotine.

METHOD

Experiment 1

Roman high-avoidance (RHA/Verh) rats, which are selected and bred at this institute for high shuttle box avoidance levels, were used. Thirty-eight pairs of naive, seven month old male rats and 12 pairs of naive, seven month old female rats were tested for shock-induced fighting in a chamber measuring 27×27×27 cm. The chamber was transparent on one side and was placed in a wooden box containing a loud speaker through which a steady back-

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ground noise, at a level barely discernible outside the box when it was closed, was emitted. The purpose of the background noise was to mask any extraneous, environmental sounds. The side of the box next to the transparent wall of the chamber contained a glass window which allowed observation of the rats at all times. The box was in a ventilated, darkened room in which the only illumination was provided by a shaded, 25 W bulb, placed directly outside of the box window, which was directed toward the subjects and away from the observer.

Each pair was given two initial sessions of 50 scrambled footshocks 4–5 days apart, with a shock intensity of 3 mA (males) or 2.5 mA (females), a shock duration of one sec and an intershock interval of ten sec. An SC injection of physiological saline solution preceded each session by 30 min. The rats were colony reared (9–12 per large cage), and were always paired with the same partner from another cage. The testing was done during the lighted part of the 12 hr light-dark cycle. The chamber, including the grid floor, was thoroughly cleaned between sessions.

Following the two initial sessions for each pair, which were sufficient to stabilize fighting behavior in these rats ([13], see also [25]), all pairs were subjected to four further 50-shock sessions under the same conditions, except that these were preceded by an SC injection of either physiological saline solution or nicotine in doses of 0.1, 0.2 or 0.4 mg/kg, given in a latin-square sequence. Each pair thus served as its own control. The injections were given 30 min before testing and all doses are expressed as free base. The following scoring system, numbered to facilitate recording, was used: (1) freezing behavior, (2) running and/or jumping around (1 and 2 were subsequently combined into a "no reaction" category for statistical purposes), (3) posturing and (4) fighting (one or both rats attacking the other with its forepaws).

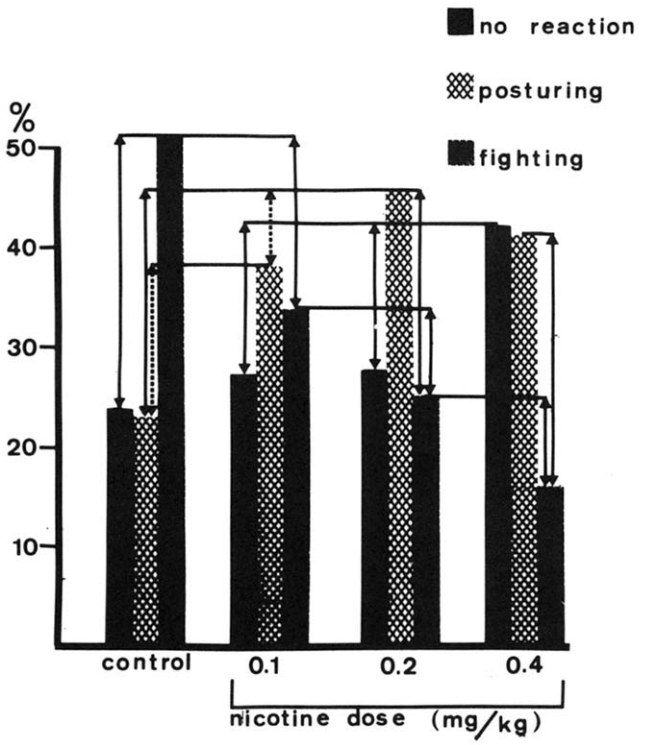

FIG. 1. Effects of acute nicotine injections on the percent of trials during which shock-induced fighting, posturing or "no reaction" were observed in 32 high-frequency fighting pairs of male rats. Control=physiological saline injection. Solid lines with arrows=$p<0.01$, dotted lines with arrows=$p<0.05$ (Wilcoxon matched-pairs, signed ranks test).

Experiment 2

The same chamber was used as in Experiment 1, through the grid floor of which it was also possible to deliver shocks of various intensities at various time intervals. Thirty-two naive, four month old RHA/Verh males were given three consecutive (ascending, descending, ascending) series of footshocks, step-wise at 0.1 mA intervals between 0 and 4.0 mA (or until the jump response was elicited in the ascending series). Each series, including the first, was preceded by a 3 min non-shock period. The shocks were of 0.5 sec duration, and the inter-shock interval was ten sec. The chamber was thoroughly cleaned between tests.

Four groups of eight rats each, on a split-litter basis, were injected SC either with physiological saline solution, or nicotine at one of the following doses: 0.1, 0.2 or 0.4 mg/kg, 30 min before testing. As with shock-induced fighting, an experienced observer, who was unaware of the treatment condition used, recorded the shock levels (thresholds) required to elicit the following responses from each animal: flinch (any detectable movement corresponding to shock presentation), shuffle (flinch followed by movement of the feet) and jump (all feet leaving the grid).

RESULTS

Experiment 1

An inhibition by nicotine of the fighting response in the 32 high-frequency fighting pairs of male rats, and the gradual replacement of that response by posturing over the two lowest dose levels, can be seen in Fig. 1. Although the level of fighting was further reduced by the 0.4 mg/kg dose, this drop was accompanied by an increase in the "no reaction" category, especially freezing behavior. The percent of trials values for freezing behavior in the "no reaction" category, for the four treatments, were as follows: control (physiological saline solution) 15%, 0.1 mg/kg nicotine 17%, 0.2 mg/kg nicotine 20% and 0.4 mg/kg nicotine 33%.

It can be seen in Fig. 2 that, in the six pairs of males selected as low-frequency fighting pairs, none of the nicotine doses had an effect on any of the three behavior categories. The percent of trials values for freezing behavior in the "no reaction" category, for the four treatments, were as follows: control 10%, 0.1 mg/kg nicotine 13%, 0.2 mg/kg nicotine 18% and 0.4 mg/kg nicotine 19%.

Within the 12 pairs of female rats (Fig. 3), it can be seen that (a) posturing was marginally increased at the 0.2 mg/kg dose of nicotine without any change in the level of fighting at that dose, (b) there was a significant reduction in fighting only at the 0.4 mg/kg dosage level and (c) this reduction was accompanied by a significant increase in the "no reaction" category, as was the case with the high-frequency fighting pairs of males. The percent of trials values for freezing behavior in the "no reaction" category, for the four treatments, were as follows: control 14%, 0.1 mg/kg nicotine 18%, 0.2 mg/kg nicotine 20% and 0.4 mg/kg nicotine 29%.

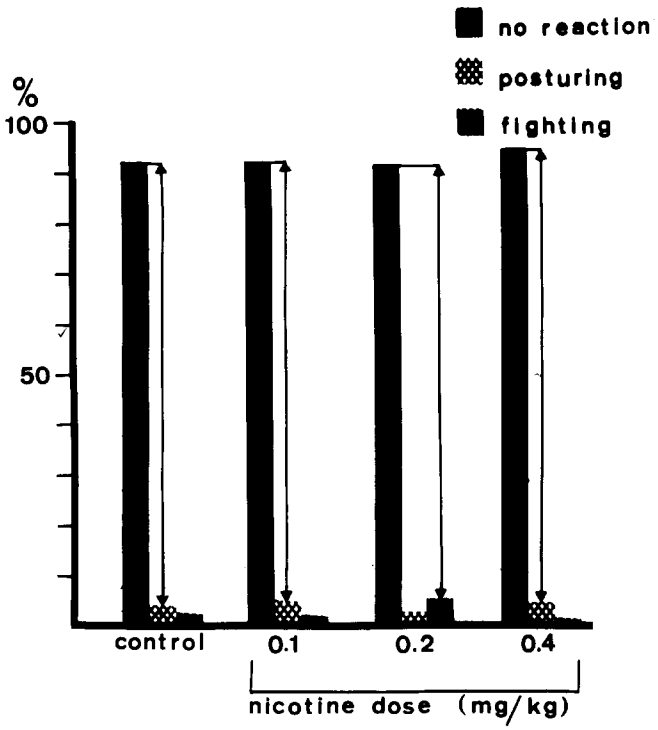

FIG. 2. Effects of acute nicotine injections on the percent of trials during which shock-induced fighting, posturing or "no reaction" were observed in 6 low-frequency fighting pairs of male rats. Control=physiological saline injection. Solid lines with arrows=$p<0.01$ (Wilcoxon matched-pairs, signed ranks test).

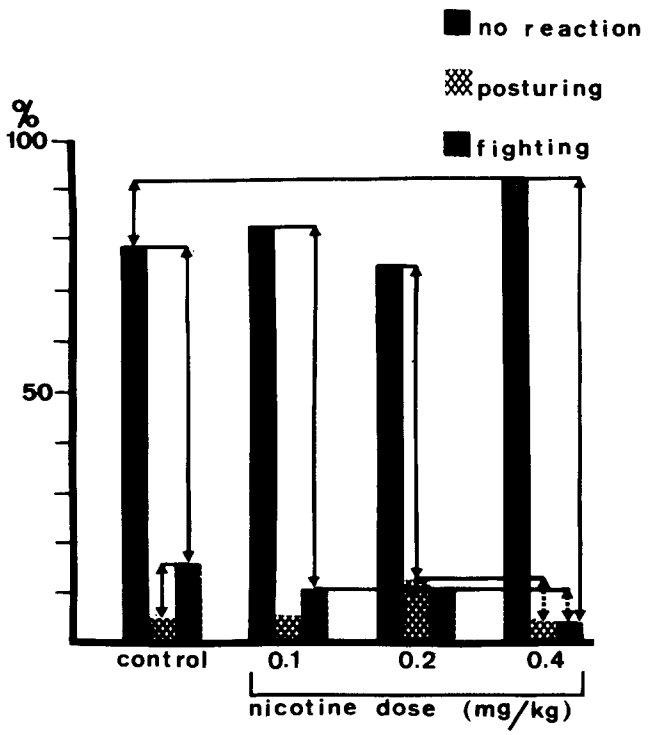

FIG. 3. Effects of acute nicotine injections on the percent of trials during which shock-induced fighting, posturing or "no reaction" were observed in 12 pairs of female rats. Control=physiological saline injection. Solid lines with arrows=$p<0.01$, dotted lines with arrows=$p<0.05$ (Wilcoxon matched-pairs, signed ranks test).

Experiment 2

Table 1 shows the results of the second experiment. The threshold for each response was analyzed across nicotine doses, using two-way analyses of variance. There were no significant differences found in any of these comparisons, indicating that the various doses of nicotine could not be differentiated from one another or from the control in regard to effect on shock thresholds.

DISCUSSION

It is interesting to note that small, "smoking doses" of nicotine have been reported to inhibit attack behavior in several species of animals, including rats ([33, 41, 44] and this present study), cats [7] and monkeys [24], whereas there have been no reports as yet denoting an increase in attack behavior after nicotine treatment. The same results have been reported for human experiments [24], and the subjective, "calming" influence of nicotine in man is well-known (e.g., [11, 14, 37, 43]). Recent studies utilizing peripheral-and central-acting nicotine antagonists have indicated that these effects of nicotine, at least in rats, are primarily central in origin [33,44].

As mentioned previously, the main difference between the two shock-induced fighting studies utilizing parenteral nicotine injections which have been conducted to date is that the other study did not measure the frequency of posturing behavior [33]. The present study has found that a significant reduction in fighting with 0.2 mg/kg nicotine was accompanied by a significant increase in posturing at that dose, without any change in the "no reaction" category and without any increase in sensitivity to footshocks. It would appear as though nicotine reduced the stimuli to provoke attack

TABLE 1

SHOCK THRESHOLDS, EXPRESSED AS mA VALUES, WITH STANDARD DEVIATIONS. 32 MALE, RHA/Verh RATS (8 PER DOSE)

	Flinch	Shuffle	Jump
Physiological saline solution (control)	0.80 (± 0.23)	1.46 (± 0.14)	2.02 (± 0.30)
0.1 mg/kg nicotine	0.74 (± 0.11)	1.39 (± 0.37)	1.86 (± 0.39)
0.2 mg/kg nicotine	0.77 (± 0.18)	1.57 (± 0.27)	2.27 (± 0.31)
0.4 mg/kg nicotine	0.77 (± 0.17)	1.41 (± 0.43)	1.99 (± 0.48)

while leaving the stimuli controlling the upright posture intact. This finding, therefore, was similar to those of other studies which have found, respectively, that the biting component of natural predatory behavior in cats was eliminated by nicotine while pawing and cuffing of the prey increased [7], and that an attack response to tail shock in monkeys was decreased by nicotine while anticipatory behaviors increased [24]. On the other hand, a suppression of threat behavior in rats, following the highest dose of intracerebraventricularly-administered nicotine used, has been recently reported [44].

The reduction of fighting seen with the highest dose of nicotine used in the present study (0.4 mg/kg) was accompanied by a significant increase in the "no reaction" category, especially in freezing behavior, and by no increase in shock thresholds, indicating that reduced activity may have been partly responsible for the decrease in fighting seen at this dosage level. This finding may be compared to the reduction in vertical activity (rearing behavior) noted in one of the other shock-induced fighting studies (but not in the fighting experiment itself) with a 1.0 mg/kg IP dose of nicotine, expressed as salt [33], which is functionally comparable to the highest dose used in the present study. Several other experiments have also shown an initial reduction in activity with 0.4 mg/kg nicotine in rats [11, 28, 29], as well as a reduction in the rate of self-administration of nicotine at high dosage levels [23]. It may also be assumed that the suppression of both fighting and threat behaviors seen in the other recent study with rats, after the highest dose of intracerebraventricularly-administered nicotine used [44], was accompanied by an increase of "no reaction" similar to that recorded in the present study.

The 12 female pairs tested in this present study showed no reduction in fighting after nicotine treatment, other than being affected by the 0.4 mg/kg dose in much the same way as the high-frequency fighting male pairs were. Since the slight increase in posturing at 0.2 mg/kg was not accompanied by any change in the level of fighting, it may be that this dose produced a tendency toward vertical activity in that group. It has been shown, for example, that nicotine increased rearing in female RHA rats, but not in male RHA rats [16]. It should be mentioned here that the slightly lower shock level used for females in the present study (2.5 mA, as compared to 3 mA for the males) reflects the consensus of opinion that female rats are more sensitive to footshocks than male rats are [6, 31, 36], a finding which has been also verified with the RHA/Verh selected line [13].

In a study which compared RHA/Verh rats of both sexes with Roman low-avoidance (RLA/Verh) rats of both sexes in regard to both shock-induced fighting and shock thresholds, male RHA/Verh pairs also showed more posturing than did female RHA/Verh pairs [13]. Fighting levels for the female RHA/Verh pairs used in the present investigation were also about the same as those seen previously [13]. The higher levels for the high-frequency fighting male pairs seen here can be attributed to (a) the division of the RHA/Verh male pairs into high- and low-frequency fighting pairs for statistical purposes in the present study and (b) the alteration of some of the testing conditions in the direction of producing higher levels of fighting (e.g., increased shock duration and shorter sessions), as well as higher levels of activity in general (as can be seen when the percent relationships between freezing behavior and running/jumping within the "no reaction" category are compared).

Numerous studies have shown behavioral stimulation following the administration of small, "smoking doses" of nicotine in rats [11, 15, 28, 29, 34], including experiments conducted with the same psychogenetic line used in this present study [4,5]. The present shock-induced fighting study, which was conducted during the lighted phase of the light-dark cycle, and that of Rodgers [33], which was conducted during the darkened phase have, however, both demonstrated an inhibition of fighting by parenterally-injected nicotine at dosage levels comparable to those earlier studies. A remarkable finding of the present study was, therefore, that although the level of fighting in the six low-frequency fighting male pairs of rats was so minimal that it was virtually impossible to achieve a further reduction in that behavior through nicotine treatment, nicotine at the 0.1 and 0.2 mg/kg dosage levels did not instead exert a stimulatory effect on shock-induced fighting in those pairs.

Discussions of central mechanisms of aggression have often focused on the cholinergic system [32], and it has been suggested that muscarinic and nicotinic compounds can exert antagonistic control over some types of attack behaviors [7,44]. Paradoxically, the previously-mentioned "calming influence" and alleviation of the effects of stress attributed to smoking in man are generally accompanied by EEG arousal [22, 30, 37, 43], and these EEG effects appear to be due to the nicotine content of tobacco smoke [2, 19, 46]. It has been suggested that smoking may alleviate a possible central adrenergic insufficiency in smokers, i.e., reduce negative mood states (anxiety, agitation, depression) by acting as a central adrenergic stimulant [43]. In this regard, it is well-known that nicotine, either directly or indirectly, through ACh, releases NE in the CNS [8, 11, 27, 38], especially in the hypothalamus, for which region it has a very high affinity [20, 35, 45].

However, although a recent review has advanced the importance of the dorsomedial and posterior hypothalamus in the triggering of "irritative aggression," and the ventromedial hypothalamus in the suppression of the same [42], the exact relationship between "aggressive behavior" and brain monoamine changes remains an unanswered question. It would appear as though treatments which promote the release of NE might reduce shock-induced fighting for that reason [1,10]. More experiments will have to be carried out along those lines, however, especially since 5-HT and DA are also believed to be involved in that behavior [18,40], possibly as antagonists to NE [1,10], and because nicotine is known to also affect those two putative neurotransmitter systems in the brain [3, 17, 34, 39].

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