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Genetic selection for nicotine activity in mice correlates with conditioned place preference

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Abstract

Genetically heterogenous stock (HS) mice are being used to develop lines which have differential locomotor response to subcutaneously administered (0.75 mg/kg) nicotine. These groups of nicotine-depressed, nicotine-activated or randomly bred control mice were tested as to conditioned place preference using the same dose of nicotine employed to determine their locomotor performance in activity tests. Results indicate that the nicotine-activated mice showed a significantly greater preference to nicotine when compared to the nicotine-depressed mice; this effect was seen in the first generation and continued in the more recently tested third generation. Evidence is offered to support the hypothesis that it is the stimulatory effects of drugs (of abuse) that can be directly correlatable with the strength of their reinforcing effect upon behavior.

Keywords: Conditioned place preference; Genetic selection; Locomotor activity; Nicotine; (Mouse)

1. Introduction

The conditioned place preference-task allows for the determination of the extent of place approach conditioning. Thus, when an experimental subject is administered a drug known to be a euphoriant in humans and confined to a cue-specific environment, it will enter and spend more time in that environment when it later is given free access to that and one other cue-specific environment. Since 1957, this technique has been employed in studies that have resulted in over 330 publications (Schechter and Calcagnetti, 1993). Of the experimental subjects used in these studies, all have been rats except for 21 reports (e.g., Cunningham et al., 1991a,b, 1992, 1993; Cunningham and Noble, 1991; Lawley and Kantak, 1990; Mucha and Walker, 1987; Risinger et al., 1991; Rogers et al., 1984; Seale and Carney, 1991; Siegfried and Frishknecht, 1989; Suzuki et al., 1991) that employed mice and a single study which used hamsters (Schnur and Morrell, 1990). The earliest report of conditioned place preference-testing of ethanol in rats indicated that ethanol produced a conditioned place preference (Black et al., 1973). This result was, subsequently, followed by a large number of reports that evidenced that ethanol either produced a neutral (Asin et al., 1985; Davis and Parker, 1990; Marglin et al., 1988; Reid et al., 1985) or, in fact, a conditioned place aversion (Bedingfield and Holloway, 1991; Stewart and Grupp, 1981, 1986, 1989; Van der Kooy et al., 1983) in that rats spent less time in their preferred side after multiple administrations of ethanol. Of interest to the present study were two reports in which the effects of either ethanol (Colombo et al., 1990) or morphine (Dymshitz and Lieblich, 1987) in the conditioned place preference-test appeared to be dependent upon differentiated rat lines developed by selective breeding.

In contrast to the general observation of neutral or aversive conditioning effects of ethanol in the rat, the mouse, when it is used as a subject in conditioned place preference experimentation, invariably experiences a rewarding effect as indicated by the production of a conditioned place preference (Cunningham et al., 1991a,b, 1992, 1993). This observation has led the authors to suggest that the conditioned place preference-test may be more sensitive to the rewarding effect

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of ethanol in mice than in rats (Cunningham et al., 1993). Nonetheless, genetic differences were also found in mice, in that the inbred C57BL\6J mouse line was shown to have an aversive reaction to ethanol, whereas the subsequently and most-often used DBA\2J line reliably exhibits a conditioned preference. In addition, HOT mice (those found to be insensitive to ethanol-induced hypothermia) were observed to experience a conditioned place preference to ethanol, whereas selectively bred COLD (sensitive to ethanol hypothermia) mice experienced an aversive effect when place conditioned to ethanol (Cunningham et al., 1991a).

When nicotine is used as the drug to condition place preference in the rat, the results have also been equivocal with some investigators reporting conditioned place preference (e.g., Acquas et al., 1989; Carboni et al., 1989; Fudala and Iwamoto, 1985, Fudala and Iwamoto, 1987; Iwamoto, 1990), whereas other reports indicated the production of conditioned place aversion (Fudala et al., 1985; Jorenby et al., 1990) or no effect at all (Clarke and Fibiger, 1987). To date, the mouse has never been employed as the experimental subject to determine the preference or aversion to nicotine in the conditioned place preference-test. Therefore, it is the objective of this study to use the first and third generation of selectively bred nicotine-activated and nicotine-depressed (in activity) mice, as well as their randomly bred controls, to test their (perhaps differential) preference to place conditioning with the (0.75 mg/kg) dose of nicotine used to differentiate activating/depressive effects on their motility. In the rat, conditioned place preference had been reported to nicotine in a 'biased', but not in an 'unbiased' procedure (Carboni et al., 1989). In this 'biased' task, animals are first tested to determine their baseline preference between two environments. The drug, in testing its rewarding properties, is then conditioned in the environment that the animal finds less preferred. In the 'unbiased' procedure, animals are trained to associate an environment with one or the other distinct chambers without regard to their innate preference. This procedure necessitates a balance in the number of animals that receive one treatment in the first environmental pairing with the number of animals that receive the second treatment in that first pairing (Schechter and Calcagnetti, 1993). In the present experimentation, the biased technique was chosen as it had been successful with nicotine conditioning in rats (Carboni et al., 1989).

The first study was undertaken to examine the effects of nicotine-induced activity, as well as the effects of nicotine in producing a conditioned place preference, in the first (G_1) and third (G_3) generations of mouse lines selectively bred for high and low levels of nicotine-induced activity. To this end, nicotine was conditioned on the side chamber found to be the least preferred of the two environments during baseline testing.

2. Materials and methods

2.1. Subjects

Male and female mice were received from the Institute for Behavioral Genetics in Boulder, CO. Each animal was individually housed during shipment and throughout experimentation. Fifteen mice of each sex were derived from one of six lines: [1 and 2] a replicate, i.e., two lines, of 'nicotine-depressed' (ND) mice whose parents showed lower activity after nicotine administration than after saline administration (G_1 $n = 20$; G_3 $n = 21$); [3 and 4] replicate of 'nicotine-activated' (NA) lines bred from parents that exhibited significantly less behavioral suppression with nicotine (G_1 $n = 20$; G_3 $n = 21$); and [5 and 6] replicate control lines that were bred at random (G_1 $n = 19$; G_3 $n = 23$). The dose used for differential activity measurements was 0.75 mg/kg calculated as base; a dose that is relatively low for a mouse but which has been reported (Smolen and Marks, 1991) to allow for successful selective breeding for the drug-related trait of nicotine-induced increase or decrease of locomotor activity in a Y-maze.

2.2. Apparatus

The apparatus consisted of two stainless steel units (Lafayette Instrument Co., Lafayette, IN, Model No. 85000) with each divided into three distinct chambers. The 'white' chamber was $30 \times 20.5 \times 18$ cm and illuminated by a 9 W light bulb fixed directly above a translucent white plastic lid. The floor of this chamber consisted of a wire mesh screen placed over stainless steel rods. The opposite side of the linear apparatus was an area designated as the 'black' chamber which was of the same dimensions and equipped with a light source from a red bulb. The floor on this side was covered by a washable, smooth, dark-grey colored rubber material. The third, or middle, chamber was unremarkable and consisted of an open-ended, light grey-colored stainless steel box. This center chamber could be isolated from the black and white chambers during conditioning by insertion of a metal plate (Model No. 80009) or left open to allow locomotion between the black and white chambers during testing. During the test trials, entry into either of the end chambers resulted in closure of a microswitch which, in turn, started a timer and, thus, the seconds of time that a mouse spent in each of the three chambers was recorded by a computer.

2.3. Conditioning and testing of place preference on non-preferred side: G_1 and G_3 mice

All G_1 mice were used in the first study, along with 13 NA, 12 ND and 12 control mice from G_3. For all mice, conditioning with saline or nicotine followed a standard cycle across consecutive days. The cycle consisted of: habituation to the training room, free access to the apparatus, baseline preference measurements allowing for assessment of baseline place preference (i.e., determination of the less or non-preferred side), place conditioning after administration of nicotine or saline and, lastly, testing of place preference in a non-drugged state.

Habituation occurred on days 1 and 2. Mice remained in their home cages and were transferred from the colony room to the training room where they stayed for 1 h each day. During this time, each animal was handled for 2–3 min. On days 3 and 4, each animal was given 10 min of free access to the conditioned place preference apparatus with the center chamber open to allow free entry into both the black and white chambers. The apparatus was cleaned after each exposure to preclude olfactory cues. On day 5, mice were placed into the center area and the seconds of time spent in each of the three chambers was monitored for 10 min; this constituted the baseline test. On the next day (day 6) and for the following 7 days, place conditioning took place. Each animal was given eight pairings, four with 0.75 mg/kg nicotine and four with saline subcutaneously (s.c.) administered on alternating days. After administration of nicotine (0.75 mg/ml as base), the mouse was placed into the side determined on the baseline day to be non-preferred, i.e., the side in which it spent the least amount of time during the 10 min baseline session. By insertion of the stainless steel plate, the animal was confined to this area for 10 min. On the following day, the animal was injected with an equal volume (10 ml/kg) of saline and it was confined for the same duration of time to the chamber that was its preferred side during its baseline test. After alternating exposures to nicotine in the non-preferred side and saline on the preferred side, the next day (day 14) was used for preference testing and this test was conducted in a manner identical to the baseline preference test day (day 5) in that the animal was tested in the absence of any injection. Seconds of time spent in each of the three chambers was measured during this preference test.

2.4. Activity measurements

Activity counts were measured in a Y-maze apparatus as previously described in detail elsewhere (Smolen and Marks, 1991). Activity was assessed as accumulated photoelectric beam crossings over a 3 min test starting at 5 min post-injection.

2.5. Conditioning and testing of place aversion on preferred side: G_3 mice

The conditioned place preference results indicated that a preference to nicotine was obtained only in NA and C animals. The absence of any effect in the ND mice suggests that nicotine *might* be aversive in these animals. If this were the case, pairing nicotine with the non-preferred side should further reduce time spent in that side. However, given that the nature of the conditioned place preference test involves locomotor behavior and exploration in the test environment, the test may not be sensitive enough to assess significant reductions in time spent on an already non-preferred side. If nicotine is, indeed, aversive in ND mice, such a 'floor effect' would prohibit assessment of this aversion. Based on this hypothesis, a second experiment was conducted to examine the aversive properties of nicotine by pairing it with the *preferred* side as assessed during baseline testing.

Additional G_3 mice (NA = 8, NP = 9 and C = 11) served as subjects. The conditioned place preference apparatus was identical to that previously employed, as was the procedure used except that nicotine was administered in conjunction with confinement in each animal's preferred side as determined in baseline testing.

2.6. Drug

Nicotine hydrogen tartrate salt ([−]-Nicotine di-[+]-tartrate salt) was purchased from Sigma Chemical Co., St. Louis, MO and the base was calculated as 35% of the salt, i.e., 2.14 mg salt were dissolved in unbuffered saline to yield 0.75 mg base. All saline and nicotine injections were made in an equal volume via the subcutaneous route.

3. Results

Data obtained from activity assessment were analyzed using a 2 × 3 × 2 (generation × line × test) mixed design Analysis of Variance (ANOVA) (Tallarida and Murray, 1987). Results indicated the presence of a significant line × test interaction ($F(2,118) = 40.76$, $P < 0.05$) suggesting that the three mouse lines responded differently to the activity suppressing effects of nicotine (Fig. 1). Furthermore, the presence of a generation × line × test interaction ($F(2,118) = 3.13$, $P < 0.05$), indicated that the differential response of the various lines to nicotine changed as a function of generation. Based on this information, two separate

3 × 2 (line × test) ANOVAs were conducted; one on the data obtained from G_1 animals, the other on data gathered from G_3 mice.

Data from the G_1 animals provided a significant line × test interaction ($F(2,56) = 11.17$; $P < 0.05$). Further examination, using interaction contrasts, indicated that whereas the difference between saline- and nicotine-induced activity did not alter between NA and C animals ($F(1,56) = 1.55$; n.s.), nicotine produced less suppression in the NA animals relative to the ND animals ($F(1,56) = 20.98$, $P < 0.05$) and ND animals exhibited greater suppression than C animals ($F(1,56) = 10.74$; $P < 0.05$; Fig. 1).

Analysis of the data obtained from G_3 animals also revealed a significant line × test interaction ($F(2,62) = 42.26$; $P < 0.05$)). Interaction contrasts revealed that nicotine produced far less suppression in NA animals relative to C or ND animals ($F(1,62) = 38.44$ and 81.08; $P < 0.05$, respectively), and ND animals showed greater activity suppression relative to C mice ($F(1,62) = 9.04$; $P < 0.05$) (Fig. 1). The fact that in G_3, unlike G_1, NA animals differed in their response to nicotine relative to *both* C and ND animals suggested evidence for progressive separation of the lines based on differences in nicotine-induced activity.

Conditioned place preference data obtained from G_1 animals were subjected to a 3 × 2 (line × test time) ANOVA examining the time spent on the NP side. Results indicated a significant main effect of test time (pre- vs. post-conditioning) ($F(1,57) = 15.33$; $P < 0.05$). Planned comparisons examined this effect and allowed that post-conditioning time spent in the NP side increased in both NA and C animals ($F(1,57) = 8.19$ and 7.45; $P < 0.05$, respectively) but not in the ND animals ($F(1,57) = 1.41$; n.s.; Table 1).

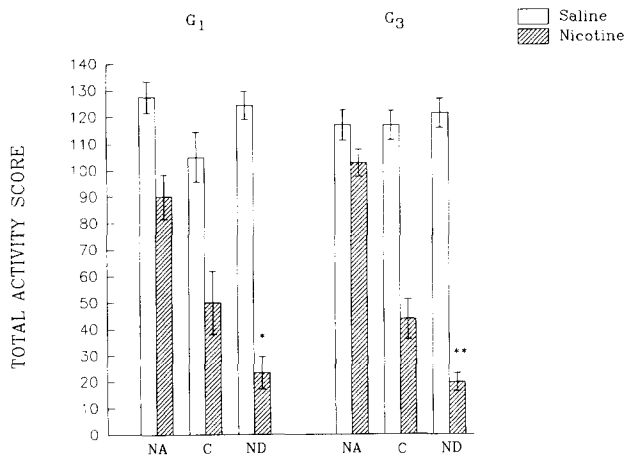

Fig. 1. Activity scores after subcutaneous nicotine (0.75 mg/kg) or saline in nicotine-activated (NA), control (C) and nicotine-depressed (ND) mice in first (G_1) and third (G_3) generation of selective breeding. *Significantly ($P < 0.05$; ANOVA) lower activity scores after nicotine administration than NA mice. **Significantly ($P < 0.05$; ANOVA) lower activity scores after nicotine administration than both NA and C mice.

Table 1
Means (±S.E.M.) of seconds of time spent in the non-preferred chamber prior to and after nicotine conditioning on the non-preferred side (A) or the preferred side (B) in mice bred for differences in nicotine effects on locomotor activity

	Nicotine-activated	Controls	Nicotine-depressed
(A) Conditioned place preference testing			
G_1			
Pre-conditioning	155.4 (11.4)	151.1 (14.4)	143.8 (13.9)
Post-nicotine	220.8 (22.5)	187.9 (28.4)	172.0 (17.7) [a]
G_3			
Pre-conditioning	146.4 (9.5)	144.2 (12.9)	152.8 (10.6)
Post-nicotine	208.6 (9.4)	208.0 (20.1)	184.1 (23.9) [a]
(B) Conditioned place aversion testing			
Pre-conditioning	167.4 (17.9)	170.5 (9.3)	156.2 (12.7)
Post-nicotine	227.6 (14.5)	227.9 (31.5)	284.9 (32.9) [b]

[a] Significantly less ($P < 0.05$; ANOVA) time spent in non-preferred side after conditioning trials with nicotine than by nicotine-activated or control mice. [b] Significantly more ($P < 0.05$; ANOVA) time spent in non-preferred side after conditioning trial with nicotine than by the other two groups of mice.

An identical analysis conducted on conditioned place preference data gathered from G_3 subjects revealed similar results. A main effect of test time ($F(1,31) = 14.32$; $P < 0.05$) was further examined using planned comparisons. These results indicated an increase in the post-conditioning time spent on the NP side in NA and C animals but not in ND animals ($F(1,31) = 6.79$ and 7.35, $P < 0.05$; $F(1,31) = 1.57$, n.s., respectively). These results suggest that for animals in G_3 (like G_1), nicotine produced a conditioned place preference in the NA and C animals only.

In keeping with analysis employed in the conditioned place preference study, the data in G_3 mice conditioned in their preferred side were analyzed based on time spent in the NP side pre- and post-conditioning. Data were examined with a 3 × 2 (line × test time) ANOVA. Results revealed a significant line × test time interaction ($F(2,26) = 5.76$; $P < 0.05$). Planned comparisons indicated that whereas both the NA and C lines failed to show an alteration in the time spent on the NP side ($F(1,26) = 3.94$ and 1.06, respectively), animals in the ND group spent significantly more time in the NP side ($F(1,26) = 26.54$; $P < 0.05$); these results suggest that nicotine produced a conditioned place aversion only in the ND animals.

4. Discussion

Selective breeding has been used to develop lines of mice based upon differential responses to nicotine (Smolen and Marks, 1991) and cocaine (Seale and Carney, 1991). The foundation population employed in

the present experiment was a genetically heterogenous stock (HS) produced by intercrossing eight inbred mouse strains (McClean et al., 1970). Mice were administered saline and their activity measurements in an automated Y-maze were compared with those obtained on a second day after the administration of 0.75 mg/kg nicotine. By identifying those animals most severely affected by nicotine's depressive effect upon locomotor activity, two replicate nicotine-depressed (ND) lines were established, whereas the mice that showed the least amount of nicotine-induced decline in locomotor activity were mated and produced replicate nicotine-activated (NA) lines of mice (Smolen and Marks, 1991). Replicate randomly bred control lines were also developed at the same time. Results of the present study indicate that the first and third generation of these mice exhibit significant differences in the locomotor decreasing effect of 0.75 mg/kg nicotine. Thus, the ND line of mice is more depressed in activity than either the controls or the NA line. The heterogeneity in the pharmacological responsiveness to nicotine's efficacy in decreasing locomotor activity was shown in the first generation of animals, enhanced by the third generation and, undoubtedly, will continue as this differential breeding program continues at the Institute for Behavioral Genetics in Colorado. It, nevertheless, seems apparent, with all three groups showing a decrease in activity after nicotine administration, that the 'outliers' from the normal distribution of mice responding to nicotine will be at the extremes of lessened decreases in activity after nicotine administration.

The 'biased' conditioned place preference test using mice as the subjects and nicotine as the drug for conditioning constitutes the first time in the literature that this combination of species and drug has been used (Schechter and Calcagnetti, 1993). In this regard, the comparison of post-conditioning times spent in the less-preferred side was shown to be significantly increased post-nicotine conditioning (142%; $P < 0.01$) in the NA mice and (124%; $P < 0.05$) in the control mice of G_1, whereas the mean change in time spent in the less-preferred side in the ND line of mice was not statistically significant. The observation that the NA mice, that were least affected in nicotine-induced locomotor decreases were most affected in the conditioned place preference-task may evidence the hypothesis that it is the psychomotor stimulatory effects of drugs (of abuse) that can be directly related to the strength of their reinforcing action (Wise and Bozarth, 1987); this has recently been determined in mice that were place conditioned with ethanol (Cunningham et al., 1993). In contrast, the locomotor-stimulatory and rewarding effects of both cocaine and amphetamine have been dissociated (Carr et al., 1988; Hemby et al., 1992). It would be expected that as the continued genetically selective breeding program in these three replicate lines of mice continues to separate nicotine motoric activation from nicotine motoric depression, the conditioned place preference of the former line may become more significantly different from both the randomly bred control and the nicotine-depressed mice lines.

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