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Differential Effects of Nicotine but Not Cathinone on Motor Activity of P and NP Rats

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GORDON, T. L., S. M. MEEHAN AND M. D. SCHECHTER. *Differential effects of nicotine but not cathinone on motor activity in P and NP rats.* PHARMACOL BIOCHEM BEHAV **44**(3) 657–659, 1993.—The locomotor stimulatory effects of nicotine (0.4 and 0.8 mg/kg) and cathinone (0.5 and 1.0 mg/kg) were assessed in alcohol-preferring (P) and -nonpreferring (NP) rats. Whereas P rats demonstrated enhanced (0.8 mg/kg) or no change (0.4 mg/kg) in spontaneous locomotor activity (SMA) to nicotine, NP animals showed no change (0.4 mg/kg) or depression of activity (0.8 mg/kg). However, following cathinone administration both P and NP rats exhibited an increase in SMA. The above results are discussed in light of the genotypic variations between P/NP rats and the potential mediation of differential neurotransmitter effects in the two lines.

Nicotine Cathinone Spontaneous motor activity P/NP Rats

SELECTIVE breeding of rats that voluntarily consume either high or low volumes of ethanol has produced divergent animal lines, each possessing specific ethanol drinking preferences, that is, ethanol-preferring (P) and -nonpreferring (NP) rats (14,21). Neurochemical analyses performed on brain limbic regions of naive P and NP animals have revealed unique differences in serotonergic [5-hydroxytryptamine (5-HT)], GABAergic, and dopaminergic (DA) systems between these two lines (14,16). Relative to NP animals, deficits in the concentration of these neurotransmitters have been found in P rats and the reduction in 5-HT has been posited to underlie the high alcohol-seeking behavior observed in the P line (13,16). Behavioral measures obtained from investigations involving ethanol-induced spontaneous locomotor activity (SMA) have also produced differential outcomes that may be attributed to phenotypic variations between these two animal lines. Whereas P rats exhibit stimulation of SMA at low ethanol dosages, NP rats remain unaltered or their SMA is actually depressed when compared to baseline activity levels. However, following high-dose ethanol administration both lines display suppression of SMA (18,22).

Additional investigations have examined nicotine-induced behavioral indices, including SMA, employing strains of rats and mice selectively bred for differences in ethanol-induced anesthesia, that is, high (HAS) and low (LAS) alcohol-sensitive rat lines and long-sleep (LS) and short-sleep (SS) mouse lines (4–6). The results of these studies demonstrate that both HAS and LS animals are more sensitive to the motor impairment and hypothermia produced by nicotine than are LAS or SS animals (6). Thus, as these authors contend, it appears that animals bred for ethanol sensitivity may share a similar genetic constitution for nicotine sensitivity.

As of this time, no investigations appear in the literature that address the sensitivity of P/NP rats to nicotine. Thus, the present experiments were designed to examine the effects of nicotine on SMA in P/NP rats. In addition, SMA was also assessed following administration of cathinone (α-aminopropiophenone), a psychostimulant with pharmacological actions similar to those of *d*-amphetamine. Cathinone was selected for investigation in this study given that the dosages employed here have been shown to generalize to nicotine in a drug discrimination paradigm (19).

METHOD

Ten male P and 6 male NP rats received from the University of Indiana School of Medicine served as subjects. Rats were 10 months of age and weighed approximately 350–450 g at the onset of the study. Subjects were housed individually in suspended wire cages with food and water available ad lib. Vivarium conditions were maintained at a constant temperature and humidity on a 12 L : 12 D cycle with light onset at 0600 h. All subjects had received previous experience in an appetitively reinforced operant discrimination task (18).

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SMA was measured by the interruption of photodetectors spaced 9.5 cm apart and 5.5 cm above the floor of a 45.5 × 35.5 × 20.5-cm clear Plexiglas chamber constructed in our laboratory. Activity counts were monitored by computer at 5-min intervals during both baseline and drug testing sessions under full overhead fluorescent lighting. All measures were conducted between 1200 and 1400 h.

Twenty-four hours prior to each of the four drug tests, baseline SMA counts were obtained. A period of 1 week separated each baseline/test session. On a test day, rats were brought to the SMA testing room and allowed 30 min for acclimation. Subsequently, each subject received an SC injection of saline on baseline measurement days or random injections or either of two doses of nicotine bitartrate (0.4 or 0.8 mg/kg, SC; bitartrate salt constitutes 65% of dose) or cathinone (0.5 or 1.0 mg/kg, IP). Ten minutes following injection, animals were placed into the activity monitors with SMA counts initiated immediately. Following 30 min, all subjects were returned to their home cages and transported to the vivarium.

RESULTS AND DISCUSSION

One-way analyses of variance (ANOVAs) comparing the four saline baseline days in each animal line revealed no differences in either P or NP animals, $F(3, 27) = 2.37$ and $F(3, 15) = 1.63$, respectively. Difference scores were calculated by subtracting each subject's saline baseline activity score from the ensuing drug test score for each baseline/drug test session.

Subsequently, data were analyzed by a two-way mixed design ANOVA defined by two levels of the animal line between factor (P/NP) repeated across three levels of the drug factor. Analysis revealed a significant animal line × drug interaction, $F(3, 42) = 6.22$, $p < 0.001$, with a significant effect of drug, $F(3, 42) = 24.24$, $p < 0.0001$, and no effect of animal line, $F(1, 14) = 0.057$. Contrast effects analysis yielded no significant differences between P and NP animals administered 0.4 mg/kg nicotine or 0.5 or 1.0 mg/kg cathinone, $F(1, 14) = 0.72$, 3.72, and 2.65, respectively. However, administration of 0.8 mg/kg nicotine produced a significant suppression of SMA in NP animals relative to P animals, $F(1, 14) = 18.88$, $p < 0.001$) (Fig. 1).

Previous work with P/NP rats has indicated that P rats are less sensitive than NP animals to the locomotor impairments produced by ethanol (22). A previous report from this laboratory (18) indicated that while both lines find ethanol aversive in the conditioned place preference task P animals show less aversion than NP rats. Additional studies have revealed differential effects between these rat lines employing the conditioned taste aversion (CTA) paradigm (8). These results demonstrate that following ethanol-saccharine pairings NP rats display more pronounced aversion to saccharine than do P rats. The current finding, showing enhanced SMA in P rats and reduced SMA in NP animals after nicotine administration, suggests that P/NP rats, bred for differences in ethanol preference, may also carry a common mechanism for nicotine sensitivity. Stimulation of SMA as a result of increased concentrations of DA in brain mesolimbic sites has been suggested by some to be an expression of the positive reinforcing characteristic of numerous drugs (1). Whether the differential sensitivity to nicotine-induced SMA observed in the current study reflects differential reinforcing properties of nicotine in the two animal lines remains to be determined. However, the present data are in agreement with an existing body of evidence employing mice bred for ethanol sensitivity. These studies, investigating ethanol–nicotine interactions in LS and SS mice, suggest that common genetic factors regulate sensitivities to both ethanol and nicotine. In addition, genetic backcrossing suggested that ethanol-induced differences in sleep time were correlated with indices of nicotine sensitivity, that is, seizure induction and hypothermia (3). In addition, CTA studies have demonstrated that similarities exist among inbred strains of mice regardless of whether the unconditioned stimulus is ethanol or nicotine (2).

Data from the present study demonstrate that nicotine, administered SC at 0.4 and 0.8 mg/kg, differentially affected SMA in P and NP rats whereas cathinone (0.5 or 1.0 mg/kg) produced robust increases in SMA in both lines of rats. Both

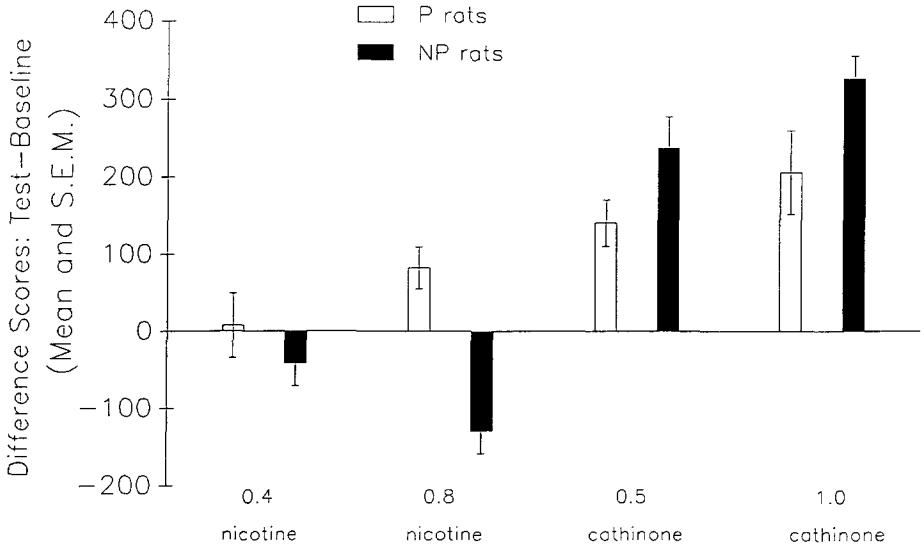

FIG. 1. Alterations in spontaneous locomotor activity in P and NP rats as a function of nicotine or cathinone administration.

nicotine (12,17) and cathinone (10,23) have been shown to stimulate mesolimbic DA activity and thus SMA, whereas concurrent administration of DA antagonists has been observed to attenuate each of these actions (17,20). While nicotine can influence multiple neurotransmitter systems (1), cathinone acts primarily through enhancement of DA release and is believed to have little or no behavioral effect relative to other systems (11). Thus, the increase in SMA in both P and NP rats following cathinone administration seen in the present study appears to reflect a dopaminergically mediated effect. Based upon this, the diametric results obtained with nicotine in the two lines, that is, increased SMA in P rats and decreased SMA in NP rats, suggest the involvement of other neurotransmitter systems.

P/NP animals have been shown to differ in CNS concentrations of 5-HT, GABA. and DA (14,16). Serotonin deficits in P animals have been associated with their ethanol-seeking behavior (13,16). However, both 5-HT and GABA activity have been shown to be altered by nicotine (1,7), and both transmitter systems have been implicated in the modulation of locomotor activity (9,15). Whether the differential effects of nicotine on SMA in P/NP animals is related to the known differences in these neurotransmitter systems remains to be determined.

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