Effects of nicotine on spontaneous locomotor activity in rats having high and low basal activity levels*

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Two groups of six rats each, preselected for high and low rates of spontaneous wheelrunning activity, were tested immediately following injections of either distilled water or nicotine hydrogen tartrate. At 0.10, 0.20, 0.40, and 0.80 mg/kg, nicotine depressed wheelrunning significantly in the high-activity Ss during the first 20 min after the injection. The performance of the low-activity Ss was not significantly affected by any dose of the drug. No evidence of tolerance development to the depressant actions of the drug was obtained.

Nicotine has been reported either to stimulate or to depress spontaneous activity in rodents, depending upon several factors, including the dosage employed (Silvette, Hoff, Larson, & Haag, 1962; Pradhan, 1970), the strain of animal tested (Morrison & Lee, 1968), and the basal activity levels of test Ss (Meliska & Rosine, unpublished observations, 1972). Morrison and Stephenson (1972) have also noted that either stimulation or depression may occur, depending upon the animals' past experience with the drug; inexperienced Ss may show behavioral depression, while experienced Ss may evidence stimulation.

The present study was designed to test, within a single design, whether rats selected for either high or low spontaneous locomotor activity would be differentially affected by nicotine at a range of dose levels. On the basis of the findings cited above, it was expected that nicotine would depress the spontaneous wheelrunning of highly active Ss, while increasing the activity of low-activity Ss.

METHOD

Subjects

Twelve experimentally naive male Harlan/Wistar rats, about 120 days old at the start of the experiment, served as Ss. They were housed individually in wire-mesh cages, with food and water ad lib throughout the experiment. Mean body weights increased from 475 to 502 g over the 11-day period of data collection.

Apparatus

Six standard activity wheels (Wahmann Mfg., Baltimore, Md.) were used. Wheels were 12 in. in diam and 4½ in. wide. Each wheel was equipped with a mechanical counter that recorded wheel revolutions in either direction of rotation. A metal sliding door at the entrance to each wheel was closed to prevent escape of the S during testing.

Procedure

The experiment consisted of two phases: (1) pretest screening, and (2) drug trials.

During the pretest period, a total of 25 rats were screened for spontaneous locomotor activity. For 6 consecutive days, each S was removed from his home cage, weighed, and placed into a wheel for 30 min. On the basis of their scores, the six most active ($\bar{X}$ = 63.2 revs/30 min) and six least active ($\bar{X}$ = 0.6 revs/30 min) animals were assigned to the "high activity" (HA) and "low activity" (LA) groups, respectively. For the next 5 days, animals were given IP injections of distilled water (1.0 cc/kg b.w.) and immediately placed into the wheels for 1 full hour. Revolutions were recorded for three consecutive 20-min intervals, hereafter referred to as T_1 , T_2 , and T_3 , respectively. Each rat was tested in the same wheel throughout the experiment. Testing took place in the morning.

Drug trials were begun immediately after these pretest trials, and this phase of the experiment was completed over 11 consecutive days. Each S received an IP injection of either distilled water (DW) or nicotine hydrogen tartrate at one of the following doses: 0.05, 0.10, 0.20, 0.40, or 0.80 mg/kg b.w. Fresh drug solutions were prepared in distilled water on each drug test day. Each S received each of the six treatments according to a Latin square design. As a control for carryover effects, drug days were alternated with control days on which all Ss received DW. This meant that all drug injections were separated by 48 h, with one exception: As part of the Latin square, each S received a DW "dose" on the drug day which followed the 0.80 mg/kg injection. This provided an extra DW administration between the 0.80 mg/kg and 0.05 mg/kg treatments, so that these doses were separated by 96, rather than 48 h.

RESULTS

Preliminary analysis indicated that variances of the HA and LA groups were inhomogeneous ($F = 91.8$, $df = 107/107$, $p < .001$). Therefore, wheelrunning scores of the HA and LA groups were analyzed separately.

HA Group

Using a repeated-measures, Latin square ANOVA, wheel revs/20 min were analyzed as a function of order (day) of drug administration (1st through 6th), drug/dose (DW, 0.05, 0.10, 0.20, 0.40, and 0.80 mg/kg nicotine) and time interval ($T_1 = 0-20$ min; $T_2 = 20-40$ min; $T_3 = 40-60$ min). As Table 1 indicates, time and drug/dose factors were significant, as was the Time by Drug/Dose interaction. Analyses of simple effects showed that the drug/dose factor was significant

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Table 1
Summary of ANOVA on Wheel Revolutions/20 Min as a Function of Order, Drug/Dose, and Time Since Injection

Source	SS	df	MS	F
Order	385.75	5	77.15	0.80
Drug/Dose	1379.53	5	275.91	2.86*
Subjects	6990.42	5	1398.05	—
Time	5943.50	2	2971.75	30.80†
Time by Order	1800.17	10	180.02	1.87
Time by Drug/Dose	2167.72	10	216.77	2.25*
Time by Subjects	2318.83	10	231.88	2.40*
Error (Pooled)	5789.00	60	96.48	—
Total	26774.92	107		

* $p < .05$ † $p < .001$

during T_1 ($p < .001$), but not during T_2 and T_3 . That is, nicotine significantly depressed wheelrunning during the first 20 min postinjection, but not during the last two 20-min intervals. Duncan's multiple range tests showed that during T_1 , wheelrunning was reduced significantly below control by all doses of the drug except 0.05 mg/kg. These results are represented in Fig. 1.

Further analyses revealed that, across drug treatments, wheelrunning was significantly greater during T_1 than during T_2 and T_3 , with the exception of the 0.10 and 0.80 mg/kg doses. At these doses, the decline in wheelrunning from T_1 to T_2 was not significant. This was apparently attributable to the drug-produced depression in responding at these doses, which reduced wheelrunning during T_1 to a level comparable to T_2 .

Table 1 also indicates that neither the order effect nor the Order by Time interaction was significant ($p > .05$). Thus, the degree of reduction in wheelrunning due to nicotine was essentially the same across repeated administrations of the drug, indicating a lack of tolerance development. These data are represented in

Fig. 2. Effects of consecutive druggings on wheelrunning across test days. (nicotine test days, ■—■, preceding control days, ●—●).

Fig. 2, which also shows the means of each preceding control day for comparison.

LA Group

Wheelrunning scores of the LA group (Fig. 1, closed bars) were subjected to the same analyses described for HA animals. No significant main effects nor interactions among any factors were found. There was also no significant effect of order of drug administration.

Summary of Results

The important results may be summarized as follows: (1) Nicotine hydrogen tartrate, at 0.10, 0.20, 0.40, and 0.80 mg/kg, significantly depressed the spontaneous

Fig. 1. Effects of various doses of nicotine hydrogen tartrate on wheelrunning activity in HA (open bars) and LA (closed bars) rats at three time intervals following injection. Vertical lines represent S. E. units. Asterisks indicate significance of differences from saline control: * $p < .05$, ** $p < .01$, *** $p < .001$.

wheelrunning of HA Ss during the first 20 min of testing, but not thereafter. (2) Spontaneous wheelrunning activity of LA Ss was not significantly affected by any dose of nicotine. (3) No significant tolerance development to the drug was detected after 5 days of nicotine administration.

DISCUSSION

The present results confirm the prediction that nicotine would retard the spontaneous locomotor activity of HA rats. The degree of depression produced appears to be fairly dose-dependent over the range tested, in contrast to reports (Silvette et al, 1962; Pradhan, 1970) of stimulation at low dosages. The depression effect occurred early in testing, during the first 20 min after the nicotine injection. Nicotine-produced reductions in wheelrunning during the last two 20-min intervals did not reach statistical significance.

The failure to detect any signs of tolerance development after repeated drug administrations contrasts with the recent findings of Morrison and Stephenson (1972) who reported that nicotine depressed activity during the first 3 days of testing, but stimulated activity thereafter. Methodological differences between the present study and Morrison and Stephenson (1972) may account for this discrepancy. For example, Morrison and Stephenson (1972) examined an activity task which involved free exploration in a darkened container, while the present work tested running in a well-illuminated wheel. It is quite possible that the different behaviors involved in these two tests are differentially sensitive to nicotine. Nicotine may potentiate exploration, while depressing wheelrunning; or, the stimulation effect may be contingent upon, or potentiated by, reduced illumination.

A second methodological difference between the present study and Morrison and Stephenson (1972) involves trial spacing. Ss were given 10 consecutive daily drug injections in the latter study while, in the present work, nicotine was given only on 6 alternate days with control injections in between. Furthermore, as a consequence of the Latin-square sequence of drug administration, the highest dose (0.80 mg/kg) was always followed by the DW dose, thereby providing three nondrug days between the 0.80 and 0.05 mg/kg doses. This extra spacing of drug treatments may be adequate to prevent the development of the tolerance observed by Morrison and Stephenson (1972).

The prediction that nicotine would stimulate activity in LA Ss was not supported. No indication of consistent behavioral stimulation was observed at any dose level of the drug. This finding is contrary to those of Meliska and Rosine (unpublished research, 1972) who observed stimulation of activity in LA rats with a 0.10-mg/kg dose of nicotine. Morrison and Lee (1968) also observed increased exploratory activity with nicotine in a low-mobility strain of (Wistar) rats—the same strain used in the present study. While no obvious explanation for this discrepancy suggests itself, it is possible that, by selecting rats for the extremes of activity and inactivity, some abnormally inactive Ss were chosen—Ss which were particularly insensitive to the stimulant actions of nicotine. However, this explanation is not particularly satisfying in view of Morrison and Lee's (1968) observation that, of the four strains they tested, Wistar rats proved to be the most susceptible to stimulation by nicotine.

While a substantial amount of current literature suggests that nicotine can stimulate activity under some circumstances, it also appears that nicotine has produced activity reductions in a number of situations (Dews, 1953; Bovet, Bovet-Nitti, & Oliverio, 1967; Morrison & Armitage, 1967; Morrison, 1969). Apparently, the critical variables which determine whether behavioral stimulation or depression will occur following nicotine injection remain to be identified.

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