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Nicotine Interactions With Ethanol Tolerance

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HJERESEN, D. L. *Nicotine interactions with ethanol tolerance.* PHARMACOL BIOCHEM BEHAV 31(3) 617–622, 1988.—Nicotine (N) administration (0.05 mg/kg SC) was paired with ethanol (E, 2.5 g/kg, 15% v/v, IP) to determine if N alters either the acquisition of extinction of tolerance to the hypothermic and sedative effects of E. During tolerance acquisition the following groups were tested: E+N (N=16), E+NaCl vehicle (V) (N=16), V+N (N=4) and V+V (N=4). For 11 days a colonic temperature was taken, both drugs were injected and the rats were tested for locomotor activity for 45 min, after which a final colonic temperature was taken. N significantly enhanced the rate of tolerance development to the hypothermic effects of E and blocked a degree of the sedative effects. On Days 12 to 17 rats in all groups received V injections to extinguish tolerance. On Days 18 to 24 rats in the E+N group were tested with either E+N or E+V and rats in the E+V group were similarly divided. Previous treatment with N significantly attenuated the extinction process which in turn enhanced the reacquisition of tolerance.

Nicotine Ethanol Tolerance Hypothermia

NO two drugs are used more frequently in combination than alcohol (E) and nicotine (N) derived from cigarettes (45, 47, 62) and both have strong reinforcing properties that contribute to continued drug use (12, 26, 28, 34, 35). N initially prolongs the sedative effects of E (4), produces behavioral depression when given in combination with E (29), and offsets the depressant effects of E on a critical flicker fusion test (39). N also has effects on cardiovascular measures that are additive to or synergistic with the effects of E (6,58). However, there is little or no information on the effects of N on the development or maintenance of E tolerance.

Tolerance to the effects of E results from the collective contributions of several physiological and central nervous system (CNS) processes: enhanced disposal of the drug, decreasing cellular responsiveness to the drug and the influence of conditioning on physiological processes. These have been referred to as dispositional, functional and learned or environment-dependent tolerance, respectively [see (33, 57, 58) for reviews]. It has been demonstrated that learned tolerance to specific effects of E (such as hypothermia and ataxia) develops independently and as a conditional response (CR) to the physiological effects exerted by E (22, 23, 30, 42). In a combined use situation N and E exert independent physiological effects. The primary issue addressed in the present study is whether the physiological effects exerted by N influence the development of tolerance to the sedative and hypothermic effects of E in rats.

METHOD

Subjects

The subjects were 40 male Long-Evans rats (Charles River Labs, Wilmington, MA; mean body weight=262.4±2.3 g, approximately 50 days of age on the first day of the experiment). Rats were individually housed in 46×24×15 cm suspended polycarbonate cages with wood chip bedding and given free access to food and water. Vivarium facilities had an ambient temperature of 21.5±0.2°C (S.E.M.) and relative humidity of 30–40% and were maintained on a 12:12 light: dark cycle with lights on at 0700. On the day preceding the onset of the experiment, the body weights and colonic temperatures of rats were measured and equivalent experimental and control groups (Table 1) were assigned to assure that test groups had neither a priori temperature differences nor differences in body weight.

Procedures

E (2.5 g/kg, 15% v/v in a 0.9% NaCl solution) was administered via bilateral IP injections to facilitate distribution. Rats were injected with N (0.05 mg/kg in a 0.9% NaCl solution, SC intrascapular) immediately after the E injection. Pilot experiments determined that this dose of N did not have a significant effect on either temperature or general activity, and previous experiments have determined this dose to be effective in drug discrimination and self-administration paradigms (36,52). Vehicle (V) injections were 0.9% NaCl, equivalent in volume to appropriate E or N injections. Colonic temperature was measured with a Bailey Instruments digital telethermometer (Model BAT-8) equipped with a RET-2 probe. The probe was lubricated with vegetable oil, and inserted 5 cm beyond the anal sphincter, and a temperature value was recorded 7 sec after insertion. This thermometer and probe have a time constant of less than 5 sec. Room temperature was determined on the rats arrival in the test room using the BAT-8 telethermometer. Relative humidity was also determined at this time with a Taylor Instruments Humidiguide meter.

TABLE 1

Group	Days −2 to 0 Baseline	Days 1 to 11 Acquisition	Days 12 to 17 Extinction	Days 18 to 24 Reacquisition
1 E+N	NaCl+NaCl	Ethanol+Nicotine	NaCl+NaCl	Ethanol+Nicotine
2 E+V	NaCl+NaCl	Ethanol+NaCl	NaCl+NaCl	Ethanol+NaCl
3 V+N	NaCl+NaCl	NaCl+Nicotine	NaCl+NaCl	NaCl+Nicotine
4 V+V	NaCl+NaCl	NaCl+NaCl	NaCl+NaCl	NaCl+NaCl
5 E+N/E+V	NaCl+NaCl	Ethanol+Nicotine	NaCl+NaCl	Ethanol+NaCl
6 E+V/E+N	NaCl+NaCl	Ethanol+NaCl	NaCl+NaCl	Ethanol+Nicotine

The first drug of each pair was delivered IP in a volume of 2.5 g/kg. The second was administered SC interscapularly at a dosage of 1.0 ml/kg. For statistical analysis, the data from Group 1 and 5 and those of Groups 2 and 6 were combined during baseline, acquisition and extinction phases of the experiment since they were treated identically and there were no significant differences between these pairs of groups.

The telethermometer was calibrated against a National Bureau of Standards traceable quartz thermometer in a temperature controlled oil bath by the Instrument Calibration Laboratory of Los Alamos National Laboratory. Repeated calibrations of the instrument indicated no deviation in accuracy from manufacturer's specifications between measurements. While calibrations reveal the instrument to have an accuracy of 0.028°C, reliability is not suggested beyond the 0.1°C accuracy specification of the manufacturer.

Immediately after the injections rats were placed in 46×24×15 cm polycarbonate cages and tested for sedation/locomotor activity for 45 min in a Coulbourn Instruments Model E 10-18 activity monitor equipped with two photocell assembly (T 22-01) and photobeam detector (S23-01) pairs mounted 17.5 cm apart. Successive disruptions of opposite beams were scored as a locomotor response. Data were collected by a Digitial Equipment Model PDP-11/73 microprocessor using a SKED-11 operating system. Temperature measurements were made immediately before and after the activity test session.

Immediately following the final colonic temperature measurement, rats were killed by decapitation and a 1-ml sample of mixed arterial-venous blood was collected in heparinized microfuge tubes (Sarstedt, CB 1000 KF 1 ml capillary tubes) and stored at 4°C. All eight rats in each test session were killed within a 4-min period. Samples were centrifuged (Savant High Speed Centrifuge for 2 min at 10,000 rpm) and the plasma was analzyed for alcohol (E) content with a Yellow Springs Instruments Model 27 Analyzer fitted with an alcohol oxidase membrane, buffer (YSI alcohol determination buffer No. 2387), and calibrated against 200, 320, and 500 mg/dl standards. The analyzer was recalibrated against a standard after every fifth sample. Results are expressed as mg/percent (mg/dl).

Testing occurred in four phases: 1) a baseline period (Days −2 to 0) where temperature and activity were determined in the absence of either N or E but with V injections; 2) an acquisition period (Days 1 to 11) where the test drugs were administered according to the schedule listed in Table 1 and the development of tolerance was monitored; 3) an extinction period (Days 12 to 17) where drug treatment was withdrawn while temperature and sedation/locomotor activity testing continued following placebo injections; and 4) a reacquisition period (Days 18 to 24) where drug treatment was reinstated according to the schedule in Table 1 and the redevelopment of tolerance was monitored.

Statistical Methods

Single factor interactions (within day comparisons) were analyzed with a one-way analysis of variance (63) with post hoc contrasts by Scheffe's multiple range tests (31,53). Multiple factor analysis was conducted using an n-way analysis of variance and covariance program and post hoc contrasts by Multiple Classification Analysis (46). Repeated measures were analyzed utilizing the harmonic mean approach of Winer (63) which reduces to a least squares analysis when sample sizes are equal. The development of tolerance was analyzed by a paired t-test comparing Day 1 temperatures to those on Day 11 within the same group. A similar test was used to analyze tolerance development during the reacquisition phase. During the baseline, acquisition and extinction phases of the study, data from Groups E+N and E+N/E+V and Groups E+V and E+V and E+V/E+N were combined since their treatment was identical and there were no significant differences between the pairs.

RESULTS

Baseline Period

There were no differences between groups during the baseline period in initial colonic temperature, change in colonic temperature (Fig. 1) or number of locomotor activity counts during the 45-min session (Fig. 2).

Acquisition Period

There were significant Group, $F(5,34)=16.6$, $p<0.01$, and Time, $F(10,50)=30.8$, $p<0.01$, effects on changes of colonic temperature during the acquisition period (Fig. 1) as well as a Group × Time Interaction, $F(50,340)=3.1$, $p<0.01$. While there were no differences between the control (V+N and V+V) groups, there was a significant Time effect, $F(10,10)=54.1$, $p<0.01$, between the experimental groups (E+N and E+V) as well as a Group × Time interaction, $F(10,300)=1.9$, $p<0.05$, with the colonic temperature of rats receiving E and N returning toward control values at a faster rate over test days than those receiving E and V. Both experimental groups acquired a significant degree of tolerance between Days 4 and 11 [E+N, paired $t(15)=12.08$, $p<0.01$; E+V, paired $t(15)=3.74$, $p<0.01$].

There were no significant differences in locomotor activity counts between control groups during the acquisition period (Fig. 2). E produced a significant decrease in activity

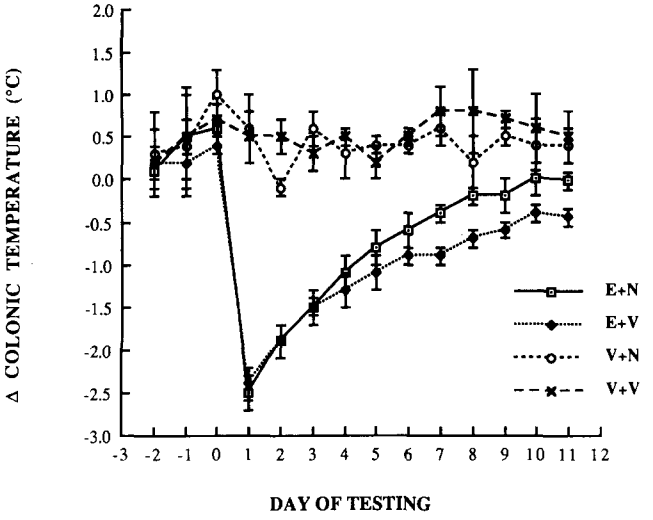

FIG. 1. Change of colonic temperature between initial and postlocomotor activity testing measurements. The period of measurement covers the baseline (Days −2 to 0) and acquisition (Days 1 to 11) periods of the experiment. The groups tested were: E+N, rats injected with ethanol and nicotine (N=16), E+V, rats injected with ethanol and NaCl vehicle (N=16), V+N, rats injected with vehicle and nicotine (N=4), and V+V, rats injected with vehicle for both treatments. Values represent the group means±S.E.M.

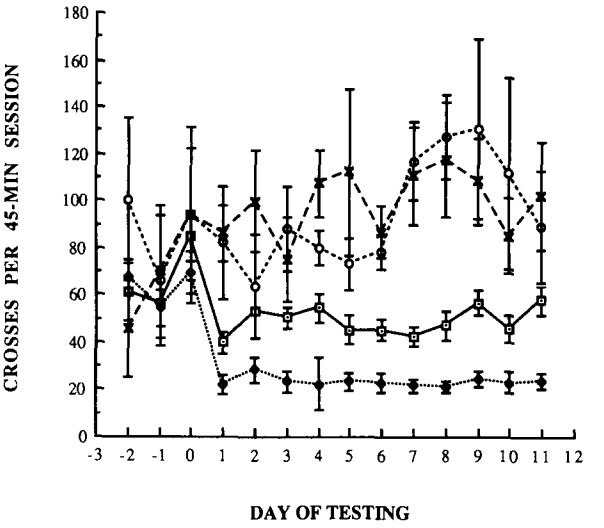

FIG. 2. Mean number of locomotor activity counts during a 45-min test session. The period of measurement covers the baseline (Days −2 to 0) and acquisition (Days 1 to 11) periods of the experiment. The groups tested were: E+N, rats injected with ethanol and nicotine (N=16), E+V, rats injected with ethanol and NaCl vehicle (N=16), V+N, rats injected with vehicle and nicotine (N=4), and V+V, rats injected with vehicle for both treatments. Values represent the group means±S.E.M. Key same as in Fig. 1.

in both experimental groups. Rats in the E+N group developed a small but significant degree of tolerance to the sedative effect of E, paired $t(15)=2.73$, $p<0.05$, but rats in the E+V group did not. N significantly attenuated the sedative effects of E during the acquisition period compared to V treatment with E, $F(1,14)=20.3$, $p<0.01$.

Extinction Period

There were no significant differences between the control and experimental groups in either colonic temperature or locomotor activity counts during the extinction period (Figs. 3 and 4). There was, however, a significant Time effect, $F(5,25)=10.9$, $p<0.01$, based on high colonic temperatures for rats in groups that had previously received E for the first 3 days of extinction. Rats in both the E+N, paired $t(15)=4.42$, $p<0.05$, and the E+V, paired $t(15)=3.69$, $p<0.05$, groups had higher initial colonic temperatures on the first day of the extinction period than the last.

Reacquisition Period

There were no differences in colonic temperature between the control groups during the reacquisition period (Fig. 5). There were significant Group, $F(5,34)=19.9$, $p<0.01$, and Time, $F(6,30)=13.0$, $p<0.01$, effects on the reacquisition of tolerance to the hypothermic effects of E as well as a Group × Time interaction, $F(30,204)=1.9$, $p<0.05$ (Fig. 5). Rats originally conditioned with E+N and then retested with this same combination were significantly less hypothermic in response to E during reacquisition than Group E+N/E+V which was similarly trained but not given N during reaquisition [Group effect, $F(1,14)=27.9$; Time effect, $F(6,6)=13.2$; Group × Time interaction, $F(6,84)=4.4$, all $p<0.01$]. Further, Group E+N/E+N developed no additional tolerance during reacquisition while Group E+V/E+V was

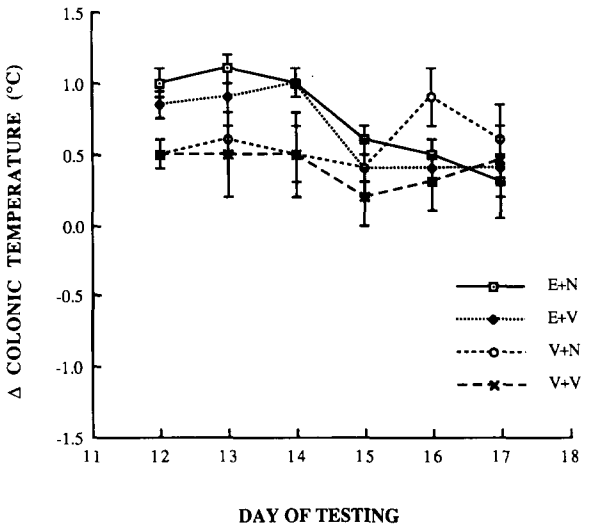

FIG. 3. Colonic temperature change between initial and postlocomotor activity testing measurements during the extinction period (Days 12–17). Values represent the group means±S.E.M.

significantly more hypothermic on the first day of reacquisition than on the last, paired $t(7)=9.93$, $p<0.01$. The difference in colonic temperature between Groups E+V/E+V and E+V/E+N was not significant. However, there was a Time effect between these groups, $F(6,6)=7.3$, $p<0.01$.

An ANOVA comparison of Day 21 colonic temperatures indicated a significant difference between the test groups, $F(5,34)=24.3$, $p<0.01$. Post hoc testing indicated that the following italicized groups did not differ significantly from

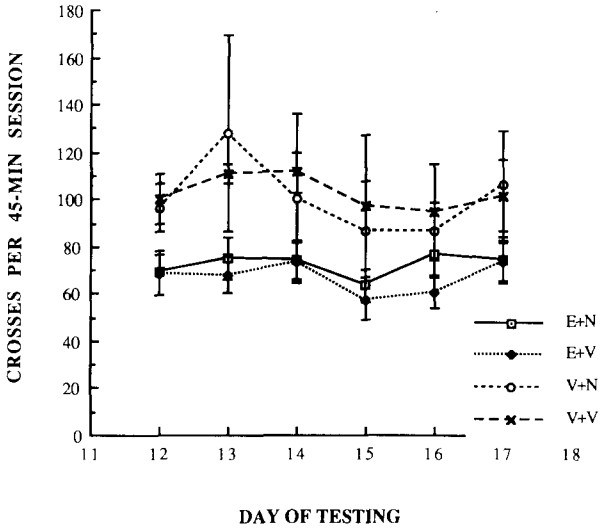

FIG. 4. Mean number of locomotor activity counts during each 45-min test session during the extinction period. Values represent the group means±S.E.M.

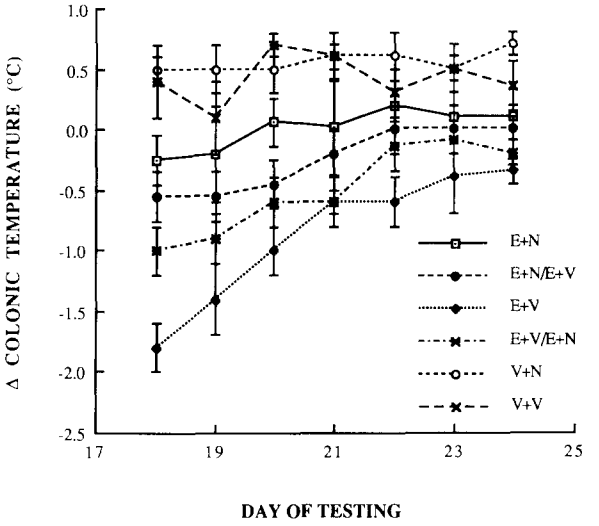

FIG. 5. Colonic temperature change between initial and postlocomotor activity testing measurements during the reacquisition period (Days 18 to 24). The first pair of drug designators (E=ethanol, N=nicotine, V=saline vehicle) represents the drug combination given during the acquisition period. The second pair represents the combination given during the reacquisition period. Half of the rats originally trained with E and N were retrained with this combination while the remainder were retrained with E and V. Half of the rats originally trained with E and V were retrained with E and N while the remainder were retrained with their original combination.

one another: *2, 5 6, 5 1 4, 1 4 3* (see Table 1). The final comparison indicates that rats trained with N and retested with N retained a greater degree of tolerance to the hypothermic effects of E through the extinction phase of the experiment.

There was also a significant Group effect, $F(5,34)=19.2$, $p<0.01$, on locomotor activity (Fig. 6) during the reacquisition period as well as a Group × Time interaction, $F(30,204)=1.7$, $p<0.05$. While there were no significant differences between the control groups during this period, there was a significant difference between Group E+N and Group E+V, $F(1,14)=16.8$, $p<0.01$, again indicating an effect of N on the retention of tolerance.

Blood E levels of the groups receiving E did not differ (Group E+N=200.6±12.2, Group E+V=208.0±11.8, Group E+N/E+V=198.0±10.5, Group E+V/E+N=191.4± 9.8; all mg/dl). This indicated that differences between the groups are not directly attributable to differences in E blood concentrations.

DISCUSSION

The results indicate a strong interaction between E and N in the development and maintenance of tolerance to E. First, a dose of N that had no effect on the colonic temperature of control (non-E treated) rats enhanced the rate of tolerance development to the hypothermic effects of E. Second, while this dose had no effect on the locomotor activity of control rats, it significantly attenuated the sedative effects of E and slightly enhanced the development of tolerance to this effect.

The results, in many ways, indicate an effect of learning processes on the development of tolerance. One interpretation of the present results is based on the hypothesis that learned tolerance develops to the specific physiological effects of a drug (22, 23, 30, 42). In the present case, frequently rendering animals hypothermic with E resulted in the development of a compensatory hyperthermic response, apparent during the initial portion of the extinction phase (Fig. 3). This compensatory hyperthermic response is common in this test paradigm (37,56). It is likely that N acted as a second

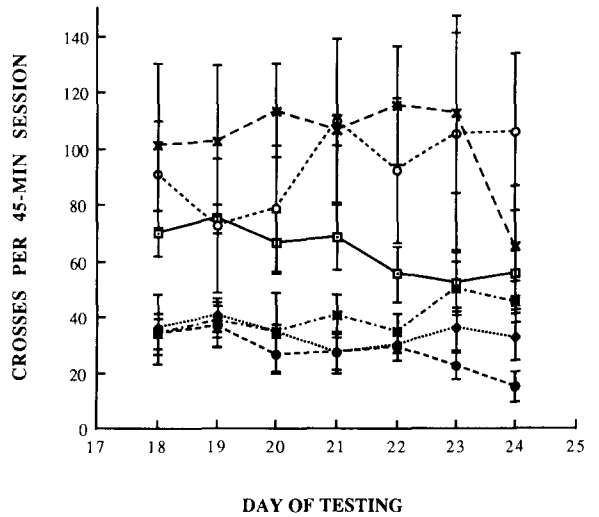

FIG. 6. Mean number of of locomotor activity counts during each 45-min test session during the reacquisition period. Key same as in Fig. 5.

physiological stimulus in this situation. Indeed, the temperature of animals trained with E+N was somewhat, although not significantly, higher on the first two days of extinction than that of E+V trained animals. This hypothesis is also supported by the results of the locomotor activity testing. Rats given both E and N developed a degree of tolerance to the sedative effects of E relative to animals receiving E without N. This view is complicated by the fact that the ability of N to attenuate the sedative effects of E was noted on the first day of testing. However, since learned tolerance has been demonstrated to occur within the first E administration session (10,38), it is possible that conditioning factors contributed in this process.

Of particular interest is the effect of N on the reacquisition of E tolerance. The data indicate that animals treated with N during the acquisition of tolerance lost virtually none of their tolerance during extinction. In contrast, rats given E without N treatment during acquisition showed a significant loss of tolerance during extinction. Consistent with the learning hypothesis, this result may be the consequence of a higher level of conditioning among the N-treated animals.

An alternative interpretation of the reaquisition data is suggested by numerous authors who have demonstrated an apparent effect of N on the retention of memory tasks (2, 7, 13, 25, 40, 61), possibly related to a N mediated release in vasopressin (5, 9, 19, 27, 49). However, it is not clear from this literature whether the effects of N on memory are attributable to direct effects on CNS memory processes or to such factors as the aversive physiological effects of the drugs. There is ample evidence that the presentation of an aversive stimulus during a learning trial can facilitate retention of that task (20). Even with neurohypophyseal peptides such as arginine vasopressin, long thought to ehance memory and the retention of drug tolerance (41, 43, 48, 59), there is considerable debate as to whether these effects are due to the aversive properties of the drug or to direct CNS actions (1, 14–16, 23, 24, 51).

While the present results are interpreted to suggest that N can act as a secondary cue in the development of learned tolerance, they do not preclude the number of other possibilities. First, depending on the dose, N is a powerful cholinergic agonist (3,50) and this effect may offset E-induced depletions of this neurotransmitter (26, 30, 44). Second, N stimulates the central release of norepinephrine and dopamine (17, 35, 50), numerous hormones (11,64) and the peripheral release of cortisol mediated by increase in ACTH (18). Since E typically depletes these compounds [see (26)], it is possible that N administration offsets these effects. Third, since the drug kinetics of both E and N affect the pharmacodynamics and pharmacokinetics of one another (21,54), it is possible that these interactions contribute to the present results.

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