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Behavioral Interactions Between Nicotine and Diazepam

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WHITE, J. M. *Behavioral interactions between nicotine and diazepam.* PHARMACOL BIOCHEM BEHAV 32(2) 479–482, 1989.—Graded doses of nicotine (0.01–1.0 mg/kg) were administered alone and together with three doses of diazepam (0.3, 1.0 and 3.0 mg/kg) to rats responding on a fixed-interval 2-min schedule of liquid food reinforcement. Nicotine (0.03–1.0 mg/kg) increased overall rate, but diazepam had little effect. Both nicotine and the two highest doses of diazepam attenuated the change in response rate through the interval. When combined with nicotine the lowest dose of diazepam increased overall rates above those produced by nicotine alone. However, it appeared to diminish the effects of nicotine on the within-interval pattern of responding. These changes appeared to be due to an elevation in the high rates at the end of the interval. In contrast, the highest diazepam dose increased overall response rates when combined with low doses of nicotine, but decreased the high rates observed after larger nicotine doses. This dose of diazepam combined in an additive manner with nicotine to reduce the degree of response rate change within the interval. The interaction between nicotine and diazepam depends on the aspect of behavior under investigation and the particular doses of the two drugs.

Nicotine Diazepam Schedule-controlled behavior Fixed-interval schedule Drug interactions

SMOKERS typically inhale about 1.0 mg of nicotine from each cigarette (1,3). Furthermore, because of the relatively long half-life of nicotine [approximately 2 hours (2,3)], there may be an accumulation of nicotine through the day even in moderate smokers. As a result, there is considerable potential for an interaction between nicotine and any other drug the smoker may take. The effects of the drug, or nicotine itself, may be modified by such an interaction. It is important, therefore, to determine whether such interactions occur, particularly those between nicotine and other commonly used psychoactive compounds.

An earlier paper described interactions between nicotine and caffeine (9). Rats were exposed to FI (fixed-interval) schedules of reinforcement and administered different doses of caffeine in combination with a range of nicotine doses. It was found that a low dose of caffeine (0.3 mg/kg) combined with nicotine increased response rates by an amount approximately equal to the effect of caffeine alone, while higher doses of caffeine combined with nicotine reduced or abolished the response rate increases produced by nicotine. In contrast, nicotine and caffeine both diminished the within-interval pattern of responding and the effects were approximately additive.

In the present study similar methods were used to examine the effects of coadministration of nicotine and the benzodiazepine diazepam. While the two come from different pharmacological classes, they share similar effects on fixed-interval responding. Moderate doses of both nicotine (8,10) and diazepam (5,11) increase overall rates of FI responding, while high doses produce only decreases. Both diminish the within-interval pattern of responding. The purpose of the present experiment was to determine whether the effects of nicotine and diazepam on fixed-interval responding are additive.

METHOD

Subjects

Four male Wistar hooded rats, bred in the Psychology Department at Monash University, served as subjects. Their free-feeding weights ranged from 244 to 350 g. During experimentation they were maintained at 85% of these weights. The animals were housed in individual cages with free access to water, in a temperature-controlled environment on a 12-hour light–12-hour dark cycle.

Apparatus

Operant chambers measuring 25 cm^3 were used. In each, there was a small recessed area in the middle of one wall. A 1.5-cm hole in this area allowed a dipper to deliver 0.15 ml of a 25% solution of sweetened condensed milk (Nestle) diluted with tap water. A single lever was located to the left of the dipper. Each chamber was illuminated by a 4-W fluorescent light and was enclosed in a sound- and light-attenuating cubicle. A small computer was used for control of the experiment and collection of data.

Procedure

The animals were trained to press the lever to obtain 3.5 sec access to the milk solution. Over 3 sessions they were exposed to FI schedules of gradually increasing duration until FI 120 sec was reached. For each animal, training continued with this schedule until response rate showed no con-

sistent directional change. An average of 30 training sessions was required. Sessions ended when 30 reinforcements had been delivered and were conducted at the same time each day, 5 days a week.

Testing was begun following stabilization. Each animal received nicotine in doses of 0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg, plus saline, in combination with each of the three diazepam doses (0.3, 1.0 and 3.0 mg/kg) and diazepam vehicle. Drugs were administered on Tuesday and Friday of each week; normal training sessions continued on other days. All animals were exposed to each nicotine dose and each diazepam-nicotine combination twice. The data presented are averages of the two determinations. All drugs and saline were administered 15 min before the session. The order of doses was randomized for each rat.

Drugs

Nicotine hydrogen (+) tartrate (BDH Chemicals Ltd., Poole, England) was dissolved in 0.9% saline. Diazepam (Roche, Australia) was suspended in 1% tragacanth gum. Both drugs were administered subcutaneously in a volume of 1.0 ml/kg body weight. Doses are expressed in terms of the free base.

Data Analysis

Data from each test session consisted of both the overall response rate and the rate in each tenth of the fixed-interval. From each within-interval pattern an index of curvature (4) was calculated. This indicates the degree of acceleration in response rate through the fixed-interval (larger values indicate greater acceleration) and is relatively independent of overall response rate.

These data were used to evaluate the nature of the diazepam-nicotine combination according to the method of Pöch and Holzmann (6). The data on the effects of nicotine alone and diazepam alone were used to calculate 'expected' effects of nicotine-diazepam combinations. To do this, an equivalent nicotine dose was determined for each diazepam dose. This was the dose of nicotine required to produce a change in the index of curvature equal to that produced by the particular diazepam dose. For each nicotine-diazepam dose combination, this diazepam-equivalent nicotine dose was added to the nicotine dose. The effects of each of these combined nicotine doses were determined by interpolation and used as the 'expected' effect of the nicotine-diazepam combination. These 'expected' index values were then compared to those actually obtained.

RESULTS

Mean overall response rates (expressed as a percentage of control values) following administration of nicotine alone, diazepam alone and nicotine plus diazepam are shown in Fig. 1. The effects of nicotine alone were similar to those found in earlier studies: low doses produce little or no change in response rate while higher doses increase overall rate. Maximal increase occurred following administration of 0.3 mg/kg of nicotine. The three doses of diazepam had little effect on overall rate when administered alone.

The effects of diazepam on the nicotine dose-response curve were highly dose-dependent. When the 0.3 mg/kg dose of diazepam was coadministered, rates were elevated above those produced by nicotine alone. This was most pronounced at the highest nicotine dose, where the mean

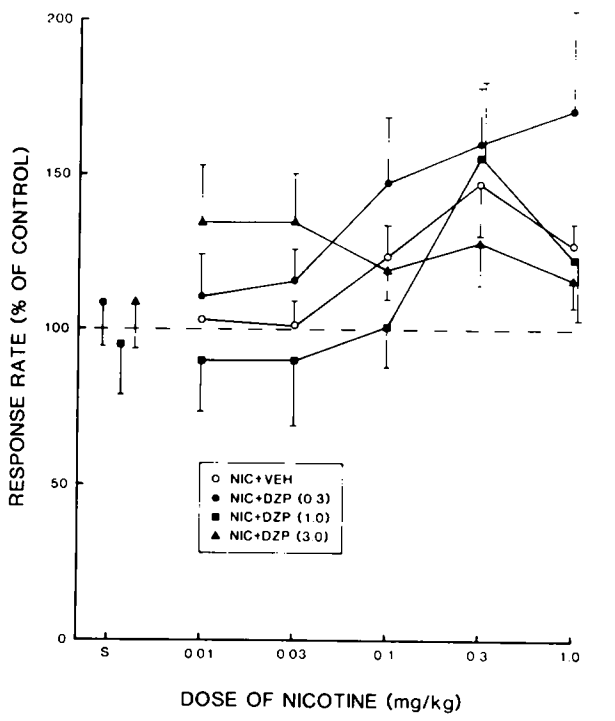

FIG. 1. The effects of graded doses of nicotine in combination with saline and 0.3, 1.0 and 3.0 mg/kg of diazepam on overall rates of FI responding. Response rates were calculated as a percentage of saline control values. S.E. bars are also shown.

changed from 127% to 171% of control following diazepam coadministration. As a result, the highest response rate was observed after the 1.0 mg/kg dose of nicotine rather than the 0.3 mg/kg dose. The intermediate dose of diazepam (1.0 mg/kg) reduced the response rates produced by low doses of nicotine alone, but had little effect on the rate following administration of 0.3 and 1.0 mg/kg of nicotine. In contrast, there was a flatter dose-response curve when 3.0 mg/kg of diazepam was coadministered with nicotine. That is, there was an elevation of the lower rates found after administration of 0.01 and 0.03 mg/kg of nicotine alone and a reduction in the higher rates produced by 0.3 and 1.0 mg/kg of nicotine.

The mean index of curvature for each nicotine-diazepam dose combination (and each drug alone) is shown in Fig. 2. Nicotine alone decreased the index in a dose-related manner, except that it was slightly higher after the 1.0 mg/kg dose compared to 0.3 mg/kg. This is consistent with results obtained in the earlier study. By itself, the lowest diazepam dose (0.3 mg/kg) increased the index, whereas the two higher doses decreased it. When the 0.3 mg/kg dose was coadministered with nicotine the index was elevated above that produced by nicotine alone. This occurred across the whole nicotine dose range. There was little change as a result of coadministering 1.0 mg/kg of diazepam, but the highest dose (3.0 mg/kg) tended to decrease the index below the levels produced by nicotine alone. In each case the minimum index was found after administration of the 0.3 mg/kg dose of nicotine.

In order to further characterize the interaction between nicotine and diazepam, observed values of the index of cur-

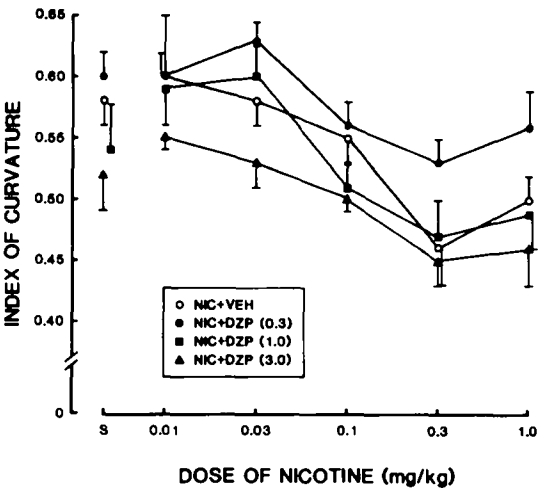

FIG. 2. The effects of graded doses of nicotine in combination with saline and 0.3, 1.0 and 3.0 mg/kg of diazepam on the index of curvature. A larger index value indicates greater acceleration in responding through the fixed-interval. S.E. bars are also shown.

TABLE 1

OBSERVED AND EXPECTED VALUES OF THE INDEX OF CURVATURE FOR EACH NICOTINE-DIAZEPAM DOSE COMBINATION

	Dose of Nicotine (mg/kg)				
	0.01	0.03	0.1	0.3	1.0
Diazepam (0.3)					
expected	0.59	0.57	0.54	0.46	0.50
observed	0.60	0.63	0.56	0.53	0.56
Diazepam (1.0)					
expected	0.53	0.52	0.49	0.47	—
observed	0.59	0.60	0.51	0.47	0.49
Diazepam (3.0)					
expected	0.57	0.50	0.48	0.47	—
observed	0.55	0.53	0.50	0.45	0.46

Expected values were not calculated where extrapolation was required.

vature were compared with those predicted from the effects of each drug alone. The two sets of values are shown in Table 1. With the 0.3 mg/kg dose of diazepam in combination with nicotine observed values were consistently higher than those expected. Similarly, when 1.0 mg/kg of diazepam was coadministered with either 0.01 or 0.03 mg/kg of nicotine, observed values were greater than those expected. Otherwise, there was good agreement between observed and expected values of the index of curvature.

The effects of the lowest dose of diazepam (0.3 mg/kg) were examined in more detail. Figure 3 shows the within-interval pattern of responding in one subject following saline, the four highest doses of nicotine and 0.3 mg/kg of diazepam with those four nicotine doses. It can be seen that the changes produced by nicotine alone depended on the dose: there was little effect following 0.03 mg/kg, some increase, particularly toward the end of the interval following 0.1 mg/kg, but more marked changes following administration of the two highest doses (0.3 and 1.0 mg/kg). The 0.3 mg/kg dose tended to increase rates in the early and middle parts of the interval, while the increase was proportionally smaller in the later part of the interval. The 1.0 mg/kg dose also increased rates in the early and middle parts, albeit to a lesser extent, but had little effect on the high rates at the end of the interval. Coadministration of diazepam consistently increased the high rates which occurred at the end of the interval. This occurred irrespective of the effects of nicotine on these rates. The effects on rates early in the interval were inconsistent: both increases and decreases were observed, but the changes were often of small magnitude. By itself, this dose of diazepam had little effect on rates in the later part of the interval (not shown). For example, response rate in the final tenth was increased by 9% in comparison to the saline rate.

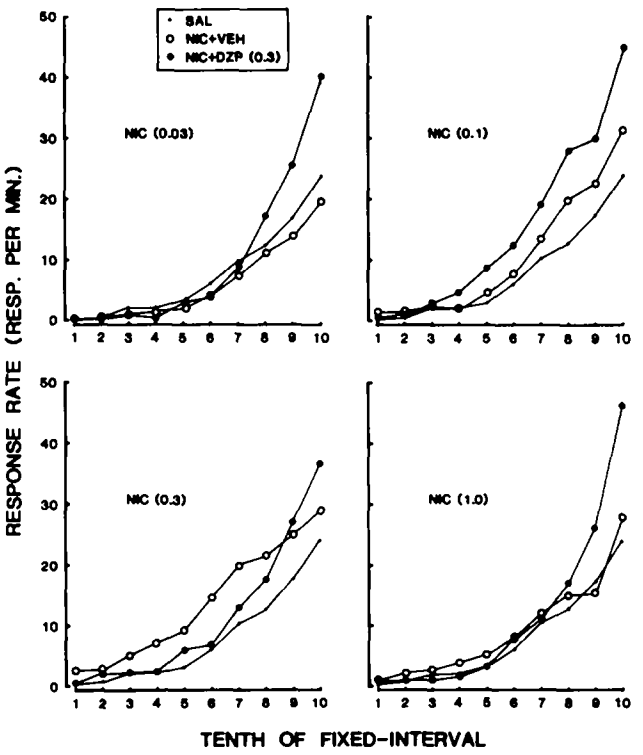

FIG. 3. The effects of the four highest doses of nicotine (0.03, 0.1, 0.3, and 1.0 mg/kg) with saline and 0.3 mg/kg of diazepam on the pattern of FI responding. The effects of saline alone are indicated on each graph. Each point represents the mean of two determinations in a single subject.

DISCUSSION

The effects of coadministering nicotine and diazepam clearly depend on the doses of the two drugs used. Particularly interesting results were obtained in the present study

with the lowest dose of diazepam (0.3 mg/kg). By itself, this dose of diazepam produced little change in overall rate, but it markedly increased response rates above those produced by nicotine alone. This effect was most pronounced when it was coadministered with 1.0 mg/kg of nicotine. More detailed analysis suggested that these changes occurred as a result of increases in rate at the end of the interval. Changes in the early and middle parts of the interval were inconsistent and often small. This may explain why the 0.3 mg/kg dose of diazepam tended to ameliorate the decrease in the index of curvature produced by nicotine alone. While nicotine increased the low rates in the early and middle parts of the interval, coadministration of diazepam increased the rates at the end.

Two aspects of the findings suggest that the interaction between nicotine and this dose of diazepam is not a simple, additive one. Firstly, diazepam alone had a smaller effect on the high rates at the end of the interval compared to the effect when nicotine was coadministered. Secondly, values of the index of curvature were larger than expected on the basis of the effects of the two drugs alone. It would be wrong to characterize this as a simple potentiating or blocking interaction. Rather, it seemed that diazepam allowed nicotine to produce high response rates at the end of the interval. It may have done so by blocking those effects of nicotine which limit its ability to increase response rate. This is further supported by the fact that the highest overall rate occurred when 0.3 mg/kg of diazepam was coadministered with 1.0 mg/kg of nicotine—a dose which, when administered alone, had smaller rate-increasing effects than the 0.3 mg/kg dose of nicotine.

In contrast, coadministration of the highest dose of diazepam (3.0 mg/kg) produced a dose-response curve flatter than that produced by nicotine alone. The lower rates produced by low nicotine doses were increased and the higher rates produced by the high nicotine doses were decreased. By itself, this dose of diazepam had a marked effect on the index of curvature. When combined with nicotine it reduced the index below that produced by nicotine alone. However, the values of the index were accurately predicted from the effects of nicotine and 3.0 mg/kg of diazepam alone. With respect to the pattern of responding, then, there seems to be a simple additive relationship between this dose of diazepam and the range of nicotine doses studied. These data also illustrate a point made in the earlier study (9): the nature of the interaction between any two drugs depends on the aspect of behavior under investigation. When combined with certain doses of nicotine, 3.0 mg/kg of diazepam diminished its rate-increasing effects, but accentuated its effects on the index of curvature.

It is interesting to compare the data here with those obtained in a study of amphetamine-diazepam interactions in cats (7). Like nicotine, amphetamine generally increased overall response rate (some decreases were seen with higher doses), but decreased the index of curvature. Very high overall rates were observed after amphetamine-diazepam combinations and diazepam reversed decreases in overall rate produced by the higher amphetamine doses. In some cases diazepam also reversed decreases in the index of curvature produced by amphetamine. The findings are very similar to those in the present study, suggesting that diazepam may modify the effects of a range of psychomotor stimulants in a similar manner.

This study has shown that the interaction between nicotine and diazepam is a complex one, determined by the doses of the drugs administered as well as the aspect of behavior under investigation. Further studies may be able to characterize this more precisely, particularly if a wider range of doses is used. Of particular interest is the observation that low diazepam doses appear to accentuate the rate-increasing effects of nicotine, especially those produced by high doses of nicotine.

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