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Behavioral Interactions Between Nicotine and Caffeine

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WHITE, J. M. *Behavioral interactions between nicotine and caffeine.* PHARMACOL BIOCHEM BEHAV **29**(1) 63–66, 1988.—Nicotine (0.01–1.0 mg/kg) was administered alone and together with three doses of caffeine (3.0, 10.0 and 30.0 mg/kg) to rats responding on a fixed-interval 2-min schedule of food reinforcement. The effects on overall response rate depended on dose: with the 3.0 mg/kg dose of caffeine response rate was increased by an amount approximately equal to the effect of the caffeine alone, while 10.0 mg/kg of caffeine reduced and 30.0 mg/kg completely abolished the increases in response rate produced by nicotine. The within-interval pattern of responding was affected in a similar, dose-related manner by both nicotine and caffeine alone. These effects added to produce large changes in the pattern when high doses of the two drugs were co-administered. The changes comprised increases in lower response rates in the early and middle parts of the interval and proportionally smaller increases or decreases in the higher rates occurring later in the interval. The interaction between nicotine and caffeine cannot be characterized simply, but depends on the particular aspect of behavior under examination.

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

NICOTINE is a widely used psychoactive compound. Smokers typically self-administer the drug a number of times each day, and the maintenance of smoking seems to depend critically on the nicotine in the tobacco [6,9]. This repeated use provides the opportunity for interactions between nicotine and other drugs taken. Such interactions may produce qualitatively or quantitatively unique effects. Unfortunately, there has been so little research on the effects of drug combinations in general, and combinations involving nicotine in particular, that we are unable to predict which drugs will interact with nicotine and what the outcome might be. The aim of the present study was to begin to characterize the effects of nicotine in combination with caffeine, another commonly used psychoactive compound.

Schedule-controlled behavior provides a sensitive baseline against which the behavioral effects of drugs can be measured. Using a variety of schedules nicotine and caffeine have been found to have qualitatively similar effects. For example, both nicotine [10] and caffeine [3] only decrease responding generated by FR (fixed-ratio) schedules, but, at intermediate doses, will increase FI (fixed-interval) response rates. These effects are shared with prototypical psychomotor stimulants, such as amphetamine [5]. In the present study rats were exposed to FI schedules of food presentation under control conditions and following administration of nicotine alone, caffeine alone and both nicotine and caffeine. Overall response rates were measured to determine if the effects of the combinations were additive or there was evidence of an interaction. Response rates within the interval were also measured to determine how the pattern of responding was affected. The effects of nicotine on the pattern of FI responding have been described in some detail [11].

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 25×25×25 cm 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) 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 consistent directional changed. 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.

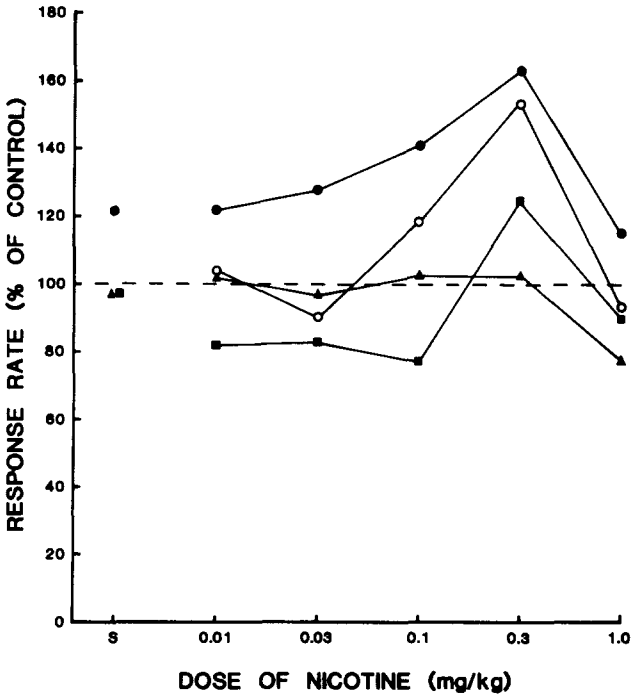

FIG. 1. The effects of saline plus graded doses of nicotine alone (○) and in combination with 3.0 mg/kg (●), 10.0 mg/kg (■) and 30.0 mg/kg (▲) of caffeine on overall rates of FI responding. Response rates were calculated as a percentage of saline control values. For the 4 subjects these were 23.6, 14.3, 11.3 and 17.3 responses per minute. Each point represents a mean based on two determinations in each of the four subjects.

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, alone and in combination with each of three caffeine doses (3.0, 10.0 and 30.0 mg/kg). 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 caffeine-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) and caffeine sodium benzoate (Sigma Chemical Co., St. Louis, MO) were dissolved in 0.9% saline. Both drugs were administered subcutaneously in a volume of 1.0 ml/kg b.wt. 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 [2] was calculated. This indicates the degree of acceleration in response rate through the fixed-interval—larger values indicate greater acceleration. For presentation of response patterns data were collapsed into fifths of the interval.

RESULTS

Average response rates following administration of nicotine alone, caffeine alone, and nicotine plus caffeine are shown in Fig. 1. Nicotine alone produced the characteristic increase in FI response rate, reaching a maximum of 150% of control following administration of 0.3 mg/kg. This increase was observed with all subjects. Caffeine alone produced much smaller, less consistent effects. There was little change from control levels following administration of 10.0 and 30.0 mg/kg and a small increase following 3.0 mg/kg. The latter result was not observed across all subjects.

When 3.0 mg/kg of caffeine was administered together with the graded doses of nicotine response rate was elevated above the rate produced by nicotine alone. This was consistent with the rate-increasing effects of this dose of caffeine. With 10.0 mg/kg of caffeine the general shape of the nicotine dose-response curve was preserved, but with a downward shift. Again, the maximum response rate was observed following administration of 0.3 mg/kg of nicotine, but it was much smaller, and was not common to all subjects. A dose of 30.0 mg/kg of caffeine completely altered the nicotine dose-response curve: there was little deviation from control values except for a slight decrease after 1.0 mg/kg of nicotine. The rate-increasing effects of nicotine were negated by this dose of caffeine. This effect was consistent across subjects.

The index of curvature was calculated for each subject and the means (±S.E.M.) are shown in Fig. 2. Caffeine had very little effect on the pattern of FI responding: the index varied from 0.57 to 0.62. When nicotine was administered alone there was little change at the lower doses, and a small decrease following administration of 0.3 and 1.0 mg/kg. When the lowest dose of caffeine (3.0 mg/kg) was combined with nicotine there was little change in index value across the

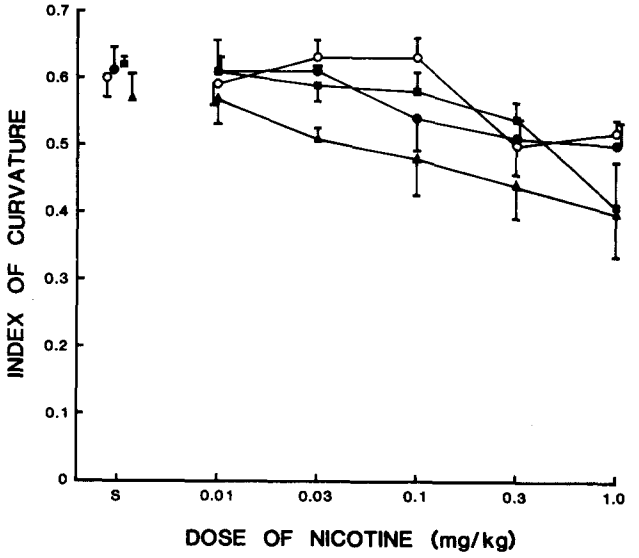

FIG. 2. The effects of saline plus graded doses of nicotine alone (○) and in combination with 3.0 mg/kg (●), 10.0 mg/kg (■) and 30.0 mg/kg (▲) of caffeine on the index of curvature. A larger index value indicates greater acceleration in responding through the fixed-interval.

nicotine dose range. Co-administration of 10.0 mg/kg of caffeine resulted in a decrease in the index when it was combined with 1.0 mg/kg of nicotine. The highest dose of caffeine (30.0 mg/kg) decreased the index across the whole nicotine dose range. At all but the 0.01 mg/kg dose of nicotine the magnitude of the decrease was slightly greater than the sum of the effects of nicotine and caffeine alone.

An example of the changes in the pattern of responding is shown in Fig. 3. The data are from a single subject and show the response rate in each fifth of the fixed interval following administration of saline and 0.3 mg/kg of nicotine alone and in combination with the three caffeine doses. Control performance shows the characteristic increase in response rate from a level close to zero in the beginning of the interval to a relatively high rate in the final part of the interval before reinforcement. Administration of 0.3 mg/kg of nicotine increased response rate throughout the interval with proportionally greater increases in the early part of the interval. The increase was of relatively small magnitude in this subject. When this dose of nicotine was co-administered with 3.0 mg/kg of caffeine there was a considerably larger increase throughout the interval. The effect of the caffeine was to increase response rate across the interval: approximately three-fold in the first three fifths and nearly two-fold in the last fifth. Response rates through the interval were also increased by administration of 10.0 mg/kg of caffeine, but to a lesser degree. Finally, the highest dose of caffeine (30.0 mg/kg) resulted in an overall response rate similar to that produced under control conditions. However, response rate in the early part of the interval was higher and in the latter part lower in comparison with response rate after saline or nicotine (0.3 mg/kg) alone.

DISCUSSION

Examination of changes in overall response rate showed that caffeine and nicotine interact in two different ways. Firstly, the lowest dose of caffeine caused the nicotine dose-response curve to shift upward by an amount approximately the same as the effect of caffeine alone. Higher doses of caffeine diminished or eliminated the rate-increasing effects of nicotine. Alone, these doses of caffeine had very little effect on overall response rate. Thus, it may be that doses of caffeine which increase response rate combine in an additive manner with nicotine, but higher doses which have little or no effect on overall response rate block the rate-increasing effects of nicotine.

Although overall response rate was at or near control level when nicotine was combined with the highest dose of caffeine, it cannot be concluded that there was no effect on FI responding. The measure of the amount of increase in response rate through the interval, the index of curvature, showed that the FI pattern was most affected when the highest dose of caffeine was administered. It is clear that doses of nicotine and caffeine which have little effect on overall rate can have a considerable effect on the temporal pattern of responding. While a high dose of caffeine may abolish the rate-increasing effect of nicotine, it may magnify the effects on response pattern.

A more detailed picture of the changes in the FI response pattern suggested that combinations of nicotine and caffeine may increase the low response rates which occur early in the interval. However, the higher response rates occurring later

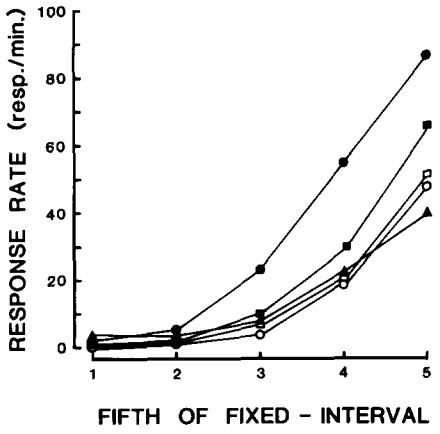

FIG. 3. The effects of saline (○) and 0.3 mg/kg of nicotine with saline (□), 3.0 mg/kg (●), 10.0 mg/kg (■) and 30.0 mg/kg (▲) of caffeine on the within-interval pattern of FI responding. Each interval was divided into five equal sections. Each point represents the mean of two determinations in a single subject.

in the interval were either increased to a lesser degree or decreased by the drug combination. This type of change has been referred to as rate-dependency [1] or rate constancy [4]. Both nicotine [10,11] and caffeine [8] have been shown to alter the pattern of FI responding in a similar manner when administered alone.

It is interesting to speculate whether the present results may help in the understanding of human patterns of caffeine and nicotine use. A recent review of a number of studies [7] reported a moderately strong positive relationship between coffee drinking and cigarette smoking. Although it is difficult to equate doses, the results here suggest that caffeine could be used to magnify some effects of nicotine. Such an interaction could be part of the pharmacological basis for the high incidence of caffeine and nicotine usage.

The results are important also because they clearly show that the nature of the interaction between two drugs depends on the particular aspect of the behavior under investigation. At certain caffeine and nicotine doses it can be shown that the addition of caffeine decreased the effects of nicotine on overall rate, but combined to produce a greater effect on the within-interval pattern of responding than either drug alone. Although the overall rate is clearly the sum of the within-interval rates, it cannot be said that one measure is primary or of more importance. Rather, an interaction can be characterized only with respect to a particular aspect of behavior.

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