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Caffeine Reduces Amphetamine-Induced Activity in Asymmetrical Interaction

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WHITE, B. C., K. L. HASWELL, C. D. KASSAB, D. HARKINS, JR. AND P. M. CRUMBIE. *Caffeine reduces amphetamine-induced activity in asymmetrical interaction.* PHARMACOL BIOCHEM BEHAV **20**(3) 387–389, 1984.— Caffeine-amphetamine interactions were studied to determine whether attenuation of amphetamine-induced activity by caffeine pretreatment (30 mg/kg) is the result of increased or decreased sensitivity to amphetamine. Caffeine pretreatment attenuated amphetamine activity in the rats without producing a horizontal shift in the dose-response curve. Results support a reduction in sensitivity to amphetamine. A cross-tolerance design revealed an asymmetrical interaction between caffeine and amphetamine. Multiple caffeine treatments (30 mg/kg) produced tolerance and attenuation of subsequent amphetamine activity (1.5 mg/kg). Amphetamine did not produce tolerance or affect subsequent caffeine-induced activity.

Amphetamine Caffeine Tolerance Drug interaction Locomotor activity Stimulants

CAFFEINE has been reported to augment the behavioral effects of several drugs that are known to have catecholaminergic actions [1, 4, 6]. We have found enhancement of hyperactivity occurs when caffeine is given within an hour before amphetamine. However, when given 12 hours before amphetamine, caffeine attenuates amphetamine-induced activity [7,8]. Our studies of amphetamine activity suggest that the enhancement from short interval caffeine pretreatments may be the additive effects of the two drugs working on separate neurochemical substrates.

Attenuation produced by long-interval caffeine pretreatment has not been reported as frequently as the enhancement, but deserves attention because of the implications for caffeine-drug interactions, intentional or otherwise. The present study expands our understanding of the attenuation phenomenon by focusing on several possible explanations including fatigue, compensatory changes in neural systems controlling arousal, and increases in sensitivity to amphetamine.

EXPERIMENT 1

Because Waldeck [6] has reported evidence that caffeine may sensitize dopamine receptors, the attenuation described above could be the result of increased sensitivity to amphetamine. This would give an otherwise moderate amphetamine dose the activity effects of a strong dose. High doses of amphetamine are well known to depress locomotor activity and produce behavioral stereotypy. To determine whether caffeine-induced attenuation of amphetamine activity is due to enhanced sensitivity to amphetamine, we tested the effects of caffeine pretreatment on a range of amphetamine doses. A shift in the amphetamine dose-response curve to the left following caffeine pretreatment would suggest sensitization of the animals to amphetamine. A shift to the right or an overall flattening of the curve would indicate a reduction in sensitivity.

Method

One-hundred twenty adult male hooded rats were habituated for one week to rectangular stabilimeter cages and randomly assigned to one of ten groups. A caffeine (30 mg/kg, IP) and a sodium benzoate (30 mg/kg IP) pretreatment group was assigned to each of the five amphetamine doses (0, 0.3, 1.0, 3.0, and 6.0 mg/kg, IP, in normal saline). The volume of all injections was one ml per kg. A series of six caffeine or sodium benzoate injections were given at twelve hour intervals to the appropriate groups. Twelve hours after the last injection of the series each group received the appropriate amphetamine dose. Activity was recorded for three hours in stabilimeter cages that rocked on a central fulcrum, activating counting circuitry.

Results

Caffeine pretreatment produced a general flattening of the dose-response curve without evidence of a shift of the peak dose in either direction (see Table 1; $\chi^2(4)=1.37$, $p>0.20$). Amphetamine doses of 0.3 and 1.0 mg/kg produced significantly less activity when preceded by caffeine ($p<0.05$, Wilcoxon Sum Rank Test. Significant violation of homogeneity of variance precluded parametric analysis.) These results indicate that 12 hour caffeine pretreatment reduces the rat's responsiveness to amphetamine rather than increasing it.

EXPERIMENT 2

Caffeine's attentuation of amphetamine-induced activity is better understood by examining whether these two drugs have similar effects on each other. If the attenuation

TABLE 1

MEDIAN AMPHETAMINE-INDUCED ACTIVITY COUNTS FOR RATS PRETREATED WITH CAFFEINE OR SODIUM BENZOATE

	Amphetamine Dose				
Pretreatment	0	0.3	1.0	3.0	6.0
Caffeine	22	28	109	206	70
Sodium Benzoate	31	61	213	242	116
Comparisons	NS	0.05	0.05	NS	NS

produced by caffeine is a result of fatigue or a general compensatory shift in the balance of excitatory and inhibitory neural systems controlling activity, then each drug would be expected to attenuate the other and subsequent treatments of the same drug. To test for these possibilities caffeine and amphetamine were used in a cross-tolerance design.

Method

Fifty-two adult male hooded rats were habituated for one week to stabilimeter activity cages and randomly assigned to four groups. One group was then given a series of ten caffeine injections (30 mg/kg, IP) at 12 hour intervals followed by a series of ten amphetamine injections (1.5 mg/kg, IP). The second group received the amphetamine series first and then the caffeine. The third and fourth groups were given ten sodium benzoate injections for the first 5 days and then caffeine or amphetamine, respectively, for 5 days. Activity was recorded over the 11 hour interval between injections. The longer interval was used in this experiment to determine whether the attenuation of amphetamine activity is associated with a delayed increase in activity that may have been missed by the 3 hour recordings used in previous experiments. Injections occurred during the first and thirteenth hours of the 16 hour light phase of the daily cycle.

Results

The top panel of Fig. 1 illustrates the initial effect of caffeine on locomotor activity in which there is a dramatic decline in activity over the first three injections. Even-numbered recording periods include the normally high activity levels of the dark phase of the daily cycle as seen in the sodium benzoate treated rats. Analysis of the effects of caffeine and sodium benzoate given during the inactive period (odd-numbered injections) revealed a significant caffeine effect, $F(1,24)=55.28$, $p<0.01$, and caffeine × injections interaction, $F(1,24)=5.01$, $p<0.05$. In the bottom panel, a similar analysis indicated a significant amphetamine effect, $F(1,24)=106.84$, $p<0.01$, but no interaction.

The right-hand portion of the top panel illustrates the effect of caffeine pretreatments on amphetamine-induced locomotor activity as supported by a significant pretreatment × injections interaction, $F(9,216)=1.94$, $p<0.05$. Caffeine pretreated animals were significantly less active ($p<0.05$) than those pretreated with sodium benzoate after the first and second amphetamine injections, $F(1,24)=5.27$ and 6.67, respectively. In contrast the bottom panel shows the absence of any effect of amphetamine pretreatments ($F's<1$) on caffeine-induced activity.

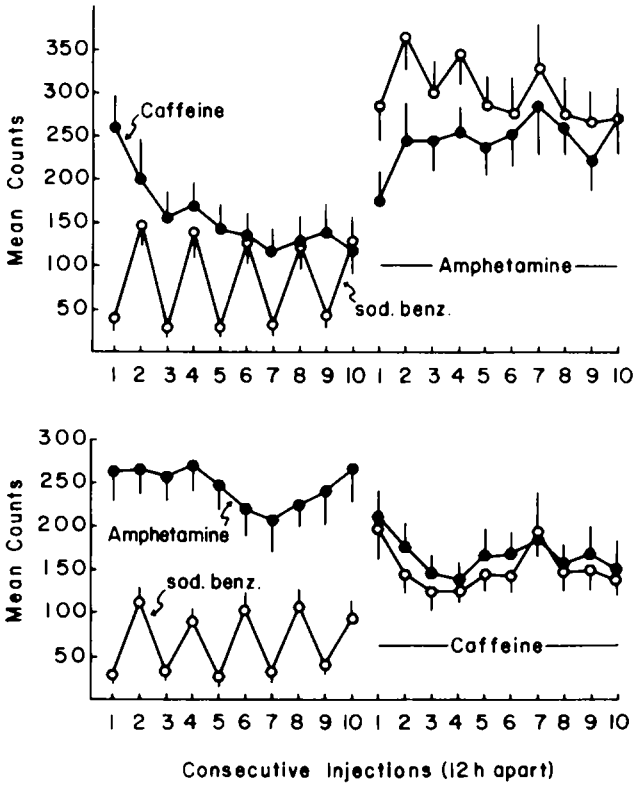

FIG. 1. Mean activity counts are illustrated as a function of consecutive injections. Top panel. The first ten injections represent the tolerance phase for caffeine and sodium benzoate groups. The second series of 10 injections refers to the cross-over phase during which both groups received amphetamine. Bottom panel. The initial ten injections of the amphetamine and sodium benzoate control groups are shown in the left half of the panel followed by the cross-over phase in which both groups received caffeine. Vertical bars represent standard error of the mean.

GENERAL DISCUSSION

The results of Experiment 1 indicate that the attenuation of amphetamine activity by caffeine pretreatment is due to a reduction in sensitivity to amphetamine rather than an increase. This is supported by the fact that attenuation occurred across the range of effective doses of amphetamine without evidence of a horizontal shift in the dose-response curve.

The reduction in responsiveness to amphetamine may be the result of fatigue or a general compensatory shift in the balance of excitatory and inhibitory influences on locomotion, produced by multiple caffeine treatments. However, the absence of any noticeable effect of amphetamine pretreatment on caffeine-induced activity argues against these explanations. Accordingly, amphetamine which produces activity levels at least as high as those of caffeine should induce as much fatigue and/or compensation in neural systems as caffeine. The asymmetry of the caffeine-amphetamine interaction suggests some dissimilarities in the mechanism by which these drugs act to produce hyperactivity.

The 30 mg/kg caffeine dose was used in this study because it produces near maximum hyperactivity under our testing conditions. However, the minimum caffeine dose for produc-

ing toxicity in the rat has been reported [3] to be between 25 and 50 mg/kg. It may be that some persistent toxic effect of caffeine limits the activity response of the animals to subsequent amphetamine or caffeine injections. Other studies from our lab have found reduced body weight gain [8] and conditioned taste aversions to the 30 mg/kg dose [9], suggesting some degree of toxicity. The problem with the toxicity explanation of the caffeine induced attenuation of activity is that increasing the dose to 60 mg/kg does not increase the attenuation [8]. On the other hand, the reduction in body weight gain and taste aversions are much stronger at doses greater than 30 mg. If some general malaise were responsible for the activity effects then higher doses would be expected to produce greater malaise and, hence, larger attenuation as with taste aversions and body weight gain.

Behavioral tolerance to the activity effects of caffeine was apparent in Experiment 2. We have found this rapid developing tolerance in other caffeine studies [8]. The lack of tolerance to the activity effects of amphetamine indicates a further distinction between these stimulants. It is tempting to suggest that the underlying process by which tolerance develops to caffeine is related to the attenuation of amphetamine. However, other work from this laboratory [8] has indicated that there is incomplete correspondence between the caffeine doses that induce tolerance and those producing attenuation of amphetamine activity.

The results of Experiment 2 revealed virtually complete tolerance to the activity effects of caffeine given during the normally active, dark phase of the daily cycle. In contrast the activity during the light phase remained high after 4 days of treatment. This pattern of caffeine tolerance is consistent with reports of human research in which caffeine has been found to alter sleep patterns more consistently than performance during wakefulness [2]. This may mean that caffeine's influence on locomotion is less direct than that of amphetamine, since the latter drug remained potent during light and dark periods even after several days of treatment. An indirect mechanism for caffeine-induced hyperactivity has been suggested by Snyder [5]. Accordingly, caffeine blocks adenosine receptors which mediate inhibition of locomotion.

As described above, caffeine pretreatment has been found to potentiate the effects of a variety of drugs used in the treatment and study of parkinsonism. As yet, we have tested only amphetamine-induced activity for attenuation by caffeine pretreatment. However, clinically this may mean that habitual or prescribed use of caffeine may enhance or attenuate the response to some catecholaminergic drugs, depending on the time of the caffeine consumption.

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