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Caffeine Potentiation of Apomorphine Discrimination

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SCHECHTER, M. D. *Caffeine potentiation of apomorphine discrimination.* PHARMAC. BIOCHEM. BEHAV. 13(2) 307–309, 1980.—Rats were trained to discriminate between the stimulus properties of intraperitoneal 0.16 mg/kg apomorphine and saline in a two-lever, food-motivated operant task. Apomorphine, at doses different than the training dose, produced a dose-response relationship, whereas, caffeine (7.5–30 mg/kg) produced saline-like responding. However, co-administered of 15 mg/kg caffeine with 0.01, 0.02 or 0.04 mg/kg apomorphine potentiated the discriminative stimulus properties of these low apomorphine doses. This potentiation was antagonized by pretreatment with 0.25 mg/kg haloperidol. The results are consistent with the idea that caffeine, by virtue of being a phosphodiesterase inhibitor, may increase post-synaptic cyclic-AMP and this, in turn, may supersensitize the dopamine receptors and result in the potentiation of the apomorphine-induced dopaminergic responses.

Apomorphine Caffeine Cyclic-AMP Dopamine Haloperidol

THE ability of dopamine to stimulate adenosine cyclic 3′,5′-monophosphate (C-AMP) in homogenates of neostriatal tissue, the brain area richest in receptors for dopamine, was first described by Kebabian *et al.* [5,6], and this work furnished evidence for the concept of an intimate coupling between neostriatal dopamine receptors and an adenylate cyclase enzyme. The discovery of dopamine-sensitive adenylate cyclase activity in the substantia nigra with properties identical to the striatal enzyme [3,7] has provided further evidence for the synaptic location of the receptors. Low doses (0.5–1.0 mg/kg) of *d*-amphetamine administered intraperitoneally to rats reproducibly increased the C-AMP content of the striatum and simultaneously increased dopamine turnover [1]. Since neither *d*-amphetamine nor its metabolites inhibit cyclic nucleotide phosphodiesterase, it is probable that the drug increases C-AMP content through its action in releasing dopamine. Indeed, low doses of the direct dopamine agonist apomorphine was observed to, likewise, increase striatal C-AMP [4].

Both *d*-amphetamine and apomorphine have been reported to elicit locomotor activity and stereotyped behavior in rats and these dopaminergically-mediated behaviors have been correlated with the ability of *d*-amphetamine to elevate brain C-AMP [8]. Another behavioral technique which has been observed to be mediated by dopaminergic systems in the rat brain is the control of discriminative stimulus performance produced by *d*-amphetamine and apomorphine [2,11]. In a previous study [10], the author reported that caffeine, a phosphodiesterase inhibitor that has been shown to potentiate the C-AMP response to suboptimal concentrations of dopaminergic agonists [9], potentiated a single low doses of *d*-amphetamine in the drug discrimination paradigm and this potentiation was antagonized by haloperidol. The present study sought to investigate the effect of caffeine on a range of doses of the direct dopamine agonist apomorphine in an effort to evidence the interaction of phosphodiesterase inhibition upon this dopaminergically-mediated behavior.

METHOD

The procedure used in the present experiments has been extensively described elsewhere [2]. Briefly, materials consisted of standard animal test cages (LVB Corporation), fitted with 2 levers, a food cup and a house light and programmed by solid-state logic modules. Eight food-deprived rats were trained to lever press (FR 10) for food (45 mg Noyes food pellets) on either of the 2 levers. Thirty minutes following the intraperitoneal (IP) injection of apomorphine (0.16 mg/kg, as base), the rats were required to press one of the levers (drug lever; DL) in order to receive reinforcement; 30 min after IP administration of an equal volume of saline (0.9% sodium chloride) they were required to press the opposite lever (saline lever, SL). Every week, each rat was run in daily 15 min sessions on 5 consecutive days. Both injection treatments were given accordingly to 2 weekly alternating sequences, i.e., D-S-S-D-D and S-D-D-S-S. The number of responses made on either of both levers before obtaining the first food pellet (and, thus, before having made 10 correct responses) was recorded after each session and the lever pressed 10 times first was designated as the selected lever. The training criterion consisted of 10 consecutive sessions in which the appropriate lever was selected according to the drug state imposed. Following training, test sessions were held on Tuesdays and Thursdays; on the 3 remaining days of the week, the training was continued to insure reliable performance. In those cases where rats did not maintain criterion performance, the data on their discriminative performance during that week of testing were not included in the results. On test days, the rats were treated with either a dose of apomorphine different than the training dose (0.16 mg/kg)

or with 15 mg/kg caffeine 5 min before the lower apomorphine dose and, 30 min after the last injection, were introduced into the test cage. Caffeine, at doses of 7.5, 15 and 30 mg/kg, was tested to establish if it, by itself, produces apomorphine-appropriate lever selection. In addition, 0.25 mg/kg haloperidol, a post-synaptic dopamine blocking agent [2], was administered 30 min before 15 mg/kg caffeine and 0.04 mg/kg apomorphine. Injection of these latter drugs was done in separate syringes 30 min prior to testing. The rats then were to select 1 of the 2 levers, i.e., the lever on which the rat first responded 10 times was considered the selected lever and the rat was immediately removed. All test treatments were given to each of the 8 trained rats on 2 occasions in a random order. Apomorphine was made fresh daily and all injections were IP at a constant volume of 1 ml/kg body weight.

RESULTS

The 8 rats required a mean of 22 sessions with each of 0.16 mg/kg apomorphine and saline to attain criterion performance. After training, apomorphine produced 98.3% of selected lever responses on the DL, whereas, saline produced 4.7% of first 10 responses on the DL (95.3% on SL). Testing of doses of apomorphine other than the training dose of 0.16 mg/kg produced a dose-responsive effect with 0.32 mg/kg producing 100% DL selection and 0.01 mg/kg producing 41.6% DL selection (Fig. 1).

Caffeine administered alone produced saline-appropriate responding with 7.5 mg/kg producing 16.7% DL responding and the highest dose (30 mg/kg) producing 33.3% DL responding. The 15 mg/kg dose of caffeine administered alone produced 29.2% DL responding, whereas, co-administration of this dose of caffeine increased the DL selection with 0.01, 0.02 or 0.04 mg/kg apomorphine. Indeed, the caffeine-0.04 mg/kg apomorphine combination produced 100% DL selection, whereas, 0.04 mg/kg apomorphine alone produced 68.8% DL selection (Fig. 1). Haloperidol (0.25 mg/kg) pretreatment prior to 15 mg/kg caffeine and 0.04 mg/kg apomorphine resulted in 25% DL responding.

DISCUSSION

Apomorphine-induced stimulus control of discriminative behavior appears to be a sensitive test for dopaminergic mechanisms in the rat brain [2]. In the present study, the administration of 7.5–30.0 mg/kg caffeine or 0.01–0.04 mg/kg apomorphine produced low levels of apomorphine-appropriate discriminative responding when compared to those produced by the training dose of 0.16 mg/kg apomorphine. However, co-administration of 15 mg/kg caffeine with these low doses of apomorphine was observed to potentiate

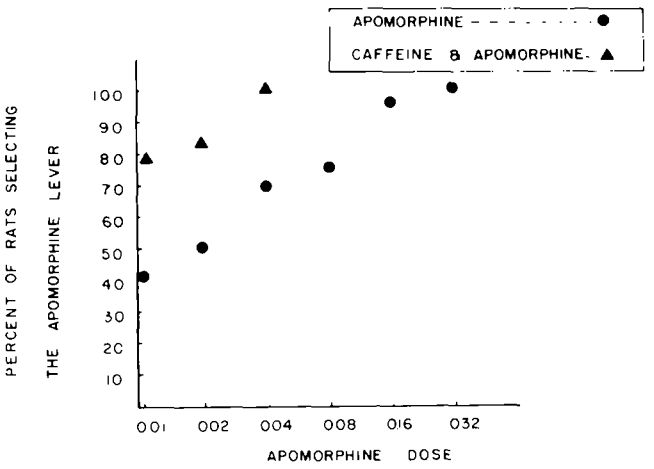

FIG. 1. Effect of caffeine (15 mg/kg) upon apomorphine discrimination. Ordinate: Percent of rats (n = 8) selecting (responding 10 times first upon) apomorphine lever. Abscissa: Apomorphine dose (circles) administered IP to each rat in 2 sessions; co-administration of 15 mg/kg caffeine and apomorphine (triangles) to each rat in 2 sessions.

the effect of apomorphine. For example, caffeine and 0.04 mg/kg apomorphine produced the same percentage DL selection (100%) as did 0.32 mg/kg apomorphine administered alone. This apparent potentiation was blocked by pretreatment with 0.25 mg/kg haloperidol suggesting a dopamine post-synaptic site of action.

An explanation for this potentiation may be found in the *in vitro* work of Kebabian *et al.* [6] in which caffeine, a potent inhibitor of phosphodiesterase that cleaves C-AMP, increased the level of adenylate cyclase. It has been suggested that adenylate cyclase may be the receptor for dopamine in mammalian brain, and, thus, caffeine may be supersensitizing these receptors to the effects of low apomorphine doses. A previous report [10] indicated that caffeine produced a similar potentiation of a single low dose of *d*-amphetamine. The present study indicates that caffeine is capable of potentiating the discriminative cueing properties produced by a range of doses of the direct dopamine agonist apomorphine.

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