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Locomotor activity stimulation in rats produced by dopamine in the nucleus accumbens: potentiation by caffeine

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The increased motor activity of reserpine-nialamide pretreated rats given dopamine into the nucleus accumbens was potentiated in a dose-dependent manner by systemically administered caffeine. Similarly, the increase in motor activity seen when the endogenous dopamine was released by intraperitoneally administered amphetamine was potentiated by systemically given caffeine. These effects might be due to an increase in the dopamine-induced accumulation of cyclic AMP in the nucleus accumbens after inhibition of the phosphodiesterase by caffeine.

Caffeine by itself is able to produce locomotor stimulation in rats (Thithapandha, Maling & Gillette, 1972) and mice (Boissier & Simon, 1965; Herz, Neteler & Teschemacher, 1968). The dose-range appears to be critical, with doses above about 25 mg kg^{-1} producing either less stimulation of, or no change in, locomotor activity. There are, moreover, a number of reports of an interaction between caffeine and other cns stimulants. Thus Strömberg & Waldeck (1973) showed that caffeine potentiated the stimulant effect of L-dopa in mice, while Waldeck (1973) found that caffeine potentiated the piribedil + clonidine reversal of reserpine-induced suppression of locomotor activity. These authors suggested that a sensitization by caffeine of central catecholamine receptors was probably responsible for the observed effect. In agreement with these findings, Fuxe & Ungerstedt (1974) found that caffeine was able to potentiate markedly the rotation produced by L-dopa, apomorphine and piribedil in rats with unilaterally 6-hydroxydopamine lesioned nigrostriatal pathways.

Recently, dopamine has been shown to produce a dose-dependent rise in coordinated locomotor activity after bilateral administration to the nucleus accumbens of reserpine-nialamide pretreated rats (Jackson, 1975; Jackson, Andén & Dahlström, 1975). This increased locomotor activity was found to be a result solely of dopamine receptor stimulation, and the functional changes observed were free of the more usual stereotypies associated with neostriatal application of dopamine (see *e.g.* Randrup & Munkvad, 1970). Because of the possible importance of the nucleus accumbens in stimulant-induced locomotor activity (Pijnenburg & van Rossum, 1973; Jackson & others, 1975), and because of the various reports showing that caffeine potentiates stimulant-induced locomotor activity (see above references), we have investigated the interaction between systemically administered caffeine and dopamine applied bilaterally to the nucleus accumbens. In addition, because we have previously shown (Jackson & others, 1975) that the locomotor stimulant effect of (+)-amphetamine may depend on the release of endogenous dopamine from the nucleus accumbens, we hypothesized that systemically administered caffeine and systemically administered (+)-amphetamine should interact in a similar manner.

MATERIAL AND METHODS

In the first series of experiments, guide cannulae were implanted bilaterally in anaesthetized (pentobarbitone sodium, approximately 40 mg kg^{-1}, i.p.) male Sprague-Dawley rats (Anticimex, Stockholm), 170–210 g, as previously described (Jackson & others, 1975). Dopamine hydrochloride, dissolved in 0·9% NaCl was applied in 1 μl containing 5 μg dopamine to each nucleus accumbens in all cases. Coordinates: A 9·4, L 1·1, dorsoventral −0·8 (König & Klippel, 1963). At least 2 days were allowed to elapse after surgery before the animals were used. Caffeine base (Merck) (15 or 60 mg kg^{-1}, i.p.) dissolved in saline, or saline as a control, was sometimes administered to animals which had had no prior surgical intervention. These two doses were chosen since caffeine by itself has been found to produce a greater stimulation of the locomotor activity at doses below than above 25 mg kg^{-1} (see introduction). Caffeine was also sometimes administered intraperitoneally at the same time as dopamine was applied to the nucleus accumbens. All animals in the first experiment were pretreated with reserpine (Serpasil, Ciba-Geigy through AB Hässle*, 10 mg kg^{-1}, i.p., 6 h premedication), and nialamide hydrochloride (Pfizer*) (110 mg kg^{-1}, i.p., 1 h premedication). After administration of dopamine and/or caffeine, individual rats were immediately placed in a plexiglass box (see Jackson & others, 1975), and locomotor activity measured every 10 min for up to 5 h using two paired Animex activity meters (Svensson & Thieme, 1969). Total activity was calculated per h.

In a second series of experiments, naive rats were administered caffeine (15 or 60 mg kg^{-1}, i.p.) (+)-amphetamine sulphate (Smith, Kline & French) (1 mg kg^{-1}, i.p.) or saline, or with various combinations of these drugs, and their locomotor activity recorded immediately after injection for 5 half hour intervals in "MOTRON" activity cages previously described in detail by Strömberg & Waldeck (1973). All cannulae placements were checked histologically using the atlas of König & Klippel (1963).

RESULTS

In the first series of experiments (Fig. 1), caffeine by itself was essentially inactive, although slight stimulation was seen with the dose of 15 mg kg^{-1}. Dopamine, 5 μg to each side of the nucleus accumbens, produced an almost immediate and sustained rise in coordinated locomotor activity, devoid of stereotypies such as gnawing, chewing and head nodding, but sometimes accompanied by intermittent sniffing (Fig. 1). When caffeine (15 mg kg^{-1}, i.p.) was administered at the same time as the dopamine, an increased response to dopamine was observed which lasted for the whole 5 h observation period. When activity was accumulated over five 1 h periods, potentiation was evident at all time intervals, but was statistically significant only during the 1st and 2nd h periods. When caffeine, 60 mg kg^{-1} (i.p.), was administered simultaneously with dopamine, the potentiation observed was much greater than that seen after the 15 mg kg^{-1} dose. Moreover, visual observation in preliminary experiments showed most animals to be distinctly fatigued after about 150 min. Thus the animals, while maintaining a high level of locomotor activity, were less alert in appearance and slightly less coordinated, with their trunks closer to the floor of the cage, than in the initial stages of activity. In the data reported here, caffeine, 60 mg kg^{-1}, is shown to increase markedly the response to dopamine in the 1st and 2nd h periods. At the conclusion of the 2 h reading, these animals received haloperidol (Leo*), 2 mg kg^{-1} (i.p.) and were then returned to the activity meter for a further hour. Haloperidol, within 10 min,

almost completely blocked the locomotor stimulation observed after combined caffeine and dopamine treatment. (Activity ± s.e.m. during 1st 10 min after haloperidol, was 421 ± 192; the 2nd 10 min interval 43 ± 41; and the 3rd 10 min interval 5 ± 4. In

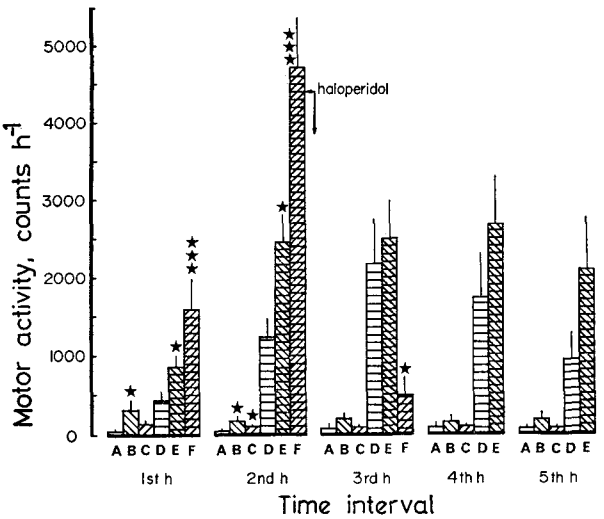

FIG. 1. The motor activity of reserpine-nialamide pretreated rats given caffeine i.p. and/or dopamine bilaterally into the nucleus accumbens. The activity of each rat was measured individually and the activity h^{-1} for 5 h was recorded. The values represent means + s.e. with the number of experiments shown in parentheses. The animals receiving caffeine, 60 mg kg^{-1}, plus dopamine, were given haloperidol, 2 mg kg^{-1}, i.p., 2 h after the beginning of the experiment, and the motor activity recorded for a further hour. The differences between the experimental groups and the saline or dopamine groups were calculated by Student's *t*-test (***$P<0{\cdot}001$, *$P<0{\cdot}05$).
A, saline (n=6). B, caffeine 15 mg kg^{-1} (n=5). C, caffeine 60 mg kg^{-1} (n=5). D, dopamine 5 μg each side (n=12). E, dopamine 5 μg + caffeine 15 mg kg^{-1} (n=12). F, dopamine 5 μg + caffeine 60 mg kg^{-1} (n=5).

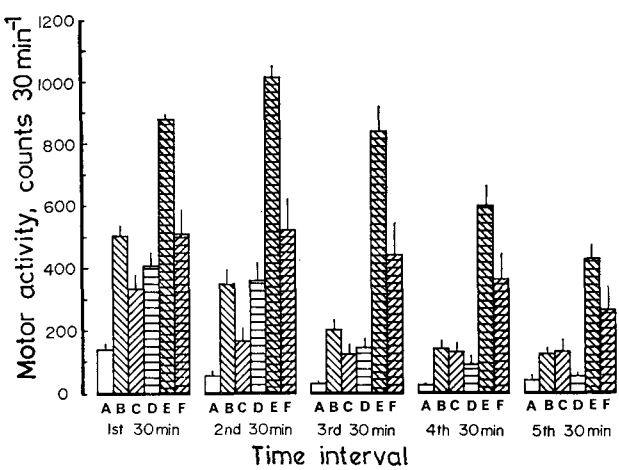

FIG. 2. The motor activity of rats treated i.p. with (+)-amphetamine and/or caffeine. The activity was measured for 150 min immediately after the administration of the drugs and the data are expressed as the total counts per 30 min. The values represent means + s.e. with the number of experiments shown in parentheses.
A, saline (n=5). B, caffeine 15 mg kg^{-1} (n=4). C, caffeine 60 mg kg^{-1} (n=5). D, (+)-amphetamine 1 mg kg^{-1} (n=6). E, caffeine 15 mg kg^{-1} + (+)-amphetamine 1 mg kg^{-1} (n=6). F, caffeine 60 mg kg^{-1} + (+)-amphetamine 1 mg kg^{-1} (n=6).

comparison, the last two 10 min readings before haloperidol were 807 ± 81 and 852 ± 85, respectively.)

In the second series of experiments, both (+)-amphetamine and caffeine produced significant increases in locomotor activity (Fig. 2) with caffeine 15 mg kg^{-1} being approximately equipotent to (+)-amphetamine 1 mg kg^{-1}. Caffeine, 60 mg kg^{-1}, was less effective than 15 mg kg^{-1}. However, when the low dose of caffeine was combined with (+)-amphetamine, an augmented locomotor response was observed which appeared to be more than an additive effect, and this is clearly seen in the last two 30 min readings where caffeine and (+)-amphetamine by themselves are only slightly active, but the combination very active. The type of interaction present between the high dose of caffeine and (+)-amphetamine is more difficult to interpret but is at least additive in nature in the last four 30 min measurements.

DISCUSSION

The data reported here confirm previous findings that caffeine is able to increase the functional response of central catecholamine receptor stimulation (Waldeck, 1973) and in particular, we have shown that the functional response to locally applied dopamine, a putative neurotransmitter in the nucleus accumbens with a clearly defined functional effect (Pijnenburg & van Rossum, 1973; Jackson & others, 1975), is markedly potentiated by simultaneous systemic administration of caffeine. Moreover, caffeine, which has not been reported to have any direct receptor stimulating properties, only changed the response quantitatively, not qualitatively. The potentiation was greater after 60 than 15 mg kg^{-1}, in contrast to the effects of these caffeine doses by themselves on the locomotor activity (see introduction), indicating a rather complex mode of action of caffeine in the intact brain. The response to the combined pretreatment was completely inhibited by the dopamine receptor blocking agent, haloperidol (Andén, Dahlström & others, 1966), confirming the specificity of the dopamine-induced functional change in the nucleus accumbens (Jackson, 1974). In addition, the interaction between (+)-amphetamine and caffeine, both administered intraperitoneally, agrees with, and indirectly confirms, these findings, as (+)-amphetamine has been shown to cause an increase in locomotor activity in rats by releasing endogenous stores of dopamine from the nucleus accumbens (Jackson & others, 1975).

The mechanisms of action behind the potentiation is at present unknown, although the recent hypothesis of Kebabian, Petzold & Greengard (1972) that adenylate cyclase may be a component of the dopamine receptor, has led several authors (Waldeck, 1973; Fuxe & Ungerstedt, 1974) to suggest that caffeine is acting as a phosphodiesterase inhibitor, leading to an increase in cyclic AMP, with consequently increased receptor sensitivity. Although the nucleus accumbens has not been examined specifically for phosphodiesterase activity (as far as the present authors are aware), a dopamine (and apomorphine) sensitive adenylate cyclase has been demonstrated in the nucleus accumbens (Horn, Cuello & Miller, 1974). At present, an interaction of caffeine with phosphodiesterase would appear to be the most probable explanation for the present results. The data here do not permit us to determine whether caffeine in this model is acting at the level of the nucleus accumbens or at some other central site.

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