Both morphine (Way & Adler, 1960; Boerner & others, 1975) and apomorphine (Kaul, Brochmann-Hanssen & Way, 1961) are metabolized mainly by glucuronidation so that competition for glucuronidating enzymes could account for the increase in half-life of apomorphine in brain.

The duration of ASB parallels brain concentrations of apomorphine (Symes & others, 1975). Thus the behavioural manifestations following morphine-apomorphine interactions at any one time presumably will depend on the degree of morphine blockade of dopamine receptors, the degree of morphine inhibition of apomorphine metabolism and the net concentration of apomorphine in brain. This would explain the findings of antagonism and potentiation of apomorphine effects reported in the literature following morphine pretreatment.

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Effect of ergotamine and dihydroergotamine on dopamine-stimulated adenylate cyclase in rat caudate nucleus

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The mode, or, better, the modes of action of ergot alkaloids are not yet completely understood. They are probably different according to the specific ergot derivative, the pharmacological effect considered and the tissue studied.

Recently, some representatives of this class of drugs were found to activate central dopamine receptors *in vivo* and have been proposed as antiparkinsonian drugs (Calne, Leigh & others, 1974; Teychenne, Leigh & others, 1975).

Some ergot alkaloids like ergocornine, CB 154 (2-bromo-α-ergocryptine), ergotamine and dihydroergotamine are able to induce circling behaviour in rats unilaterally injected in the nigrostriatal bundle with 6-hydroxydopamine (Corrodi, Fuxe & others, 1973; Fuxe, Agnati & others, 1975). Also LSD, which is a synthetic ergot derivative, has been proved to be active in this experimental model (Pieri & Pieri, 1974). Spano, Kumakura & others (1975) recently demonstrated that in homogenates of rat striatum LSD may stimulate the activity of dopamine-sensitive adenylate cyclase, the enzyme related with the dopamine receptor. The same authors observed that LSD, in addition to being an agonist, may reduce the stimulation of the enzyme activity elicited by dopamine, thus behaving as a mixed dopamine agonist-antagonist. Trabucchi, Spano & others (1976) demonstrated that bromocriptine is a non-competitive inhibitor of dopamine-stimulated adenylate cyclase in rat striatal homogenates. In contrast, bromocriptine stimulates *in vivo* the

* Correspondence.

formation of cAMP in various dopaminergic areas. Recently Struyker Boudier, Teppema & others (1975) demonstrated in electrophysiological experiments on the suboesophageal ganglia of *Helix aspersa* the existence of two types of dopamine receptors. These authors observed an antagonistic action of ergot alkaloids, like ergometrine, on those dopamine receptors which mediate neuronal inhibition. We have therefore investigated the action of ergotamine and its derivative dihydroergotamine on dopamine stimulated adenylate cyclase of rat striatum.

Sprague-Dawley rats (125–150 g) were decapitated and the brain quickly removed and the striata dissected. Tissue samples were gently homogenized at 4° in 25 volumes of 0·8 M tris-maleate buffer pH 7·5. Adenylate cyclase activity was measured as described by Carenzi, Gillin & others (1975) using [8-^{14}C]adenosine triphosphate (ATP) as substrate. The final incubation mixture of 500 μl contained 0·8 M tris-maleate buffer pH 7·5, 0·5 mM EGTA, 2 mM $MgSO_4$, 10 mM theophylline, 1 mM ^{14}C-ATP (0·98 mCi mM^{-1}) and about 150 μg of tissue protein.

After incubation for 4 min at 30° the reaction was stopped by heating the tubes in boiling water for 3 min. Radioactive [^{14}C]cyclic 3′,5′-adenosinemonophosphate (cAMP) was separated from radioactive ATP using aluminum and Dowex columns as described by Guidotti & Costa (1974).

Protein was measured according to Lowry, Rosebrough & others (1951). [^{14}C]ATP was obtained from the Radiochemical Centre, Amersham. Ergotamine and dihydroergotamine were a gift from Sandoz S.p.A. (Milan).

The *in vitro* addition of various concentrations of ergotamine or dihydroergotamine to rat striatal homogenates does not change the basal adenylate cyclase activity. On the contrary, both ergotamine and dihydroergotamine reduce in a dose related fashion the dopamine activation of striatal adenylate cyclase. As shown in Fig. 1 the blocking activity of ergotamine seems to be greater than that of dihydroergotamine.

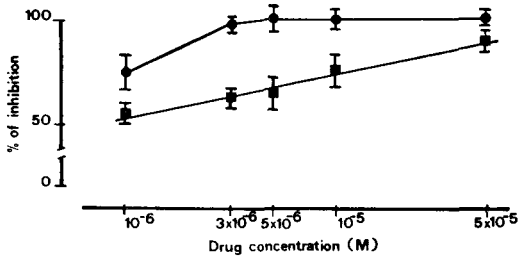

FIG. 1. Effect of various concentrations (M) of ergotamine and dihydroergotamine on dopamine (5×10^{-6}M) stimulation of rat striatal adenylate cyclase. In absence of dopamine or drugs 237 ± 16 pmol (mean ± s.e.m.) of cAMP was formed mg^{-1} protein min^{-1}.

Each point represents the mean ± s.e.m. of at least 10 determinations. ●—● Ergotamine, ■—■ dihydroergotamine.

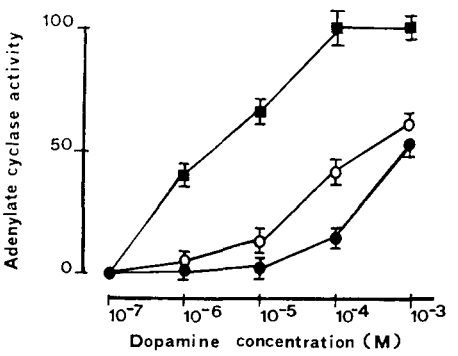

FIG. 2. Stimulation by dopamine of adenylate cyclase activity (% of max. dopamine response) in rat striatal homogenates in the presence and absence of ergotamine of dihydroergotamine. The control values of cAMP formation are 230 ± 15 pmol mg^{-1} protein min^{-1}. Each point represents the mean ± s.e.m. of at least 8 determinations. ■—■ Dopamine, ○—○ dopamine + dihydroergotamine (5×10^{-5}M) ●—● dopamine + ergotamine (5×10^{-5}M).

The stimulation of striatal adenylate cyclase using different concentrations of dopamine and apomorphine in the presence and absence of ergotamine and dihydorergotamine (5×10^{-5}M) is presented in Figs. 2 and 3. It appears that the blocking activity showed by ergotamine and dihydroergotamine towards the dopamine-induced stimulation of adenylate cyclase (Fig. 2) is less pronounced than the one towards apomorphine induced stimulation. Dopamine 10^{-4}M in the presence of ergotamine or dihydroergotamine (5×10^{-5}M)

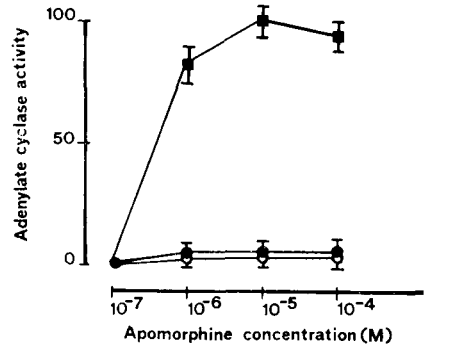

FIG. 3. Stimulation by apomorphine of adenylate cyclase activity (% of max. dopamine response) in rat striatal homogenates in the presence and absence of ergotamine or dihydroergotamine. The control values for cAMP formation are 217 + 18 pmol mg^{-1} protein min^{-1}. Each point represents the mean ± s.e.m. of at least 8 determinations. ■—■ Apomorphine, ●—● apomorphine + dihydroergotamine (5×10^{-5}M), ○—○ apomorphine + ergotamine (5×10^{-5}M).

produces a stimulation which is 14 and 52% respectively of the dopamine response obtained without the addition of ergot derivatives.

Apomorphine in the presence of either ergotamine or dihydroergotamine (5×10^{-5}M) does not stimulate striatal adenylate cyclase above basal values, which corresponds to an inhibition of 100 %.

These results parallel the data of Makman, Brown & Mishra (1975) who showed that ergotamine inhibits the activation of adenylate cyclase in calf retina. On the other hand, our results are in contrast with *in vivo* experiments using rotational behaviour tests which have indicated a possible agonist action of these drugs on the dopaminergic receptor in rat striatum (Corrodi & others, 1973; Fuxe & others, 1975). Moreover Enz, Iwangoff & others (1975) demonstrated that dihydrogenated alkaloids of ergotoxine do not modify the cAMP content of rat corpus striatum but lower it in cortex and cerebellum. It is possible that the *in vivo* effects of this family of drugs reflect their capacity to interact with different populations of receptors in the cns, such as dopaminergic, noradrenergic and serotoninergic receptors (Corrodi, Farnebo & others, 1974). Moreover, it has been proposed that different dopamine receptors exist either in peripheral tissues or in the central nervous system of vertebrates and invertebrates (Goldberg, 1975; Struyker Boudier & van Rossum, 1974; Struyker Boudier, Gielen & others 1974; Spano, Kamakura & others, 1976). The differences observed between the block of the dopamine and apomorphine stimulation of striatal adenylate cyclase by ergot derivatives may be a further indication of the existence of distinct central dopamine receptors.

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