Pre- and postsynaptic striatal dopamine receptors: differential sensitivity to apomorphine inhibition of [^{3}H]dopamine and [^{14}C]GABA release in vitro

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Several studies have indicated at least two different populations of dopamine receptors in the striatum. One population appears to have a postsynaptic location and to be responsible for mediating the dopamine-activation of adenylate cyclase in striatal tissue (Mishra et al 1974; Laduron et al 1976; McGeer et al 1976). A second population appears to be located presynaptically and to function in the inhibitory regulation of both dopamine synthesis and release in the striatum (Farnebo & Hamberger 1971; Kehr et al 1972; Westfall et al 1976). Inhibitory presynaptic dopamine receptors, which are often called autoreceptors, are also found in the substantia nigra, where the cell bodies of the nigrostriatal dopaminergic neurons are located (Nagy et al 1978). Electrophysiological studies indicate that the dopaminergic autoreceptors in the substantia nigra may participate in the inhibitory regulation of the firing rate of the nigrostriatal dopaminergic neurons (Aghajanian & Bunney 1973; Groves et al 1975).

On the basis of behavioural studies with the direct-acting dopamine receptor agonist apomorphine, it has been postulated that presynaptic autoreceptors are more sensitive to some dopamine receptor agonists than are the postsynaptic receptors (Strömbom 1976). A recent electrophysiological study by Skirboll et al (1979) demonstrated that the inhibition of the firing rate of striatal neurons by iontophoretically-applied dopamine required a larger dose than that required for inhibiting the firing rate of neurons in the substantia nigra. Similar results were produced by the systemic administration of apomorphine.

I have concentrated mainly on studying the release of [^{3}H]dopamine from superfused rat striatal slices (Brase 1978). In some preliminary experiments on the release of [^{14}C]GABA from superfused rat striatal slices it was found that 100 μM apomorphine caused an approximately 50% inhibition of the KCl-stimulated release of [^{14}C]GABA (Fig. 1). The effects of apomorphine HCl in four concentrations from 10 to 100 μM on the KCl-induced simultaneous release of ^{3}H and ^{14}C from superfused rat striatal slices preincubated with both [^{3}H]dopamine and [^{14}C]GABA is now reported.

The experimental procedure, with the use of an automated 8-channel brain slice superfusion apparatus, was essentially that of Brase (1978). Briefly, striatal slices from adult male Sprague-Dawley rats injected 1 h before death with the monoamine oxidase inhibitor nialamide (100 mg kg^{-1}, i.p.), were incubated for 20 min at 37 °C in oxygenated (95% O_2, 5% CO_2) artificial cerebrospinal fluid (c.s.f.) in the presence of 0·1 μM [^{3}H]dopamine, 0·5 μM [^{14}C]GABA, 0·57 mM ascorbic acid and 0·1 mM amino-oxyacetic acid. The slices were rinsed and superfused at 0·5 ml min^{-1} with oxygenated artificial c.s.f. at 37 °C. A total of 15 4-min fractions were collected from each superfused slice. Neurotransmitter release was stimulated by superfusion with artificial c.s.f. containing 53 mM KCl (NaCl was decreased by 50 mM) for two 4-min periods, S_1 and S_2, which were separated by a 24-min interval. During each experiment, four striatal slices served as controls and another four slices were exposed to apomorphine during the 24-min interval and during S_2. After the radioactivity in each 4-min fraction had been determined by double-label liquid scintillation counting, the KCl-induced increases in ^{3}H and ^{14}C release (expressed as percentages of these radiolabels remaining in the slices at each fraction) were corrected for the baseline release

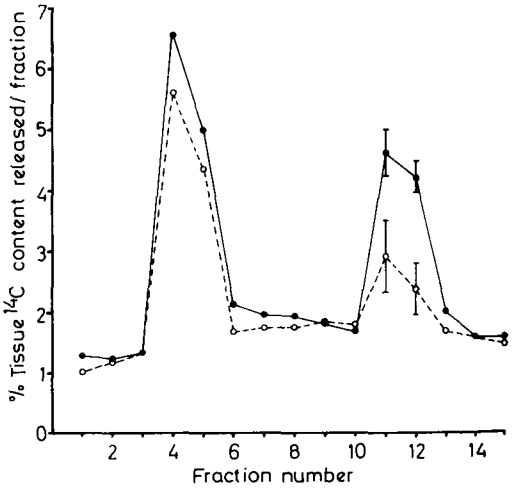

FIG. 1. The effect of apomorphine on the KCl-induced release of radioactivity from rat superfused striatal slices preincubated with [^{14}C]GABA. Closed circles represent the mean release from 8 control slices, and the open circles represent the mean release from 8 slices exposed, between the 2 KCl-stimulations (at fractions 4 and 11) and during the second KCl-stimulation, to 100 μM apomorphine. Vertical bars represent the s.e.m. and are present only at those points where the experimental release significantly differs from the controls ($P < 0.05$ at fraction 11 and $P < 0.005$ at fraction 12). Ordinate: % of tissue ^{14}C content released at each fraction. Abscissa: fraction number.

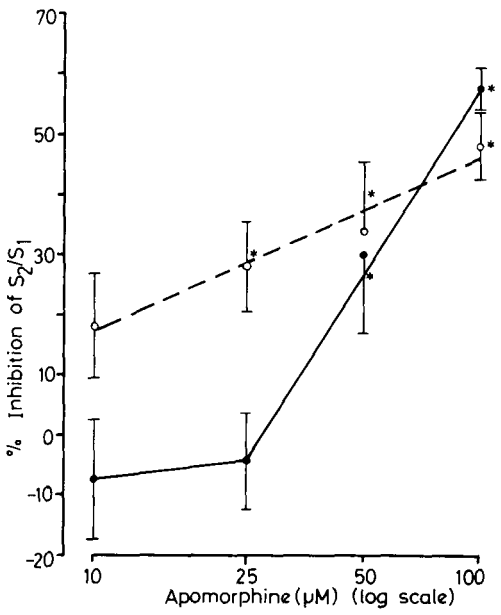

FIG. 2. Concentration-dependency of the inhibitory effect of apomorphine on the KCl-induced release of ^3H (open circles) and ^{14}C (closed circles) from superfused rat striatal slices preincubated with both [^{3}H]dopamine and [^{14}C]GABA. Vertical bars represent the s.e.m. for 4 experimental slices at each point. Asterisks (*) denote a significant difference ($P < 0.05$) from 4 control slices studied simultaneously at each apomorphine concentration. Ordinate: % inhibition of S_2/S_1. Abscissa: concentration of apomorphine, μM.

and expressed as a ratio, S_2/S_1. In the double-label experiments, the S_2/S_1 of the control slices for ^3H was 0·62 ± 0·04 and for ^{14}C was 0·74 ± 0·04 (mean ± s.e.m., n = 16).

The results in Fig. 2 indicate that apomorphine at 25μM caused a significant inhibition of [^{3}H]dopamine release but did not significantly affect [^{14}C]GABA release. Apomorphine, 50 and 100 μM, produced a similar inhibition of both [^{3}H]dopamine and [^{14}C]GABA release. Although apomorphine produced a concentration-dependent inhibition of both [^{3}H]dopamine and [^{14}C]GABA release, the slope was steeper for [^{14}C]GABA. These results are comparable with those of Skirboll et al (1979), who found that iontophoretically applied dopamine selectively inhibited the firing rate of nigral neurons at the smaller doses of dopamine, but the dose-inhibition curve for striatal neurons had a steeper slope at the larger doses of dopamine.

The present studies have shown that apomorphine can inhibit the KCl-induced release of [^{14}C]GABA from rat striatal slices. This is in contrast with the reported stimulatory effect of dopaminergic agonists on GABA release from slices of the rat substantia nigra (Reubi et al 1977). It may be that the inhibition of GABA release from the striatum results from the interaction of apomorphine with dopamine receptors on GABAergic neurons, which may have a postsynaptic location in relation to the dopamine-containing nerve terminals. On the other hand, the inhibitory effect of apomorphine on dopamine release from the striatal slices involves a presynaptic receptor (autoreceptor) on the dopamine-containing nerve terminals (Farnebo & Hamberger 1971; Westfall et al 1976). Thus, it is concluded from the present results that the presynaptic dopaminergic autoreceptors on the striatal terminals, like the autoreceptors in the substantia nigra studied by Skirboll et al (1979), are more sensitive to apomorphine than are the postsynaptic striatal dopamine receptors. This differential sensitivity, however, is only observed at low concentrations of apomorphine.

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