Further evidence for the stimulation of rat brain dopamine receptors by ergometrine

Unilateral lesions in the nigro-striatal tract can be induced in rats by the injection of 6-hydroxydopamine into one substantia nigra. In these lesioned animals the intraperitoneal injection of substances believed to stimulate dopamine receptors causes the rats to turn towards the innervated side; this is thought to be due to an increased sensitivity of the dopamine receptors on the denervated side. After treatment with amphetamine, which is thought to act indirectly by releasing dopamine, the animals turn towards the denervated side (Ungerstedt, 1968, 1971).

Ergometrine has recently been shown to cause a strong and long-lasting stimulation of locomotor activity when injected into the nucleus accumbens of conscious rats (Pijnenburg, Woodruff & van Rossum, 1973) and there is evidence that this action results from a direct stimulation of dopamine receptors. We have therefore studied its effect in rats with unilateral 6-hydroxydopamine-induced lesions of the nigro-neostriatal pathway.

Eight rats were injected unilaterally into the substantia nigra with 6-hydroxydopamine hydrobromide (8 μg in 4 μl of 0·9 % NaCl containing ascorbic acid, 0·2 mg ml^{-1}), using the method of Ungerstedt (1968). The animals were used between 7 and 30 days later. All animals responded to (+)-amphetamine (3 mg kg^{-1}) by turning towards the side previously injected with 6-hydroxydopamine, indicating that unilateral degeneration of the nigro-neostriatal tract had taken place. The number of times the animals turned was measured using a microswitch and an electronic counter (Ungerstedt & Arbuthnott, 1970). Ergometrine maleate was injected intraperitoneally in doses of 10, 25, 50 mg kg^{-1}. Each animal received several different injections of ergometrine. A minimum of two days was allowed to elapse between injections into any one animal.

Each animal responded to every injection of ergometrine by turning away from the side previously injected with 6-hydroxydopamine, i.e. towards the innervated side. The effect of ergometrine came on within 5 to 12 min. The mean duration of action of ergometrine (25 mg kg^{-1}; 22 injections) was 2·87 h $\pm$ 0·13 (s.e.) and the mean total number of turns following each injection was 1345 $\pm$ 250 (s.e.). There was a

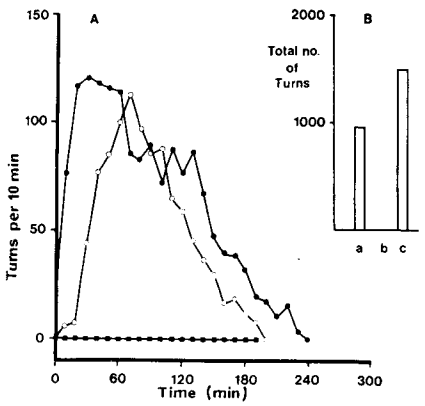

FIG. 1. Turning of a lesioned rat induced by the intraperitoneal injection of ergometrine (10 mg kg^{-1}). The turning was towards the innervated side. In 'A' the time course of turning is shown following the ergometrine injection at 0 min. In 'B' the total number of turns is shown. ○——○ and 'a' is the control response produced 9 days after the injection of 6-hydroxydopamine, ■——■ and 'b' is the same rat 2 days later. In this experiment haloperidol (1·0 mg kg^{-1}) completely abolished the effect of ergometrine. ●——● and 'c' is the same rat 13 days after the induction of the lesion. Ergometrine again caused strong turning.

tendency for the animals to become increasingly sensitive to ergometrine between days 13 and 23 after the operation; for this reason no attempt was made to relate the total number of turns to the dose of ergometrine injected. The intraperitoneal injection of 0·9% NaCl caused no turning behaviour.

The effect of ergometrine (10 mg kg^{-1}) was completely abolished by haloperidol (1·0 mg kg^{-1}), injected 30 min before the ergot alkaloid (Fig. 1). With higher doses of ergometrine this same dose of haloperidol caused attenuation of the response, but not complete block.

Recently, Corrodi, Fuxe & others (1973) have shown that ergocornine and 2-Br-α-ergocryptine cause a similar turning towards the innervated side in unilaterally lesioned rats. The effect of 2-Br-α-ergocryptine was 'markedly reduced' by a high dose of pimozide (1 mg kg^{-1}).

Our results lend support to the suggestion (Pijnenburg & others, 1973; Pijnenburg & van Rossum, 1973) that the central stimulant action of ergometrine is due to a direct action on dopamine receptors in the brain.

A. O. Elkhawad was supported by a research scholarship from the University of Khartoum. A. R. Crossman is a M.R.C. Postdoctoral Research Fellow.

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January 18, 1974

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The effect of β-phenethylamine on noradrenaline and dopamine turnover in rat brain

β-Phenethylamine (PE) has recently been found in various animal tissues including brain (Nakajima, Kakimoto & Sano, 1964; Jackson & Temple, 1970; Inwang, Mosnaim & Sabelli, 1973). PE on injection into animals produced a depletion of brain noradrenaline in guinea-pigs (Jackson, 1971), both noradrenaline and dopamine in rats (Jonsson, Grobecker & Holtz, 1966; Fuxe, Grobecker & Jonsson, 1967; Jackson & Smythe, 1973) and noradrenaline, dopamine and 5-hydroxytryptamine in mice (Jackson & Smythe, unpublished observations). The central nervous stimulant effect of PE on locomotor activity in mice has been shown to be mediated via dopamine receptors (Jackson, 1972, 1974). In addition the distribution of (4T)- PE in rat brain after the administration of a behaviourally active dose (100 mg kg^{-1}, i.p.) paralleled the distribution of dopamine. We therefore decided to examine the effect of PE on noradrenaline and dopamine turnover in rat brain. Male Sprague-Dawley rats (150–300 g) were given two doses of PE (each 50 mg kg^{-1}, i.p.) 4 and 1 h before death.