Acute administration of reserpine has been reported to produce supersensitivity in structures innervated by the sympathetic nervous system. Enhanced α-adrenoceptor activity was noted in aortic strip of rabbit (Taylor & Green, 1971), in dog isolated carotid arteries (MacMillan, Smith & Jacobsen, 1962), in perfused femoral vessels of dogs (Carrier & Holland, 1965), and in the cat nictitating membrane (Fleming & Trendelenburg, 1961) after acute or subchronic administration of reserpine. We found a 5 fold increase in the sensitivity of the α-adrenoceptors in the femoral arterial strips of the reserpine-treated dog; but no such alteration was noted in the receptor sensitivity in the mesenteric strips from the same animals. Clarke, Adams & Buckley (1970) found there was a significant reduction in the responses of perfused mesenteric vessels of the treated dogs to sympathetic nerve stimulation, no significant changes were observed in α-adrenoceptor activity. It, therefore, seems that adrenoceptor sensitivity in vascular tissues or beds is not uniformly influenced by chronic reserpine treatment. Prolonged reserpine treatment did not produce any qualitative or quantitative alteration in receptors, as indicated by the pA_2 values for phentolamine obtained both in treated and control animals. This observation confirms the findings of Taylor & Green (1971).

This work was supported by U.S. Public Health Service Grant No. G.M. 15587 from the National Unit of General Medical Science.

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July 7, 1971

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Evidence for a new type of dopamine receptor stimulating agent

It is well known that apomorphine is a shortlasting dopamine receptor stimulating agent (Ernst, 1967; Anden, Dahlström & others, 1967) an action which probably is the neurochemical basis for its marked stimulation of locomotion and stereotyped activities (see Randrup & Munkvad, 1968). It decreases dopamine turnover probably as a result of stimulating the dopamine receptor eliciting a feedback which causes a compensatory reduction in the activity of the dopamine neurons. Furthermore, in rats in which degeneration of one nigro-neostriatal dopamine pathway has been induced by 6-hydroxydopamine (Ungerstedt, 1968, 1971), apomorphine will cause rotation of the rats towards the unoperated side, probably as a result of development of supersensitivity of the dopamine receptors on the denervated side. Therefore, the operated side will become overactive compared with the intact side. Amphetamine, on the other hand, which is a catecholamine-releasing agent (Carlsson, Fuxe & others, 1966), will make the intact side overactive and cause rotation of the animal towards the operated side, since no dopamine release will occur on the denervated side. On the basis of its dopamine receptor stimulating property the potential usefulness of

apomorphine in treatment of Parkinson's disease has been pointed out (Cotzias, Papavasilou & others, 1970) and has, in fact, been shown recently (Düby, Cotzias & others, 1971). Therefore, for some time we have tested drugs in the turnover and rotation models mentioned above for a possible dopamine receptor stimulating property in order to develop new therapeutic tools in the treatment of Parkinson's disease. Apomorphine derivatives have so far proved to lack activity or to be only weakly active in the case of 7- and 11-hydroxy-apomorphines (Granchelli, Neumeyer & others, 1971). In the present paper evidence has been obtained that 7-(2''-pyrimidyl)-4-piperonyl-piperazine (ET495, Servier; Regnier, Canevari & others, 1968) when given systemically is a powerful dopamine receptor stimulating agent.

Male Sprague-Dawley rats (150–180 g) were used.

Chemical experiments. The effects of ET495 on dopamine and noradrenaline turnover in the brain have been examined with the help of the tyrosine-hydroxylase inhibitor α-methyl-tryosine-methylester (H44/68) (Corrodi & Hansson, 1966; Andén, Dahlström & others, 1966) biochemically and histochemically (Bertler, Carlsson & others, 1958; Carlsson & Waldeck, 1958; Carlsson & Lindqvist, 1962; Falck, Hillarp & others, 1962). ET495 was given intraperitoneally 15 min before the inhibitor. The biochemical determinations were made on whole brain (the numbers of rats used are given in Table 1) and the histochemical observations (made on some 40 rats) on the neocortex, the neostriatum and the hypothalamus.

Functional experiments. The effects of ET495 and apomorphine on dopamine receptor activity were evaluated in the rotometer model described (Andén, Dahlström & others, 1966; Ungerstedt, 1968, 1971). The rotations were registered quantitatively in a specially designed "rotometer" (Ungerstedt & Arbuthnott, 1970). Doses of ET495 were from 1–150 mg/kg (i.p) and 4 rats per dose were tested.

The biochemical results are summarized in Table 1. With a dose of 50 mg/kg of ET495 there was a reduction of H44/68-induced depletion of dopamine and an increase in the H44/68-induced depletion of noradrenaline. The histochemical results revealed similar changes. In a dose of 50 mg/kg, ET495 caused a reduction in the rate of H44/68-induced disappearance of dopamine fluorescence from the neostriatum and the limbic forebrain, and the rate of disappearance of noradrenaline fluorescence from the neocortical and the hypothalamic noradrenaline nerve terminals was increased. With a dose of 15 mg/kg of ET495, while a retardation of disappearance of dopamine fluorescence was observed there were no observed effects on the disappearance of noradrenaline fluorescence.

In the rotometer model it was found that ET495 induced rotations towards the unoperated intact side in a dose-dependent manner mimicking the action of apomorphine. The effects of ET495 were rapid in onset and lasted for 7–10 h at a dose of

Table 1. *Noradrenaline (NA) and dopamine (DA) concentrations in whole rat brain after treatment with ET495 i.p. followed by H44/68 treatment 15 min later (250 mg/kg, i.p.).* Four h after H44/68 the animals were killed and the catecholamines determined spectrofluorimetrically. Values in ng/g ± s.e. (n = number of experiments). Statistical evaluation by analysis of variance.

Treatment	Dose (mg/kg)	n	DA	NA
No drug treatment		10	515 ± 10	455 ± 10
ET495	50	4	541 ± 17	423 ± 13
H44/68		16	155 ± 6	225 ± 7
ET495 + H44/68	50	4	274 ± 16	115 ± 9
Significance of differences between H44/68 alone and ET495 + H44/68				$P < 0.001$

50 mg/kg in contrast to the short-lasting action of apomorphine. Clearcut rotations were observed at doses down to 1–5 mg/kg, and at 25 mg/kg a total of about 1000 rotations were observed. Apomorphine was effective in doses down to 0·1 mg/kg, but only short-lasting effects (30 min) were obtained (see Ungerstedt, 1971). With higher doses, stereotyped licking and biting behaviour was induced which abolished the rotation behaviour. This was not observed with ET495.

Experimental evidence has thus been given for the view that ET495 and/or an active metabolite is a new dopamine receptor stimulating agent with powerful and prolonged actions as revealed in both the amine turnover and the rotational model. In both these models the drug mimicks the effects of apomorphine, but not that of amphetamine, by reducing dopamine turnover and causing stimulation of the dopamine receptors in the denervated neostriatum. The reduction of dopamine turnover is probably the result of the dopamine receptor stimulation inducing a compensatory feedback to reduce activity in the dopamine neurons. In higher doses an increase in the noradrenaline turnover was found which may be secondary to the dopamine receptor stimulation (see Persson & Waldeck, 1970) or e.g. due to a direct action of ET495 on the noradrenaline neurons. The present results suggest ET495 has potential in the treatment of parkinsonism.

Acknowledgements. This work has been supported by grants (14X-1015-06; B72-14X-3574-01) from the Swedish Medical Research Council and by "Ollie och Elof Ericssons Stiftelse". We are grateful to Servier Laboratories for generous supply of ET495.

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