Prolonged effects of reserpine administration on adrenoceptor activity in dogs

This report is a part of an investigation dealing with a group of mongrel dogs (10 to 12 kg) treated with 0·137 mg of reserpine (Serpasil-Ciba) twice a day for twelve months, and an equal number receiving an inert control substance. Femoral and mesenteric arterial strips were obtained from these animals under sodium pentobarbitone anaesthesia and prepared according to Furchgott & Bhadrakom (1953). The strips were suspended in Krebs-Hanseleit solution and isometric contractions measured after 2 h of stabilization with 4 g tension. Two cumulative dose-response curves for noradrenaline (base) were obtained by adding progressively higher doses at $1/2 \log_{10}$ intervals. The strips were exposed to phentolamine (base) ($1{\cdot}66 \times 10^{-6}$ g) for 15 min and cumulative dose-response curves to noradrenaline again were obtained. Regression line equations were calculated from the responses between 20 and 80%. The points corresponding to 25, 50, and 75% of maximum responses were then pooled and the mean value was used to plot Fig. 1. pD_2 for noradrenaline (negative log of molar concentration of drug producing 50% of the maximal effect) and pA_2 for phentolamine (negative log of the molar concentration of drug reducing the effect of a double dose of noradrenaline to that of a single dose) were calculated as described by van Rossum (1963) (Table 1).

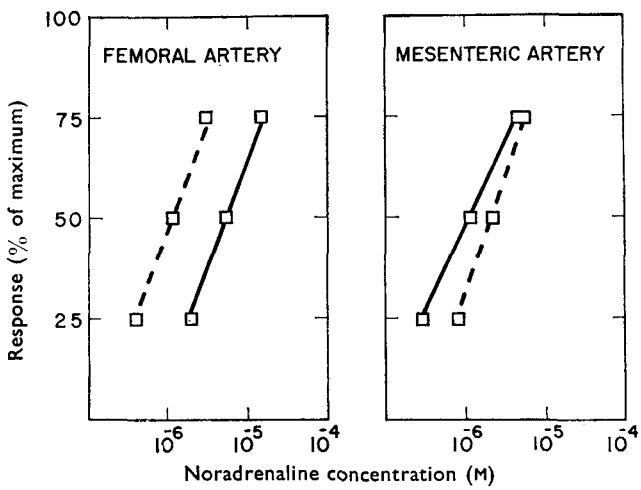

FIG. 1. Cumulative dose-response curves for femoral and mesenteric arterial strips obtained from reserpine-treated and control dogs. Percent of maximum responses to various molar concentrations of noradrenaline are represented. Broken line (□- - - - □) indicates reserpine-treated group and the solid line (□——□) control group.

Table 1. *pD_2 for noradrenaline and pA_2 for phentolamine from cumulative dose-response curves of spirally cut femoral and mesenteric arterial strips on reserpine-treated and control dogs.*

	Mesenteric		Femoral	
	Reserpine mean ± s.e.	Control mean ± s.e.	Reserpine mean ± s.e.	Control mean ± s.e.
pD_2	5·66 ± 0·16	5·93 ± 0·20	5·96 ± 0·12*	5·27 ± 0·07*
pA_2	7·15 ± 0·10	7·23 ± 0·15	7·33 ± 0·13	7·29 ± 0·12

* Statistically different ($P < 0{\cdot}01$). A = 4.

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).

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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