Evidence for a centrally mediated hypotensive effect of L-dopa in the rat

It is well established that administration of L-dopa to experimental animals produces a syndrome which involves effects elicited both from the central and the peripheral nervous system (for references see e.g. Butcher & Engel, 1969a, b; Carlsson, 1969). The influence of L-dopa on blood pressure is complex and shows species variation. Intravenous injection to cats results in a protracted hypertensive effect (Holtz & Palm, 1966) whereas rabbits respond with a decrease in blood pressure after small doses of L-dopa (Gaillard, Schaeppi & Tissot, 1969). On intravenous injection in man, L-dopa may produce increased blood pressure (for references see Holtz & Palm, 1966); on the other hand, long term oral administration of L-dopa may result in hypotension (see below).

L-Dopa itself is regarded to be pharmacologically inert (Carlsson, Lindqvist & Magnusson, 1957; Blaschko & Chruschiel, 1960; Carlsson, 1964) and therefore its actions are probably due to its catecholamine metabolites. Several mechanisms are possible, e.g. (1) effects of the metabolites dopamine or noradrenaline, or both, in the central nervous system, either on specific receptors (noradrenaline, dopamine) or indirectly (displacement in catecholamine as well as 5-hydroxytryptamine neurons); (2) analogous actions in the peripheral sympathetic system; (3) combined central and peripheral effects.

Potent inhibitors of dopa-decarboxylase in peripheral tissues but with little effect in the central nervous system have proved to be valuable tools in dissociating central and peripheral actions of L-dopa (Butcher & Engel, 1969a, b) or its α-methylated analogue, α-methyldopa (Henning, 1969a). This study was undertaken to examine the effects of L-dopa on blood pressure in conscious rats before and after pretreatment with α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)propionic acid (MK 485), a decarboxylase inhibitor with minimal central actions (Porter, Watson & others, 1962; Bartolini & Pletscher, 1969). In an attempt to analyse further the central effects of L-dopa after inhibition of peripheral decarboxylase, we also studied the influence of pretreatment with an inhibitor of dopamine-β-hydroxylase, FLA-63. This compound has recently been described as a more potent inhibitor of this enzyme than disulfiram to which it is structurally related (Svensson & Waldeck, 1969; Carlsson, A., Corrodi, H., Florvall, L., Ross, S. & Sjöberg, B., unpublished data; cf. Svensson & Waldeck, 1969).

Male Sprague-Dawley rats weighing 250–350 g were used. Mean arterial blood pressure was recorded on a Grass Polygraph using conscious unrestrained animals with in-dwelling arterial catheters (Henning, 1969b). The following drugs were injected intraperitoneally: L-3,4-dihydroxyphenylalanine (L-dopa), α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)propionic acid (MK 485), a disulfiram derivative (FLA-63). For doses and time intervals see below. Tests of significance were conducted by Student's *t*-test or analysis of variance with two independent criteria of classification.

Injection of L-dopa (50 mg/kg) alone gave a rapid increase in mean arterial blood pressure. At maximal effect 20 min after administration the pressure had increased significantly ($P < 0.005$) from 117 mm Hg (s.e. = 4·6, n = 9) to 144 mm Hg (s.e. = 4·6, n = 9). The duration of the increase was at least 60 min. After L-dopa the animals showed exophthalmus and piloerection. Increasing doses of L-dopa alone (50–200 mg/kg) never gave decreases in blood pressure but at the highest doses tested the rats rapidly deteriorated and died.

The changes in mean arterial blood pressure induced by L-dopa (200 mg/kg) after pretreatment with MK485 are shown in Fig. 1. MK 485 alone did not seem to

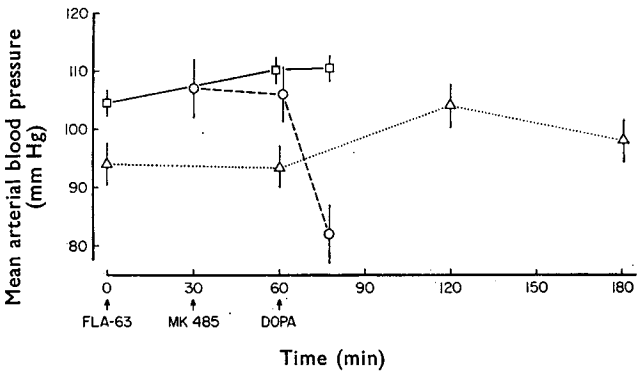

FIG. 1. Changes in mean arterial blood pressure in conscious rats (means with s.e.) after the following treatments: L-dopa (200 mg/kg) 30 min after MK 485 (100 mg/kg) (13 experiments; circles); L-dopa (200 mg/kg) 30 min after MK 485 (100 mg/kg) and 60 min after FLA-63 (40 mg/kg) (8 experiments; squares); FLA-63 (40 mg/kg) (2–4 experiments; triangles). All drugs were given i.p. The values after L-dopa represent averages of the blood pressure 15–20 min after the injection. All other values are averages of 10 min periods.

influence blood pressure. The hypertensive response to L-dopa was reversed. With minimum 15–20 min after L-dopa there was now a significant lowering of blood pressure when compared to the levels before and after MK 485 ($P < 0.001$). The duration seemed to be shorter than the hypertensive reaction to L-dopa alone. In spite of the larger dose of L-dopa used, the peripheral sympathomimetic symptoms were less pronounced after pretreatment with MK 485. There was also a slight tendency to a decrease in blood pressure in experiments using 50 mg/kg of L-dopa (not shown here) after pretreatment with MK 485.

As seen in Fig. 1, pretreatment with FLA-63 40 mg/kg abolished the fall in blood pressure after MK 485 plus L-dopa ($P > 0.10$). FLA-63 alone had no significant effect on blood pressure (Fig. 1). Since this dose of FLA-63 results in a marked inhibition of dopamine-β-hydroxylase (Svensson & Waldeck, 1969; Carlsson & others, unpublished data) it may be assumed that FLA-63 to a large extent prevented the synthesis of noradrenaline from L-dopa in our experiments. The results thus point to the importance of noradrenergic mechanisms in the hypotensive response to L-dopa after peripheral decarboxylase inhibition. This assumption is supported by preliminary results using spiroperidol, which in a dose of 0·1 mg/kg appears to block the central dopamine but not the noradrenaline receptors in the rat (Andén, N.-E., Butcher, S. C., Corrodi, H., Fuxe, K. & Ungerstedt, U., unpublished experiments). Pretreatment with this drug (0·1 mg/kg) did not seem to influence the drop in blood pressure caused by L-dopa after MK 485 in the same doses as used in the previous experiments.

In conclusion, the present studies show that systemic administration of L-dopa to rats results in a pronounced increase in mean arterial blood pressure which seems to be due to peripheral actions. At the same time, L-dopa produces a centrally mediated hypotensive action which is unmasked following inhibition of the peripheral metabolism of L-dopa to catecholamines. The results also make it less probable that this central effect is mediated via dopamine but point to the importance of noradrenergic mechanisms, the nature of which is being investigated. Actions of this kind may be involved in e.g. the episodes of postural hypotension or permanent lowering of blood pressure which are sometimes observed during oral treatment of Parkinsonian patients with L-dopa (Calne, Stern & others, 1969; Cotzias, Papavasilion

and Gellene, 1969; Godwin-Austen, Tomlinson & others, 1969; Yahr, Duvoisin & others, 1969).

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Multiple-drop formation in emulsions

The term "multiple emulsion" has been used to describe the phenomenon in which drops of the disperse phase themselves contain smaller droplets which are normally considered to have the same composition as the continuous phase (Clayton, 1943). Multiple-drops appear to form most readily where an emulsion is inverting from oil-in-water to the water-in-oil type or vice-versa—conditions under which no one form of the emulsion is favoured (Seifriz, 1925). Various theories have been suggested to explain their formation (Bancroft, 1912; Parke, 1934; Pavlushenko & Yanishevski, 1959).

We have recently been making a phase rule investigation of a model four-component emulsion, and wish to report a case of multiple-drop formation arising from the presence of three liquid phases under certain conditions.

The present case of multiple-drop formation, which is restricted to the three-phase region, indicates the possibility that some of the former reports may arise from a similar cause, since three-phase formation in systems containing surfactants may be