Cardiovascular effects of 5-hydroxytryptophan in anaesthetized dogs

Intravenous doses of L-dopa (10 mg kg^{-1}, i.v.), that had little effect in normal anaesthetized dogs, caused transient rises in blood pressure and heart rate followed by profound hypotension and bradycardia in monoamine oxidase (MAO)-inhibited dogs (Robson, 1971). Inhibition of cerebral and extracerebral decarboxylase prevented both effects, but only the early pressor response was prevented by selective extracerebral decarboxylase inhibition with MK-486 [L-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)propionic acid] (Robson, 1971). Hypotension after L-dopa appeared reliant on the central formation of noradrenaline in rats (Henning & Rubenson, 1970) and cats (Torchiana, Lotti & others, 1972), whereas Robson (1971) attributed the action to dopamine in dogs. These results with the inactive precursor amino-acid of dopamine and noadrenaline led us to test the short-term effects of the precursor amino-acid of 5-hydroxytryptamine (5-HT), 5-hydroxytryptophan, on the same test systems.

Mongrel or beagle dogs, 8·0 to 16·2 kg, were anaesthetized with sodium pentobarbitone (32·5 mg kg^{-1}, i.v.). Blood pressure was measured from a cannulated femoral artery and drugs were injected into the femoral vein. Heart rate was measured with a Beckman calibrating cardiotachometer triggered from the blood pressure pulse. Monoamine oxidase inhibition was obtained by pretreating dogs with Su 11739 [L-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)propionic acid] (Heubner, Donoghue & others, 1966), 3 mg kg^{-1}, s.c. for 24 h.

In MAO-inhibited dogs, 5-HTP (10 mg kg^{-1}, i.v.) caused a marked fall in mean arterial blood pressure of gradual onset and long duration (Fig. 1A). The decrease in blood pressure was maximum at 90 min after 5-HTP administration when mean

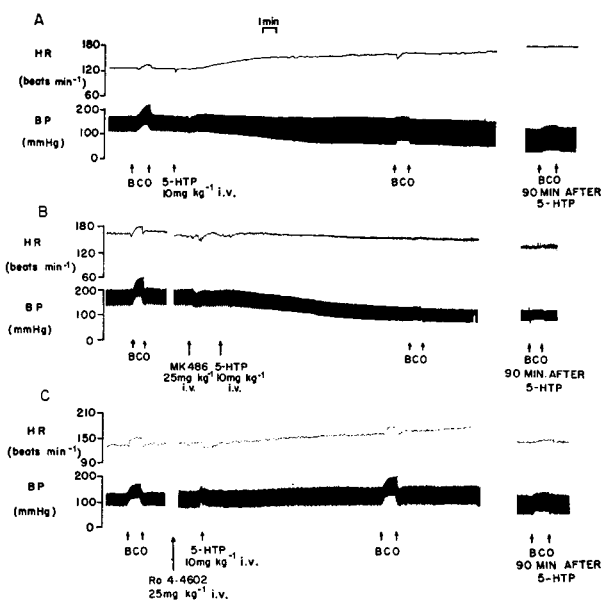

FIG. 1. Effects of 5-hydroxytryptophan (5-HTP) on blood pressure (BP), heart rate (HR) and responses to bilateral carotid artery occlusion (BCO) in MAO-inhibited anesthetized dogs. A. No decarboxylase inhibition. B. After extracerebral decarboxylase inhibition with MK 486. C. After cerebral and extracerebral decarboxylase inhibition with Ro 4-4602.

Table 1. *Effects of 5-HTP* (10 mg kg^{-1}, i.v.) *on blood pressure, heart rate and reflex responses to bilateral carotid artery occlusion (BCO) before and after selective decarboxylase inhibition in MAO-inhibited dogs.*

Drug pretreatment	n	Maximum changes after 5-HTP (% of control)			
				BCO	
		BP	HR	Δ BP	Δ HR
None	6	−50·2 ± 3·2**	+30·9 ± 4·2*	−80·9 ± 3·6**	−95·5 ± 3·1**
MK-486 (25 mg kg^{-1}, i.v.)	4	−42·0 ± 31·0*	−10·1 ± 4·6	−82·7 ± 6·1**	−96·4 ± 3·8***
Ro 4-4602 (25 mg kg^{-1}, i.v.)	5	−25·0 ± 6·3*	+ 4·1 ± 3·8	−24·4 ± 4·1	−53·1 ± 6·1

* P 0·05.
** P 0·01.
*** P 0·001.

arterial blood pressure was decreased by 71·2 ± 3·5 mm Hg (Table 1). Heart rate increased gradually after 5-HTP administration and was highest at the end of the 2 h observation period (Table 1). The reflex pressor and positive chronotropic responses to bilateral carotid artery occlusion (BCO) were also progressively and severely depressed by 5-HTP (Fig. 1A and also Table 1).

After extracerebral decarboxylase inhibition by MK-486 (25 mg kg^{-1}, i.v.) in MAO-inhibited dogs, 5-HTP (10 mg kg^{-1}, i.v.) again caused a marked decrease in blood pressure of the same time course and magnitude as that observed in animals not receiving MK-486 (Table 1). However, heart rate was decreased rather than increased in decarboxylase-inhibited dogs (Table 1), an effect which may explain the lack of pulse pressure widening in these dogs (Fig. 1B). Reflex responses to BCO were reduced in the MK-486-treated dogs (Fig. 1B) to the same degree as those dogs not receiving MK-486 (Table 1).

Inhibition of both extracerebral and cerebral decarboxylase by Ro 4-4602 [N^1-(DL-seryl)-N^2(2,3,4-trihydroxybenyl)hydrazine) (25 mg kg^{-1}, i.v.) markedly inhibited the effects of 5-HTP both on blood pressure and the BCO reflex (Table 1) (see also Fig. 1C).

Neither tryptophan nor 5-HTP had any effect on blood pressure or heart rate in non-MAO-inhibited dogs and tryptophan also had no effect in MAO-inhibited dogs (not shown).

Thus 5-HTP decreased blood pressure and inhibited the reflex response to BCO in MAO-inhibited dogs. These effects were apparently due to the conversion of 5-HTP to 5-HT since inhibition of extracerebral and cerebral decarboxylase by Ro 4-4602 markedly attenuated the effects of 5-HTP. Also, 5-HTP had no effects on blood pressure in non-MAO-inhibited dogs, presumably because of the rapid breakdown of the 5-HT formed (Bogdanski, Weissbach & Udenfriend, 1958). The effects of 5-HTP on blood pressure and BCO responses were mainly central in origin since inhibition of peripheral decarboxylase by MK-486 did not alter the onset or duration of the effects of 5-HTP. Heart rate was increased by 5-HTP in MAO-inhibited dogs, probably from the formation of 5-HT in the periphery which can directly cause increases in heart rate (Reid, 1952). After peripheral decarboxylase inhibition by MK-486, 5-HTP caused only decreases in heart rate.

The induction and modification by the selected enzyme inhibitors of the hypotensive action of 5-HTP, which was apparently due to the central formation of 5-HT, is reminiscent of the hypotensive action of L-dopa. The latter substance or its decarboxylation products release and deplete 5-HT from peripheral and central tissues (Everett & Borcherding, 1970; Ng, Chase & others, 1970; 1972; Murphy, 1972). Murphy (1972) has suggested that some behavioral effects caused by L-dopa may be

the result of release of 5-HT, and preliminary results suggest that the hypotensive action of L-dopa in dogs may be similarly mediated.

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Potentiation of leptazol seizures by 6-hydroxydopamine

A considerable body of evidence suggests that monoaminergic systems in the brain act to decrease the seizure susceptibility of animals (reviewed by Maynert, 1969). For example, injections of monoamine oxidase inhibitors, which raise brain monoamine levels, inhibit audiogenic seizures in rodents (e.g. Lehmann & Busnel, 1963), while treatment with 5-hydroxytryptophan, the immediate precursor of 5-hydroxytryptamine, decreases the photogenic seizure response of epileptic baboons (Wada, Balzamo & others, 1972). Conversely, administration of L-amino-acid decarboxylase inhibitors or reserpine, which non-specifically lower the levels of monoamines, increases seizure susceptibility (e.g. Jenney, 1954; Rudzik & Mennear, 1966).

It is of interest to determine the extent of the participation of catecholaminergic systems as opposed to 5-hydroxytryptaminergic systems in these effects. Unfortunately, however, the non-specificity of the pharmacological treatments previously employed does not permit such a discrimination. Non-specificity must be considered even when putative neurotransmitters or their precursors are administered, since there is evidence for the uptake of externally applied doses of these agents into cells that do not normally contain them (e.g. Butcher, Engel & Fuxe, 1972; Ng, Chase & others, 1972).

The use of 6-hydroxydopamine (6-OHDA) provides a partial solution to this question since relatively small doses of this drug injected intracerebrally have been shown to produce selective destruction of catecholaminergic but not 5-hydroxy-