Precursors of 5-hydroxytryptamine reduce the pressor response to clonidine in the rat

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Intravenous injection of clonidine causes a brief pressor response which precedes its hypotensive action (Zaimis, 1970). We have now found that the magnitude of the pressor effect can be markedly reduced by prior administration of either L-tryptophan or L-5-hydroxytryptophan (5-HTP).

Male hooded unanaesthetized rats (200–300 g) were initially used, arterial blood pressure and heart rate in each being directly recorded. Clonidine injected intravenously caused a rise in blood pressure lasting approximately 15 min, and bradycardia. The pressor response was significantly smaller in groups pretreated with either tryptophan or 5-HTP and this inhibition was prevented by prior administration of Ro4-4602 (Benserazide) or methysergide (Table 1).

In anaesthetized rats (700 mg/kg urethane i.p.), tryptophan (100 mg/kg, s.c.) given 90 min before, caused a parallel shift to the right (2.2 fold) of the regression line relating mean rise in blood pressure to log intravenous dose of clonidine hydrochloride (16–64 μg/kg). Analogous curves for (−)-adrenaline bitartrate (2–8 μg/kg) or angiotensin II amide (0.16–4.0 μg/kg) were not significantly changed. The inhibitory effect of tryptophan was reduced by pithing, Ro4-4602 (200 mg/kg, i.p.), carbidopa (100 mg/kg, i.p.) and methysergide maleate (1.5 mg/kg, i.p.) given respectively 60–120 min, 120 min and 30–120 min before clonidine.

The magnitude of clonidine's pressor effect depends on the equilibrium established between the rise in arterial pressure due to vasoconstriction and opposing depressor influences. The latter include reflex

Table 1 Mean changes (±s.e. mean) in blood pressure and heart rate caused by clonidine hydrochloride (25 μg/kg) intravenously in rats pretreated with drugs affecting tryptaminergic mechanisms

Pretreatment (doses in parentheses)	*Time (min) administered before clonidine*	*Route*	*No. of animals*	*Mean BP (mmHg)*	*Mean rise in BP (mmHg) due to clonidine*	*Mean HR (beats/min)*	*Mean Bradycardia (beats/min)*
1. Saline controls	90	S.C.	25	119 ± 2	27 ± 2	366 ± 11	80 ± 9
2. L-tryptophan (100 mg/kg)	90	S.C.	9	113 ± 4	4 ± 6*	390 ± 25	60 ± 16
3. 5-hydroxytryptophan (100 mg/kg)	90	S.C.	7	86 ± 5*	3 ± 1*	393 ± 8	9 ± 8 *
4. Ro4-4602 (2 × 100 mg/kg)	180 60	I.P.	7	123 ± 5	32 ± 1	332 ± 17	75 ± 21
5. L-tryptophan (100 mg/kg)	90	S.C.	7	119 ± 3	29 ± 3	332 ± 18	90 ± 14
+							
Ro4-460– (2 × 100 mg/kg)	180 60	I.P.					
6. Methysergide maleate (3 × 0.5 mg/kg)	120 60 30	I.P.	6	104 ± 2*	48 ± 6*	278 ± 14*	38 ± 9*
7. L-tryptophan (100 mg/kg)	90	S.C.	6	99 ± 5*	46 ± 7*	284 ± 9*	53 ± 6
+							
Methysergide maleate (3 × 0.5 mg/kg)	120 60 30	I.P.					

* Significantly different from mean response of saline controls ($P < 0.05$, Analysis of variance, F-test)

barostatic mechanisms and depression by the drug of bulbar efferent sympathetic tone (Schmitt, Schmitt, Boissier & Giudicelli, 1967) and peripheral adrenergic nerve function (Boura, 1975). Present results suggest that the point of this equilibrium can be specifically affected by tissue levels of 5-hydroxytryptamine. That this effect was mediated by a peripheral mechanism was suggested by the action of carbidopa, a selective inhibitor of peripheral L-aromatic amino acid decarboxylase (Bartholini & Pletscher, 1969) but the abolition of the inhibitory effect by pithing indicated that the central nervous system may also be involved.

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Responses of the hepatic arterial vascular bed of the dog to intra-arterial injections of noradrenaline, adrenaline and phenylephrine: the role of β-adrenoceptors

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In the sympathetically-denervated hepatic arterial vascular bed of the dog, intra-arterial (i.a.) injections of noradrenaline cause dose-dependent hepatic arterial vasoconstriction (Richardson & Withrington, 1976a). Whilst previous reports have suggested that the effect of adrenaline on this vascular bed is essentially vasoconstrictor (see Greenway & Stark, 1971), isoprenaline injected i.a. causes dose-dependent hepatic arterial vasodilatation, due to stimulation of β_2-adrenoceptors (Richardson & Withrington, 1976b). The contribution of β-adrenoceptor stimulation to the effects of the catecholamines has therefore been examined in the sympathetically-innervated hepatic arterial vasculature.

The hepatic arterial vascular beds of 15 chloralose-urethane anaesthetized dogs (13.1 ± 2.2: mean $\pm$ s.d. kg) were perfused as described by Richardson & Withrington (1976c): under control conditions, the hepatic arterial perfusion pressure was 117.7 ± 15.4 (s.d.) mmHg and the hepatic arterial blood flow 210.7 ± 56.9 ml/min. The calculated hepatic arterial vascular resistance (HAVR) was 1.80 ± 0.76 mmHg ml^{-1} min 100 g, the livers weighing 301.6 ± 50.1 grams.

When noradrenaline was injected i.a., there was an immediate dose-dependent increase in the calculated HAVR at doses above 5 ng, with a maximum rise in HAVR of $308.5 \pm 81.1\%$ (mean $\pm$ s.e. mean; $n=10$) occurring between 50 and 200 µg. In addition, over the dose range 50 ng–10 µg in most experiments, there followed a secondary reduction in HAVR which reached a maximum of $17.2 \pm 3.4\%$ and had a time course similar to that of i.a. injections of isoprenaline (see Richardson & Withrington, 1976c).

The responses to i.a. adrenaline were similar to those of noradrenaline, with dose-dependent rises in HAVR at doses above the threshold (5–100 ng) reaching a maximum of $504.5 \pm 79.8\%$ ($n=11$) at 50–200 µg. These were followed by vasodilatation at doses between 50 ng and 50 µg reaching a maximum of $21.7 \pm 3.3\%$. In all experiments where both catecholamines were administered, noradrenaline was on a molar basis a more potent vasoconstrictor than adrenaline.

Phenylephrine caused dose-dependent rises in HAVR above the threshold of 1 µg i.a., reaching a maximum of $412.9 \pm 87.2\%$ ($n=4$) at 50–200 µg, but in contrast to noradrenaline and adrenaline, there was no secondary reduction in HAVR.

In 3 experiments, propranolol (0.25 mg kg^{-1}, i.v.) markedly attenuated the secondary dilatation due to i.a. noradrenaline and adrenaline. In addition, both catecholamines were more potent hepatic arterial vasoconstrictors; the increase in vasoconstrictor potency of adrenaline, but not of noradrenaline, being statistically significant (Paired t-test; $P<0.02$). The mean dose of adrenaline which doubled the HAVR