Some properties of 5-hydroxytryptamine receptors in the hindquarters of the rat

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Vascular reactions to 5-hydroxytryptamine (5HT) are complex and often biphasic in the whole animal; so we have attempted to study them in a preparation which eliminates effects arising from the brain, heart, lungs and other organs.

Wistar rats (mean wt 300 g) were decapitated and Krebs' solution warmed to 36°C was pumped at a constant rate of 10 ml/min into the distal aorta; the returning effluent escaped through a laceration of the interior vena cava. Perfusion pressure was recorded; 1-min infusions of 5HT, noradrenaline and some other substances provoked rapid, reproducible dose-related elevations in perfusion pressure. After constructing a dose-response curve to a particular agonist an antagonist was added to the perfusion medium and, after equilibration, a new dose-response curve was made; the antagonists studied could be washed out again with return of sensitivity to near the original value. Both methysergide and cyproheptadine showed a non-competitive type of block whereas phentolamine and a homologous series of phenothiazines produced parallel displacement of the dose-response curves compatible with competitive antagonism (Table 1). On this preparation 5HT never showed any vasodilator activity. Vasospasm produced by 5HT and noradrenaline was mediated by different receptors but no evidence was obtained of heterogeneity of the 5HT-receptors. Activity of the phenothiazines against 5HT-induced vascular spasm ran parallel with their potency as tranquillizers.

Table 1 pA_2 values in perfused hindquarters of rats

Agonist	*Antagonist (B)*	*No. of expts.*	*Mean slope of regression of log (DR-1) on log (B) & 95% conf. limits*	*Mean value of pA_2 and 95% conf. limits*
5HT	Promazine	12	1.08 (0.77–1.39)	7.72 (6.99–8.65)
5HT	Chlorpromazine	19	0.88 (0.65–1.11)	8.97 (7.94–10.23)
5HT	Triflupromazine	12	0.76 (0.48–1.04)	10.34 (9.19–12.17)
5HT	Phentolamine	9	0.76 (0.48–1.03)	6.62 (5.68–7.80)
Noradrenaline	Phentolamine	8	0.96 (0.86–1.06)	8.23 (7.92–8.57)
Tryptamine	Chlorpromazine	10	0.89 (0.63–1.15)	9.07 (8.43–9.92)
Tryptamine with Nialamide 0.1 mM	Chlorpromazine	7	1.01 (0.46–1.56)	9.15 (7.99–11.22)
5-Methyltryptamine with Nialamide 0.1 mM	Chlorpromazine	4	1.24 (0.66–1.83)	8.54 (7.98–9.64)
5-Methoxytryptamine with Nialamide 0.1 mM	Chlorpromazine	6	1.04 (0.81–1.27)	8.86 (8.38–9.43)

The effect of SQ 14225 on baroreceptor reflex sensitivity in conscious normotensive rabbits

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SQ 14225 (2-D-methyl-3-mercaptopropanoyl-L-proline) is a new dipeptidase inhibitor which prevents angiotensin II formation and bradykinin inactivation (converting enzyme inhibitor, C.E.I.). It has been shown to have a hypotensive effect in essential and renovascular hypertension in man (Gavras, Brunner, Turini, Kershaw, Tifft, Cuttelod, Gavras, Vukovich & McKinstry, 1978), not significantly increasing heart rate in spite of significant falls in blood pressure. In the salt depleted dog another C.E.I. SQ 20881 was found to reduce the increase in cardiac output in response to a pressure fall (Conway, Hatton & Keddie, 1978). We have investigated the effects of intravenous

SQ 14225 on the blood pressure and heart rate of conscious normotensive rabbits and measured baroreceptor reflex sensitivity.

SQ 14225 (1.0 mg kg^{-1}) had no effect on the pressor action of angiotensin II, but produced a profound inhibition of the pressor response to angiotensin I and potentiation of the depressor response to bradykinin for at least two hours. SQ 14225 (0.1–10 mg kg^{-1}) had no consistent dose related effect on mean arterial pressure but caused a small increase in heart rate at all doses.

Plasma noradrenaline was not changed 45 min after vehicle injection but was significantly increased from 0.400 ± 0.067 μg/l before to 0.545 ± 0.105 μg/l after SQ 14225 ($P < 0.05$). Similar increases in noradrenaline have been reported after the angiotensin II antagonist, saralasin in man (McGrath, Ledingham & Benedict, 1977). The effects on heart rate and plasma noradrenaline could be baroreceptor reflex mediated or a result of direct release of catecholamines (Peach, 1971).

Baroreceptor sensitivity was assessed by measuring the heart period (heart $rate^{-1}$) after pharmacological manipulation of mean arterial pressures. Blood pressure was increased using bolus intravenous doses of phenylephrine (10–50 μg) and reduced by sodium nitroprusside (100–500 μg). There was a highly significant linear relationship between heart period and mean arterial pressure in each animal (r = 0.83–0.96). The slope of the linear regression of heart period against mean arterial pressure was used as an index of baroreceptor reflex sensitivity.

Mean baroreceptor sensitivity was 3.7 ms mm Hg^{-1} before C.E.I. ($n = 7$). 45–75 min after SQ 14225 1 mg/kg, there was a significant reduction in baroreflex sensitivity to 2.3 ms mm Hg^{-1} ($P < 0.001$). In a further group of 5 rabbits baroreflex sensitivity was determined before and after the same volume of 0.9% saline vehicle. There was no significant difference in slope (3.2 and 3.0 ms mm Hg^{-1} before and after). The present experiments, however, do not permit a precise localization of this effect nor can they distinguish between effects of angiotensin II formation, bradykinin degradation or other unidentified actions of the agent. Resetting of baroreceptor reflex sensitivity may be therapeutically useful in reducing tachycardia resulting from a pressure fall after this drug.

References

CONWAY, J., HATTON, R. & KEDDIE, J. (1978). Haemodynamic response to converting enzyme inhibitor and saralasin in salt-depleted dogs; relation to plasma renin activity. *Br. J. Pharmac.*, **62**, 448P.

GAVRAS, H., BRUNNER, H., TURINI, G., KERSHAW, G., TIFFT, C., CUTTELOD, S., GAVRAS, I., VUKOVICH, R. & McKINSTRY, D. (1978). Antihypertensive effect of the oral angiotensin converting enzyme inhibitor SQ 14225 in man. *New Eng. J. Med.*, **298**, 991–995.

McGRATH, B.P., LEDINGHAM, J.G.G. & BENEDICT, C.R. (1977). Plasma catecholamines and the pressor response to Sar^1 ala^8 angiotensin II in man. *Clin. Sci. Molec. Med.*, **53**, 341–348.

PEACH, M.J. (1971). Adrenal medullary stimulation by Angiotensin I, Angiotensin II and analogues. *Circ. Res.*, **28**, Suppl. 2, II-107–II-116.

The effect of SQ 14225 on fluid intake in DOCA/salt hypertensive rats

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SQ 14225 (2-D-methyl-3-mercaptopropanoyl-L-proline; Captopril), an orally active inhibitor of angiotensin I-converting enzyme has been shown to reduce blood pressure in 2 kidney Goldblatt hypertension in rats (Leffan, Goldberg, High, Schaeffer, Waugh & Rubin, 1978) and to produce enzyme inhibition in man (Ferguson, Brunner, Turini, Gavras and McKinstry, 1977). We have examined this compound on fluid intake and on the development of hypertension in DOCA/salt rats.

Male Wistar rats (200 g) were made hypertensive by implanting a DOCA pellet (25 mg s.c.) and providing them with 1% w/v NaCl solution (saline) to drink; eight rats were given SQ 14225 (10 mg/kg p.o.) once daily for 14 days (20 mg/kg on the 12th day only) while nine control rats were given equivalent volumes of water p.o. Other animals were sham-operated and drank water; 8 of them were treated with SQ 14225 as above and 7 controls received water. Three to five rats were kept in each cage and mean daily fluid intake was estimated from the total consumption of each group. Systolic b.p. was measured by a tail cuff method.

In all DOCA/salt rats the blood pressure began to rise on the 6th day after implantation, no significant effect being produced by SQ 14225. By contrast, SQ 14225 had a marked effect on fluid intake in these rats. The mean (± s.e. mean) daily intake of saline,