AN INVESTIGATION OF THE CARDIOVASCULAR ACTIONS OF ANGIOTENSIN IN MAN

A THESIS

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GARRY CAMPBELL SCROOP, M.B., B.S.

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GENERAL SUMMARY

An historical survey of the events leading to the discovery of angiotensin was presented in the introduction to the thesis. In a review of the previous observations upon its cardiovascular actions in man and animals, reference was made to the indirect mechanisms in its cardiovascular action. These were of particular interest since the greater part of this thesis is devoted to an exploration of such mechanisms in man.

Initially a comparison was made of the cardiovascular effects of angiotensin and noradrenaline and these experiments are described in the second section. The hand vascular responses were of particular interest and provided the first evidence of an indirect vasoconstrictor mechanism in man. It was found that the local action of angiotensin on the hand vessels was only one half to one third as potent as that of noradrenaline (on a weight basis), whereas on intravenous infusion angiotensin greatly enhanced its constrictor potency in this vascular bed to become eight to ten times more active than noradrenaline. Although the mechanism of this enhanced effect of angiotensin during systemic infusions was not clear from these experiments angiotensin had been shown to release adrenal medullary catecholamines in cats and to stimulate the ~~systemic~~ sympathetic nervous system in dogs and this evidence provided the necessary clues for a further

exploration in man.

The explanation of this phenomenon was presented in the third section of the thesis where angiotensin was shown to have a stimulating action on the sympathetic vasomotor system in man. This action was only seen with systemic infusions and the site of action is preganglionic, possibly in the medullary vasomotor centres. There was no evidence of an increase in the circulating levels of catecholamines and a postganglionic sympathetic stimulating action was excluded.

The contribution of this sympathetic stimulating action to the blood pressure response during acute intravenous infusions of angiotensin in man seems to be a minor one since neither systemic alpha-adrenergic receptor blockade nor various forms of sympathetic denervation were able to reduce the response.

The suggestion that angiotensin may enhance its vasoconstrictor effect by interaction with other circulating vasoactive substances was examined in the fourth section of the thesis. When combinations of angiotensin and noradrenaline and of angiotensin and serotonin were administered to the hand vessels by intra-arterial infusion the constrictor response was greater than could be accounted

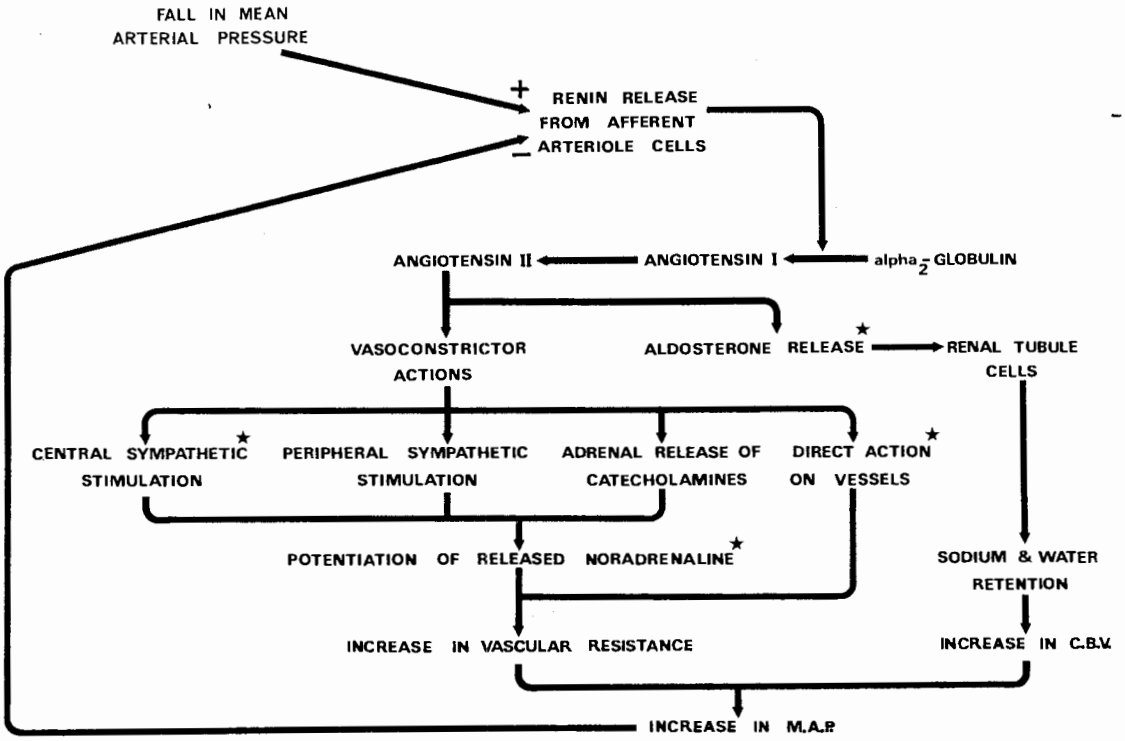
for by summation of effects alone. However, the degree of potentiation was often small and was not seen in the forearm making it unlikely that such interactions make a major contribution to the overall vasoconstrictor action of angiotensin.

To gain some idea of the importance of angiotensin in hypertension a group of such patients were studied in section five and the responses of their hand vessels to local infusions of angiotensin and noradrenaline were examined and correlated with their plasma renin activities. Only the patients with renovascular hypertension exhibited responses which were significantly different from normal. The reduction in vascular sensitivity seen in these patients is to be expected on the basis of the elevated plasma angiotensin levels, although there was no close relationship between the level of plasma renin activity and the hand vascular responses.

The possibility that the small doses of angiotensin permissible in the human experiments were insufficient to fully activate the sympathetic stimulating action of the drug or release detectable amounts of adrenal catecholamines was examined in the last section of the thesis, using anaesthetized dogs as subjects where larger doses could be given. However, the results from these experiments were basically the same as those in man in that,although angiotensin stimulated sympathetic vasoconstrictor fibres to the upper limb,

total alpha- and beta-receptor blockade did not reduce the pressor response. In fact, the pressor response was greatly enhanced following alpha-receptor blockade. There was no evidence of an increase in the circulating levels of catecholamines.

In conclusion, the vasoconstrictor action of angiotensin is a complex of direct and indirect factors. Some of these are indicated in Fig. 7-1. The work described in this thesis provides the first evidence of a sympathetic component in the vasoconstrictor action of angiotensin in man and evidence was also presented of potentiating interactions between angiotensin and other vasoactive substances. However, the direct action of angiotensin, which is presumably on specific receptors, makes the most important contribution to its overall vasoconstrictor effect, at least during short-term infusions in man.



Fir. 7-1 A simplified version of the renin-angiotensin system with emphasis on the components of the vasoconstrictor action. Those indirect mechanisms of action for which there is evidence in man are indicated thus * .