REVIEW OF THE LITERATURE

EFFECTS ON CIRCULATION

1. Heart:- In the intact animal the intravenous infusion of angiotensin leads to a slowing of the heart rate and a decrease in cardiac output secondarily (16,26). In the intact non-anaesthetised animal, however, the influence of the peripheral circulation and the nervous system as well as hormonal effects, such as the release of adrenaline from the suprarenal (33), have to be taken into account.

It is important to turn to studies on the isolated heart. An earlier study was that of Bianchi et al.(11) on the isolated heart of guinea-pigs and rabbits; very large doses of angiotensin (100-1,000/ug) produced a decrease of contractile force and coronary flow, followed by an increase. Berry et al. (10), using an isolated heart with an oxygenator, found slowing of sinus rate when the angiotensin reached the heart, followed by rise in rate and force of contraction. They suggested that the direct effect on either the myocardium or coronary vessels was responsible for the initial depressor effect. The beta blocker pronethalol (nethalide) in a dose of 2.5 mg per kg prevented the change in rate and contractile force; this suggests an action

via the sympathetics. Fowler and Holmes (36) showed in the dog that there was a decrease of cardiac output and ventricular force with rise of atrial pressure. In the cat, when left ventricular function was studied relatively independently, continuous infusion of angiotensin led to myocardial depression and lowered coronary blood flow.

In contrast, noradrenaline caused a large increase in ventricular contractility and an increase in coronary flow (32). The effect of angiotensin on isolated ventricular and atrial muscle shows varying results. Koch-Weser (53) used isolated kitten papillary muscle and claimed a consistent positive inotropic action. It was not as potent as noradrenaline (wt/wt). Fowler and Holmes (36) confirmed this in the cat. On the isolated atrium, the resting and stretching tension development was unaffected. No ectopic impulses arose and there was no direct effect on the sino-atrial node. Unlike sympathomimetic amines, angiotensin caused no increase in duration of systole. The increased force of contraction appeared with concentrations of 10^{-9}M in the bath. Appreciably higher concentrations were obtained in the blood during therapeutic or experimental administration of angiotensin at rates of 1.6 to 5.2 µg per minute (53).

Previously Yu et al. (89) suggested that infusion of 1 µg per kg per minute increased myocardial contractility, but this was in the intact subject. Beaulnes (8), using cat papillary muscle and the atria of cat and rabbit, found increased rate and strength of contraction at concentrations of angiotensin less than 0.1 µg per ml; above this, depression occurred. The concentration of 0.1 µg per ml represents an enormous dose in the whole animal. The action on isolated cardiac muscle was blocked by dichloroisoproterenol (DCI) as well as by noradrenaline; this result suggests that part of the action was due to liberation of catecholamines. However, the dose-response curve on the atria of the rabbit was not altered by reserpine, which causes depletion of catecholamines.

In discussing cardiac function, apart from a direct action on cardiac muscle, the effect of angiotensin on the coronary arteries is important (67). Fowler and Holmes (36) found that direct injection of 1 ug into the coronary artery of the dog caused constriction, as did infusion intravenously, with blood levels calculated at 0.42 µg per litre. In the cat heart Downing and Sonnenblick (32) found slight reduction of coronary blood flow, whereas noradrenaline produced an increase.

Bianchi et al. (11), using massive doses of angiotensin also found a decrease. Further studies with much lower doses of angiotensin injected into the coronary artery would seem to be desirable to draw a final conclusion.

Despite difficulties of interpretation of the effect of angiotensin in the whole animal, there is general unanimity about cardiac actions. In man the bradycardia induced as the pressure goes up decreases the cardiac output when the infusion rate is between 0.02 and 0.1 µg per kg per minute (26). The bradycardia is almost certainly mediated reflexly through the vagus, for it can be blocked by atropine (19). As the systemic pressure rises, cardiac work increases, and, probably for this reason, the venous pressure rises in every species studied (2,16,26,34). When the rise in arterial pressure was buffered by a mechanical compensator in dogs, there was little change in heart rate. Denervation of the sino-aortic area led to increase of blood pressure and heart rate with intravenous injection of 10 µg angiotensin (68). Interpretation of direct cardiac action in the intact animal at the smaller dose range is difficult to analyse. There is little evidence of a marked direct stimulating or depressive action on the heart in the dose range which produces marked peripheral haemodynamic effects.

2. Regional circulation:- There has been dispute as to whether angiotensin constricts pulmonary arteries. In normal man, when angiotensin is infused intravenously, pulmonary artery pressure rises before any rise in the systemic pressure; this points to pulmonary vaso-constriction (26). The most likely conclusion is that there is an increase of pulmonary artery resistance and pulmonary artery pressure. This is not as marked as the effect on the systemic vessels and it is overshadowed by the systemic effects.

The general effect of intravenous infusion of angiotensin is to increase the total peripheral resistance (18,26,34,48). This is brought about by increased resistance in all territories studied, e.g., skin (18,26), muscle (18), splanchnic area and liver (6,25,26,78), and the kidney (7,15,17,26,34,91). Barer's study directly on renal blood flow in the cat (7) confirms the conclusions of studies of renal and splanchnic blood flow by indirect means in man. Bradykinin could antagonise the reduction in renal flow due to angiotensin.

There have been few measurements of cerebral flow but Ikeda et al. (47), using the unanaesthetised rabbit, showed that angiotensin constricts the vascular bed

of both the internal carotid and external carotid, in contrast to noradrenaline, which had a definite effect only on external carotid flow. The dose comparison is interesting since 0.1 µg of angiotensin octapeptide reduced internal carotid flow, whereas 5 µg noradrenaline did not. Doses upto 5 µg per minute of angiotensin had no obvious effect on cerebral performance in man (26).

In the human retina (31) the arteriolar calibre was more markedly reduced with angiotensin than with noradrenaline and, somewhat surprisingly, the retinal veins were reduced more by angiotensin than by noradrenaline. This effect on the veins will be discussed later since noradrenaline is a more potent venoconstrictor than angiotensin (wt/wt). Measurement of pressure drops down the arterial tree in the upper limb suggested that the major site of action of angiotensin was on the small arterioles (50).

3. Effects on small vessels:- It has already been suggested that the major effect of angiotensin is on the arterioles and that the rise in venous pressure is mainly associated with increased cardiac work (26). Haddy et al. (42), using the dog forelimb and mesentery and the rabbit ear, showed that the effect was largely on the arterioles, especially in the mesentery.

There was little effect on venous pressure in small veins. With a predominantly arteriolar effect, one of the consequences of intra-arterial administration would be a sharp fall in post-capillary venous pressure. Watson (86) studied this problem by measuring the vascular distensibility of the veins in the hand.

Angiotensin reduced the venous distensibility as would be expected. Folkow and his colleagues (35) measured inflow pressure and limb volume simultaneously in the cat forelimb and showed that while angiotensin raises the inflow arterial pressure more markedly than noradrenaline, it has little effect on limb volume, in contrast to the large reduction produced by noradrenaline. This means that there is little constriction of veins by angiotensin and much by noradrenaline. In the forearm veins of man, de Pasquale and Burch (28) could not show an effect of angiotensin on venous tone, in contrast to noradrenaline. There were similar findings on pre- and postcapillary vessels in the finger (27). The reduction of the calibre of the retinal veins observed by Dollery et al. (31) is presumably due to reduction in blood flow through the arterioles.

4. Effects on the kidney:- The effect of angiotensin in general on renal function in different animals is variable. In normal man, intravenous infusion at all dose levels produced an antidiuresis and reduction in excretion of electrolytes (17,26). In the rabbit or rat, diuresis and increased excretion of electrolytes are the rule (46,72,73,79). The effect on renal function is almost immediate and, as Barer (7) has shown in the cat, there is always a reduction in renal blood flow. In man, reduction in urine flow and sodium output is accompanied by reduction in the clearance of inulin, creatinine and para-aminohippurate.

It seems likely that, whithin the dose range 0.04 to 0.4 µg per kg per minute intravenously, a reduced glomerular filtration rate dué to a vascular effect might cause the decreased sodium output. It has been strongly suggested that angiotensin must have a direct action on tubular re-absorption of sodium to explain the diuresis and natriuresis seen in the rat, rabbit and dog.

In man with hypertension, infusion of doses of the order of 0.04 to 0.4 µg per kg per minute causes diuresis with natriuresis (22). The return of the blood pressure to normal achieved by either surgical correction of unilateral obstruction of the renal artery or

unilateral nephrectomy, or by the use of hypotensive drugs, leads to a return of the normal antidiuresis. The effect of angiotensin on inulin and PAH clearance is negligible in the hypertensive subject and marked in the normal. This fact suggests that the renal resistance vessels show little response to angiotensin at the high pressures, and when the blood pressure is brought down, the response to angiotensin is restored to normal. This interpretation implies that it is the effect of the blood pressure on the vessels which prevents the action of angiotensin. A direct tubular action of angiotensin, preventing sodium re-absorption, might be revealed because the renal vessels in the hypertensive subject have become insensitive.

Since it is possible to bring about both antidiuresis in normal man and diuresis in hypertensive man without altering the perfusion pressure (22), there must be a local effect. Changes in glomerular filtration rate too small to be measured with current techniques, produced by variations in afferent and efferent arteriolar pressure, would probably be enough to allow for some of the changes in water and sodium output. In patients with cirrhosis and ascites there was a diuretic response like that shown in subjects with hypertension (55,56).

As these subjects usually have high rates of aldosterone secretion with sodium retention and low urinary sodium, the relation of angiotensin to aldosterone has to be considered. Since angiotensin stimulates the production of aldosterone (38,54) in doses which are subpressor or marginally pressor in man (13,54) or dog (82,83), then the possible modifying role of aldosterone on the renal response to angiotensin needs evaluation. As pointed out earlier, the effect of angiotensin on renal performance is immediate and leads to a decrease in excretion of sodium and potassium. The effect of aldosterone injected into the renal artery is delayed for half an hour and then causes sodium retention and increased potassium excretion. Even though some of the renal action of angiotensin must be exerted through aldosterone, a large part of it cannot.

Some normal subjects deprived of sodium and presumed to have a high secretion of aldosterone, may show a diuresis and natriuresis with angiotensin (55). One might speculate that in these circumstances angiotensin is acting directly as an aldosterone antagonist comparable to spironolactone. The adrenals are not essential to the antidiuretic action of angiotensin (80), nor is the posterior pituitary, as in

patients with diabetes insipidus (26). Since angiotensin has such marked actions on renal function, it is important to consider the possible effects of local intra-renal release, shown by the presence of renin and angiotensin in renal lymph (59). Alteration in blood flow even with cortical necrosis, or direct effect on tubular re-absorption, could occur.

5. Modes of action:- The relation of angiotensin to the nervous system, and also release of catecholamines from the adrenal medulla, has also received attention. The first observation was in the cat where, after cocaine, angiotensin caused contraction of the nictitating membrane and phenoxybenzamine blocked this effect (75). This was possibly the first indirect demonstration of the release of adrenaline and noradrenaline from the adrenal medulla by angiotensin. Subsequently, direct intra-arterial injection of angiotensin was shown to release adrenaline, as indicated by contraction of the nictitating membrane (33).

In the rat, suprarenalectomy reduced the action of angiotensin, and direct perfusion of the suprarenals with angiotensin led to increased output of catecholamines (24). It has been shown in the dog that infusion of DMPP (1, 1-dimethyl-4-phenylpiperazinium iodide),

a ganglion stimulating agent, caused increased pressor response to angiotensin (49). It was believed this was a form of sensitisation, but obviously adrenal discharge of adrenaline and noradrenaline occurred, since phentolamine or adrenalectomy removed the response. Stimulation of the superior cervical ganglion of the cat by angiotensin (0.1 to 0.3 µg), causing contraction of the nictitating membrane, has been reported (60). Ganglionectomy or cutting the postganglionic fibers abolished the response. Whether these effects are important in the haemodynamic actions of angiotensin is further raised by the work of Buckley et al. (12,23) who showed that angiotensin (0.2 to 0.4 µg per kg) had a central action in the internal carotid artery territory. The central pressor responses could be blocked by benzodioxane while the effects of intravenous injection of angiotensin were unchanged. Denervation of the carotid sinus area had no effect. There were similar observations on the rat brain (58).

McCubbin and Page (64,65) claimed that infusion of angiotensin or renin in small amount increased the response to various drugs or reflexes initiated in the sympathetic nervous system. Since response to injected noradrenaline was little affected, this action depended upon some other factor in the sympathetic

nervous system. They suggested that this mechanism, which appears very quickly after renal artery constriction in the dog, may indicate that one aspect of renal clip hypertension might be an increased responsiveness of the vascular system to some substances like tyramine. Direct application of angiotensin to the carotid sinus had little effect on its activity compared with that of noradrenaline (66).

Another relation of angiotensin to the nervous system is brought out by the contraction of the isolated intestine. Robertson and Rubin (77) found that a natural angiotensin was blocked by an anticholinesterase. Botulinum toxin denervated the ileum by interference with the cholinergic supply, and, while the response to acetylcholine was unaltered, that to angiotensin was abolished. Khairallah and Page (51,52) had previously found that atropine would antagonise angiotensin on the guineapig ileum. The direct action of angiotensin on ileal smooth muscle was shown to be slight.

Both the oxytocic action and gut contraction were decreased by adrenaline and noradrenaline. Adrenergic blockers, such as phenoxybenzamine and phentolamine, also blocked the action of angiotensin on these two tissues. This is an odd occurrence and is perhaps to

be attributed to a non-specific action of the adrenergic blockers. Walaszek et al. (85) confirmed the blocking effect of atropine on the ileum and found that the action of substance P was similarly blocked. Morphine shared with phenoxybenzamine the property of blocking the effect of angiotensin, although that of bradykinin was not affected. In another study (9), contraction of the vas deferens of the guinea-pig, stimulated via the hypogastric nerve, was strongly potentiated by angiotensin, which did not itself cause contraction.

Spleenic contraction in the cat behaved similarly. Further, in anaesthetised and spinal cats in which sympathetic post-ganglionic transmission was blocked by nicotine or tetramethylammonium, the pressor responses were reduced. In keeping with the other evidence, this supports the idea that angiotensin may increase the local release or effect of noradrenaline on stimulation of the nerve but is incapable of releasing noradrenaline from stores in smooth muscle tissue despite its ability to release adrenaline from the suprarenal. The pressor response that slowly develops over a few days when small concentrations of angiotensin (0.006 to 0.02 μg per kg per minute) are given intravenously to the rabbit, may be related to an effect either on ganglia or on the brain (30).

The oxytocic action of angiotensin on the rat uterus seemed to depend upon the presence of calcium for its action (29). The use of various smooth muscles to distinguish between angiotensin, bradykinin, oxytocin, vasopressin and substance P has been described (14). It was shown that the rat uterus and guinea-pig ileum seemed to be the most sensitive structures for angiotensin, followed by the rat colon. Recently the rat colon has been described as a discriminating and sensitive test for angiotensin (74).

It is possible that there are two different contractile systems for vascular muscle, the one for transient regulation of tension, the other for the maintenance of tonic contraction. The tension of the latter seems to depend on the concentration of potassium in muscular cells (57).

The evidence at present for this seems a little indirect but the idea is of considerable interest. In view of the effects of angiotensin on renal function, its lack of effect on sodium transport in the abdominal skin of the toad, in contrast to vasopressin, is striking (4,5).