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A COMPARISON OF THE ABILITY OF TWO ANGIOTENSIN II RECEPTOR BLOCKING DRUGS, 1-SAR, 8-ALA ANGIOTENSIN II AND 1-SAR, 8-ILE ANGIOTENSIN II, TO MODIFY THE REGULATION OF GLOMERULAR FILTRATION RATE IN THE CAT

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1 Modest stimulation of the renal nerves in the anaesthetized unilaterally nephrectomized cat resulted in a 15% fall in renal blood flow, no change in glomerular filtration rate and significant falls in both the absolute and fractional rates of sodium excretion.

2 The haemodynamic responses to nerve stimulation were not modified by angiotensin II blockade with 1-Sar, 8-Ala angiotensin II although the fall in absolute, but not fractional sodium excretion was significantly larger. In contrast, stimulation of renal nerves following administration of 1-Sar, 8-Ile-angiotensin II caused a significant fall in glomerular filtration rate. The reductions in both absolute and fractional sodium were of the same magnitude as in the absence of drug.

3 Both renal blood flow and glomerular filtration rate were autoregulated during the reduction of renal perfusion pressure and this was associated with reductions in both absolute and fractional sodium excretions.

4 In the presence of 1-Sar, 8-Ala angiotensin II, the haemodynamic and sodium excretory responses to reductions in renal perfusion pressure were not significantly different from those recorded in the absence of drug. However, following administration of 1-Sar, 8-Ile angiotensin II, renal blood flow but not glomerular filtration rate, was autoregulated during reduction in renal perfusion pressure. The falls in absolute and fractional sodium excretions caused by this manoeuvre were of similar magnitude to those obtained in the absence of drug.

5 The results obtained using the 1-Sar, 8-Ile angiotensin II are consistent with angiotensin II having an important intra-renal site of action to regulate glomerular filtration rate, possibly via an action at the efferent arteriole. Administration of 1-Sar, 8-Ala angiotensin II was without effect on the regulation of renal haemodynamics which it is suggested reflects a limitation in the use of this particular compound as an intrarenal angiotensin II antagonist.

Introduction

Two major groups of compounds have been developed which block the activity of the renin-angiotensin system. Firstly there are the converting enzyme inhibitors, captopril (SQ14,225) and teprotide (SQ20,881), which block conversion of angiotensin I to the active angiotensin II. However, converting enzyme is also responsible for the breakdown of bradykinin (Erdös, 1977; Rubin, Antonaccio & Horovitz, 1978) and its action is therefore potentiated in the presence of these compounds. The other major group of compounds are the angiotensin II analogues in which different amino acids are substituted into the peptide chain and which act as angiotensin II receptor blocking drugs. Many of these analogues have been shown to have agonist properties (Marshall, 1976; Wallace, Case, Laragh, Keim, Drayer & Sealey, 1979) which may become more important than their antagonist properties under certain conditions. The limitations of both groups of compounds may well hinder the interpretation of experimental results concerning the renin-angiotensin system particularly at intrarenal sites of action.

At present the intrarenal role of angiotensin in the control of either renal haemodynamics or tubular electrolyte handling is uncertain. Several recent reports have suggested that angiotensin II has an important action at the level of the arterioles particularly at the efferent arteriole where it influences the rate of glomerular filtration. The evidence for this is found in the papers of Hall, Coleman, Guyton, Balfe & Salgado (1979) and Johns (1979) who found that following administration of SQ20,881, autoregulation

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of glomerular filtration rate in response to changes in renal perfusion pressure was much reduced.

However, studies in which angiotensin II receptor blocking drugs have been used to examine the control of renal function have produced conflicting results. Administration of 1-Sar, 8-Gly angiotensin II (Anderson, Taher, Cronin, McDonald & Schrier, 1975) or 1-Sar, 8-Ala angiotensin II to isolated perfused kidneys (Kaloyanides & DiBona, 1976) did not impair autoregulation of glomerular filtration rate in response to changes in perfusion pressure. In contrast, in the study of Hall, Guyton, Jackson, Coleman, Lohmeirer & Trippodo (1977b) in which 1-Sar, 8-Ile-angiotensin II was used, a marked reduction was found in the ability of the kidney to control glomerular filtration rate when perfusion pressure was altered. In all studies, the ability to autoregulate renal blood flow was unaffected. The reason for these different results is not clear, but could result from the differing characteristics of the various receptor blocking drugs used.

In our previous studies a somewhat different approach was used to examine the role of angiotensin in the local control of renal haemodynamics. We observed that stimulation of the renal nerves resulted in renin release which, if blocked by propranolol (Johns, Lewis & Singer, 1976) or its activity inhibited by SQ20,881 (Johns, 1979) led to an inability to regulate glomerular filtration appropriately thereby providing further support to the suggestion that angiotensin II was involved in the regulation of filtration rate. To discover whether similar observations would be recorded in the presence of angiotensin II receptor blocking drugs was one of the objectives of this investigation.

In the present study a comparison has been made of the effectiveness of two angiotensin II receptor blocking drugs, 1-Sar, 8-Ala angiotensin II and 1-Sar, 8-Ile angiotensin II, in blocking the ability of the kidney to regulate glomerular filtration rate. Two differing experimental manoeuvres were used, that of reduction of renal perfusion pressure and modest stimulation of the renal nerves, during which regulation of glomerular filtration had been previously shown to occur.

Methods

Male cats in the weight range 2.4 to 4.7 kg, were maintained on a regular cat food (Whiskas, Pedigree Petfoods) which provided a normal sodium intake. Anaesthesia was induced with sodium pentobarbitone (168 μmol/kg i.p.) and supplemented with small intravenous doses as necessary. The carotid artery was cannulated to allow measurement of blood pressure (Statham p 23 Dc transducer connected to a Grass model 7 Polygraph) and removal of blood samples. The right jugular vein was cannulated to allow infusion of saline (150 mM/l NaCl) and drugs. Heart rate was monitored by means of a tachygraph (Grass) triggered by the arterial pulse wave.

In all experiments the right kidney was removed retroperitoneally while the left kidney was exposed using a similar approach. Renal blood flow was measured by means of a non-cannulating flow probe (Biotronix) and flowmeter (S.E. Labs. M275). The left ureter was cannulated to allow collection of urine. Heparin was administered (1000 iu/kg) on completion of all surgical manoeuvres.

Experimental protocol

Renal nerve stimulation Preparation of the nerves for stimulation was as previously described (Coote, Johns, Macleod & Singer, 1972). The distal cut ends of the nerve were placed on silver wire electrodes and stimulated for periods of 18 min with square wave stimuli of 15V, 0.2 ms duration obtained from a stimulator (Grass S8). Renal blood flow was reduced by approximately 15% during this period which required frequencies of between 0.8 and 6.0 Hz.

Reduction of renal perfusion pressure Renal perfusion pressure to the denervated kidney was reduced by tightening a cotton loop that had been placed around the aorta 1 to 2 cm above the level of the renal artery (Johns & Singer, 1974). Renal perfusion pressure was recorded from a cannula the tip of which lay in the aorta at the level of the renal artery and which had been introduced via the femoral artery. Renal perfusion pressure was reduced, for periods of 18 min, by 25 mmHg such that the lowered pressure was still within the autoregulatory range.

Blood sampling Blood samples (0.6 ml) were removed at regular intervals throughout the experiment. Following centrifugation at 0°C, the plasma was removed, the cells resuspended in saline and then reinfused after removal of the subsequent sample.

Infusions As soon as the jugular vein was cannulated an infusion of saline at 12 ml/h was begun. On completion of the surgical procedures, a priming dose of inulin was given (i.v.) and the infusion changed to one containing inulin (Johns, 1979). No experiments were begun less than 60 min after the administration of the inulin priming dose. The angiotensin antagonists were dissolved in saline and given at 1.2 ml/h. Two analogues were used, 1-Sar, 8-Ile angiotensin II (Bachem, California) which was administered between 3 to 7 μg kg^{-1} h^{-1}, and 1-Sar, 8-Ala angiotensin II (Bachem, California) which was administered at 6 μg kg^{-1} h^{-1}. A bolus injection of 50 ng (on one occasion 100 ng) of angiotensin II (Hypertensin, CIBA Ltd.) was given in-

travenously. In the 14 animals tested this resulted in a prompt rise in arterial blood pressure of between 20 and 36 mmHg. Infusion of the appropriate analogue was begun and after 10 to 15 min of infusion a second dose of 50 ng (or 100 ng) angiotensin II was given. The blood pressure response to this dose of angiotensin was found to be completely abolished in all animals. A similar test dose of angiotensin II at the end of the experiment confirmed maintenance of the blockade.

Experimental procedure Usually up to 3 experiments were carried out in any one animal although in 2 cats 4 experiments were undertaken. Each experiment consisted of five sequential clearance periods of 15 min duration each; two immediately before the experimental procedure; one period during either nerve stimulation or pressure reduction, which was begun 3 min after application of the experimental manoeuvre; two clearance periods immediately after the end of the experimental procedure. Comparisons were made between the variable measured during either nerve stimulation or reduced perfusion pressure, and a mean of the two clearance periods before and the two clearance periods after the experimental manoeuvre. The drugs were administered usually after the first or second experiments. The absolute and percentage changes were calculated as a mean of the individual changes recorded in each experiment.

In order to determine the effect of administration of the angiotensin II antagonists, a comparison was made between the mean value of the two clearance periods before and the two clearance periods after angiotensin II blockade had been achieved.

Analyses Plasma and urinary sodium concentration were determined with a Beckman Flame Photometer. Absolute sodium excretion was the product of urinary flow rate and sodium concentration and expressed as μmol min^{-1} kg^{-1}. Fractional sodium excretion was calculated as absolute sodium excretion divided by glomerular filtration rate and expressed as a percentage times 10^{-3}, which took into account any changes in the rate at which sodium was filtered. Duplicate estimation of inulin were performed on deproteinised plasma and urine (Somoggi, 1930) by the method of Bojesen (1952). Glomerular filtration rate was measured as the clearance of inulin and expressed as ml min^{-1} kg^{-1} body weight.

Statistics An unpaired Student's t test was applied to determine the significance of differences between the magntiude of the responses in the various groups. A paired Student's t test was used to determine the significance of the changes within a group following administration of the angiotensin analogues.

Results

Administration of angiotensin analogues

Administration of 1-Sar, 8-Ala angiotensin II in 5 animals and 1-Sar, 8-Ile angiotensin II in 6 animals caused no significant changes in systemic blood pressure, renal blood flow, glomerular filtration rate, or fractional sodium excretion. Although the infusion of 1-Sar, 8-Ala angiotensin II did not influence absolute sodium excretion, in those animals given 1-Sar, 8-Ile-angiotensin II absolute sodium excretion fell significantly from 17.18 ± 3.56 to 13.44 ± 2.6 μmol min^{-1} kg^{-1} ($P < 0.05$).

Renal nerve stimulation

The changes in renal function resulting from nerve stimulation in the absence and presence of the angiotensin II antagonists are presented in Table 1. The results obtained in the absence of drug were from 7 animals, the 1-Sar, 8-Ala angiotensin II results from 6 animals and the 1-Sar, 8-Ile angiotensin II results from 4 animals. Stimulation of the renal nerves reduced renal blood flow by 2.11 ± 0.19 ml min^{-1} kg^{-1} when no drug was present and by 1.87 ± 0.12 ml min^{-1} kg^{-1} following 1-Sar, 8-Ile angiotensin II administration which were not different statistically ($P > 0.2$). In the experiments carried out in the presence of 1-Sar, 8-Ala angiotensin II, control values of renal blood flow were higher than in the absence of drug but during stimulation were reduced by a mean of 3.13 ± 0.42 ml $min^{-1}kg^{-1}$ which was slightly but statistically larger ($P < 0.05$) than the reduction recorded in the absence of drug, which was due to the slightly larger control values in the animals receiving 1-Sar, 8-Ala angiotensin II. However, these changes in renal blood flow represented reductions of 14.8% in the absence of drug, 16.8% in the 1-Sar, 8-Ala angiotensin II experiments and 16.3% in the 1-Sar, 8-Ile-experiments, responses which could not be distinguished statistically.

Glomerular filtration rate was not significantly changed during nerve stimulation (Table 1), a response which has been demonstrated previously (Johns, 1979). Stimulation of the renal nerves during 1-Sar, 8-Ala angiotensin II infusion caused a slight fall in glomerular filtration rate (0.19 ± 0.12 ml min^{-1} kg^{-1} or 7%) which was not statistically different from the response recorded in the absence of drug, whether analysed in terms of absolute changes or percentage changes. In those experiments in which 1-Sar, 8-Ile-angiotensin II was administered, glomerular filtration rate fell by 0.37 ± 0.11 ml min^{-1} kg^{-1} (or 18%) during renal nerve stimulation which was a significantly greater ($P < 0.01$) response than that observed in the absence of drugs.

Table 1 Effect of renal nerve stimulation on renal function in the absence and presence of 1-Sar, 8-Ala angiotensin II or 1-Sar, 8-Ile angiotensin II

	No drug		*1-Sar, 8-Ala angiotensin II*		*1-Sar, 8-Ile angiotensin II*	
	Control ($n = 7$)	*Stimulation* ($n = 7$)	*Control* ($n = 9$)	*Stimulation* ($n = 9$)	*Control* ($n = 12$)	*Stimulation* ($n = 12$)
Renal blood flow (ml $min^{-1}kg^{-1}$)	13.66 ± 0.41	11.56 ± 0.67	19.74 ± 0.77	16.61 ± 1.26*	12.17 ± 0.31	10.31 ± 0.70
GFR (ml $min^{-1}kg^{-1}$)	1.72 ± 0.09	1.78 ± 0.16	2.46 ± 0.15	2.24 ± 0.26	1.84 ± 0.08	1.47 ± 0.04*
Fractional sodium excretion ($\times 10^{-3}$%)	38.4 ± 4.0	21.0 ± 5.0	73.9 ± 7.7	43.0 ± 13.9	29.0 ± 2.0	11.0 ± 1.0
Absolute sodium excretion (μmol $min^{-1}kg^{-1}$)	10.30 ± 1.10	6.04 ± 1.70	20.17 ± 0.81	10.30 ± 2.33*	7.99 ± 0.44	2.56 ± 0.34

Mean values ± s.e. mean are shown; GFR = glomerular filtration rate. n = no. of trials.
*$P < 0.05$. Values for P are for comparisons of the absolute change for each variable, in response to renal nerve stimulation, in the absence and in the presence of each drug

Stimulation of the renal nerves caused large reductions in fractional sodium excretion of 18.0 ± 4.0 × 10^{-3}% in the absence of drug which was a response not statistically different from that observed following 1-Sar, 8-Ala angiotensin II administration (30.8 ± 6.9 × 10^{-3}%) or from that measured following 1-Sar, 8-Ile angiotensin II administration (18.0 ± 1.0 × 10^{-3}%). Absolute sodium excretion fell by 4.35 ± 1.00 μmol min^{-1} kg^{-1} during stimulation of the nerves and by 5.52 ± 0.40 μmol min^{-1} kg^{-1} when the nerves were stimulated in the presence of 1-Sar, 8-Ile angiotensin II, responses which were not significantly different. However, stimulation of the nerves in the presence of 1-Sar, 8-Ala angiotensin II resulted in a large fall in absolute sodium excretion (9.87 ± 1.81 μmol min^{-1} kg^{-1}) which was significantly different from the response in the absence of drug ($P < 0.02$). The rate of absolute sodium excretion in the 1-Sar, 8-Ala group of animals was much higher than that recorded in the group of animals in which no drug was present, and if the data are compared on a percentage basis, there was a fall of 46% in absolute sodium excretion during nerve stimulation when no drug was present and of 51% in the presence of 1-Sar, 8-Ala angiotensin II, responses which were not statistically different.

Reduction in renal perfusion pressure

It was the aim of this study to examine the renal responses to a reduction in renal perfusion pressure of approximately 25 mmHg and within the autoregulatory range both before and following administration of the angiotensin II antagonists. Eight experiments were carried out in 5 animals in the absence of drug in which renal perfusion pressure was reduced from a mean of 133.4 ± 3.8 to 108.0 ± 4.7 mmHg during constriction. Ten experiments were carried out in 3 animals following 1-Sar, 8-Ala angiotensin II administration, and renal perfusion pressure was reduced from a mean of 121.8 ± 2.9 to 98.6 ± 4.1 mmHg during constriction. Eight experiments were carried out in 4 animals following 1-Sar, 8-Ile angiotensin II administration with renal perfusion pressure being reduced from a mean of 127.5 ± 4.0 to 101.0 ± 4.7 mmHg during constriction. In each group of experiments the value of renal perfusion pressure reached during aortic constriction was well within the accepted range for autoregulation and the magnitude of reduction was very similar in each of the groups.

The responses in renal function to reduction of renal perfusion pressure are shown in Table 2. In the absence of antagonists, a reduction in perfusion pressure caused a minor fall in renal blood flow of 0.33 ± 0.14 ml min^{-1} kg^{-1} (amounting to 2%). A similar small fall in renal blood flow of 0.55 ± 0.32 ml min^{-1} kg^{-1} was recorded following the reduction in perfusion pressure during 1-Sar, 8-Ala angiotensin II administration. However, during 1-Sar, 8-Ile angiotensin II infusion, renal blood flow rose slightly by 0.25 ± 0.17 ml min^{-1} kg^{-1} (amounting to a 1% rise) when pressure was reduced which was significantly different from the response in the absence of drug ($P < 0.05$). It is probable that these small changes are of only minor physiological significance.

Glomerular filtration rate rose slightly (by 4%) when pressure was reduced in the absence of drug and fell slightly (by 0.62%) in those experiments carried out in the presence of 1-Sar, 8-Ala angiotensin II. However, glomerular filtration rate fell (by 5.4%)

Table 2 Effect of reduction in renal perfusion pressure on renal function in the absence and presence of 1-Sar, 8-Ala angiotensin II or 1-Sar, 8-Ile angiotensin II

	No drug		*1-Sar, 8-Ala angiotensin II*		*1-Sar, 8-Ile angiotensin II*	
	Control ($n = 8$)	*Pressure reduction* ($n = 8$)	*Control* ($n = 10$)	*Pressure reduction* ($n = 10$)	*Control* ($n = 8$)	*Pressure reduction* ($n = 8$)
Renal blood flow (ml $min^{-1}kg^{-1}$)	14.87 ± 0.48	14.54 ± 0.87	13.71 ± 0.27	13.10 ± 0.57	15.66 ± 0.77	15.91 ± 1.77*
GFR (ml $min^{-1}kg^{-1}$)	2.02 ± 0.04	2.10 ± 0.08	1.72 ± 0.06	1.69 ± 0.10	2.29 ± 0.06	2.16 ± 0.13*
Fractional sodium excretion ($\times 10^{-3}$%)	50.6 ± 3.6	23.5 ± 3.6	44.4 ± 3.6	18.6 ± 3.7	40.3 ± 2.8	23.6 ± 4.7
Absolute sodium excretion (μmol $min^{-1}kg^{-1}$)	14.66 ± 0.92	7.22 ± 1.00	11.26 ± 0.97	4.96 ± 1.12	13.35 ± 0.69	7.04 ± 1.09

Mean values ± s.e. mean are shown; GFR = glomerular filtration rate. n = no. of trials
*$P < 0.05$. Values for P are for comparisons of the absolute changes for each variable, in response to reduced renal perfusion pressure, in the absence and in the presence of each drug

when pressure was reduced in the presence of 1-Sar, 8-Ileu angiotensin II which was a response significantly different from that observed in the absence of the antagonist ($P < 0.02$).

Both fractional and absolute excretion of sodium fell when renal perfusion pressure was reduced (by 53% and 50% respectively) when no drug was present. Similar reductions were seen in the presence of 1-Sar, 8-Ala angiotensin II (62% and 61% respectively) and 1-Sar, 8-Ile angiotensin II (47% and 49% respectively) which were not statistically different from the responses observed in the absence of antagonist whether analysed in terms of either percentage or absolute changes.

Discussion

Previous publications from this laboratory have shown that the ability of the kidney to control glomerular filtration rate when the renal nerves are modestly stimulated is reduced when neurally mediated renin release is inhibited using the β-blocker propranolol (Johns *et al.*, 1976) or when angiotensin II production is blocked by administration of the converting enzyme inhibitor SQ20,881 (Johns, 1979). Further, in a somewhat different situation, that of reduction of renal perfusion pressure, it was found that renal blood flow was maintained at control values but glomerular filtration rate could not be autoregulated appropriately in the presence of SQ20,881 (Johns, 1979). These findings supported the suggestion that intrarenally generated angiotensin II, resulting from either nerve stimulation or reduction of renal perfusion pressure, had a primary site of action at the efferent arteriole such that it could importantly influence the rate of glomerular filtration. Such a proposal was contained in the papers of Hall and coworkers (Hall, Guyton & Cowley, 1977a; Hall *et al.*, 1977b; 1979): it was found that in the sodium-depleted dog, glomerular filtration rate but not renal blood flow autoregulation was impaired in response to reductions in perfusion pressure during administration of the converting enzyme inhibitor SQ20,881. It has to be recognised that there are serious limitations in the use of SQ20,881 particularly its ability to potentiate the action of bradykinin. Therefore it is important that other methods of blocking the renin-angiotensin system should be used in order to support this suggested role of angiotensin in the regulation of glomerular filtration.

One such manoeuvre is that of deoxycorticosterone acetate (DOCA) administration associated with dietary sodium loading for several weeks which chronically suppresses renin production. However, the effect of such renin depletion on regulation of renal function has produced a variety of findings. Hall *et al.* (1977a) found that renin depletion resulted in an impaired ability to autoregulate glomerular filtration rate but not renal blood flow, during reduction of perfusion pressure, while Kaloyanides, Bastron & DiBona (1974) used isolated perfused kidneys from sodium-loaded dogs and found that the autoregulatory ability of both filtration and flow were reduced. More recently, however, Murray & Malvin (1979) were unable to show any effect on the ability of the kidney to autoregulate flow or filtration after up to seven weeks of sodium loading. It is clear that use of this approach for the study of the importance of angioten-

sin in the control of renal haemodynamics is proving unreliable.

A further option is to block the renin-angiotensin system with angiotensin II receptor blocking drugs and to examine their effect on the regulation of renal function. In the present study administration of 1-Sar, 8-Ala angiotensin II was found to have no effect on the ability of the kidney to regulate glomerular filtration rate in response to either of the two experimental procedures used, renal nerve stimulation or reduction of renal perfusion pressure. A similar lack of effect on the control of renal function in response to changes in renal perfusion pressure was observed in the dog by Anderson *et al.* (1975) using 1-Sar, 8-Gly angiotensin II and by Kaloyanides & DiBona (1976) using 1-Sar, 8-Ala angiotensin II infused into the isolated perfused kidney. Such findings were very different from those of Hall *et al.* (1977a) who found that following administration of 1-Sar, 8-Ile angiotensin II, the kidney was unable to autoregulate glomerular filtration rate during reduced perfusion pressure.

The possibility existed that the reason for such lack of agreement was caused by the particular blocking drug used. We therefore examined the control of renal function in the presence of another drug, 1-Sar, 8-Ile-angiotensin II. The results clearly show that during administration of 1-Sar, 8-Ile angiotensin II, renal nerve stimulation caused a significant fall in glomerular filtration rate and further, that during the period of reduced perfusion pressure, the kidney was unable to maintain glomerular filtration rate at control levels. Such responses were very similar to those obtained in our previous papers (Johns *et al.*, 1976; Johns, 1979) and clearly support the findings of Hall and co-workers (1977a,b; 1979) which are consistent with an important intrarenal role for angiotensin II, in the control of filtration rate.

It is clear from the present study that even though both 1-Sar, 8-Ala angiotensin II and 1-Sar,8-Ile-angiotensin II were given at dose rates sufficient to block the systemic vasopressor and renal vasoconstrictor effects of fairly large doses of angiotensin II, they were very different in their ability to block the more subtle effects of locally generated angiotensin II which were the subject of this investigation. It is well known that both 1-Sar, 8-Ala- and 1-Sar, 8-Ile-angiotensin II are amongst the most potent of the angiotensin II antagonists (Pals, Masucci, Denning, Sipos & Fessler, 1971; Turker, Page & Bumpus, 1974), however, the partial agonist properties of 1-Sar, 8-Ala-angiotensin II have been recognised for some time (Mimran, Hinricks & Hollenberg, 1974) and have been a source of continuing comment (Laragh, Case, Wallace & Keim, 1977; Anderson, Streeten & Dalakos, 1977; Wallace *et al.*, 1979). Possibly one of the causes of our inability to demonstrate blockade of this local and specialised action of angiotensin II could be its partial agonist activity. It is possible that accessibility of the blocking drugs to the intrarenal angiotensin II receptor sites is different and that some, as yet unrecognised, feature of the drugs make one drug more able to reach these sites than another.

Administration of 1-Sar,8-Ala- and 1-Sar,8-Ile-angiotensin II caused no change in the basal level of renal blood flow. This is consistent with the earlier findings observed with SQ20,881 administration in the cat (Johns, 1979) and those of Abe, Kishimoto & Yamamoto (1976), Anderson *et al.* (1975), Kimbrough, Vaughan, Carey & Ayres (1977) in the dog and Arendshorst & Finn (1977) in the rat which suggest that under normal dietary sodium conditions renal blood flow is very little influenced by circulating angiotensin II. However, it is clear that in states where the plasma levels of angiotensin II are raised, such as following low dietary sodium (Gagnon, Rice & Flamenbaum, 1974; Kimbrough *et al.*, 1977; Hall *et al.*, 1977*b*, 1979) or inferior vena caval constriction (Freeman, Davis, Vitale & Johnson, 1973) angiotensin II can greatly influence the rate of renal blood flow.

It is now generally considered that the renal nerves can have a direct action on the renal reabsorptive processes to decrease the rate of sodium excretion (DiBona, 1977), which recent micropuncture studies have shown to occur mainly at the proximal tubule (Colindres & Gottschalk, 1978). In the present study, part at least, of the reductions in absolute and fractional excretions of sodium could result from this mechanism. The effectiveness of renal nerve stimulation in causing a decreased fractional excretion of sodium was not affected by prior administration of either of the analogues in the present study. The magnitude of the decrease in absolute sodium excretion was not significantly different in animals given 1-Sar, 8-Ile angiotensin II, but there was a significantly greater fall in absolute sodium excretion following 1-Sar, 8-Ala angiotensin II administration. It is possible that this simply reflects the higher baseline rates of sodium excretion in that group of animals. These changes in sodium handling would support the suggestions made earlier by ourselves (Johns *et al.*, 1976; Johns, 1979) and others (Zambraski & DiBona, 1976) that it is unlikely that angiotensin II is involved in the increased reabsorption resulting from renal nerve stimulation.

The rate of sodium excretion has been clearly shown to be pressure-dependent (Selkurt, 1951). Reduction of renal perfusion pressure in this study is associated with large falls in both absolute and fractional excretion of sodium. Neither 1-Sar, 8-Ala- nor 1-Sar, 8-Ile angiotensin II had any significant effect on the magnitude of the reduction in the rate of sodium excretion. This observation is similar to that obtained with SQ20,881 (Johns, 1979) and may provide further evidence which makes it unlikely that angiotensin II

is involved in the mechanism causing the decreased sodium excretion during reduction of renal perfusion pressure.

Stimulation of the renal nerves or reduction in renal perfusion pressure within the autoregulatory range results in the regulation of glomerular filtration rate such that it remains unchanged. Following administration of the angiotensin II blocker, 1-Sar, 8-Ile-angiotensin II, the kidney was no longer able to regulate glomerular filtration rate appropriately. These results are similar to those obtained previously with the converting enzyme inhibitor, SQ20,881. However, administration of blocking doses of 1-Sar, 8-Ala-angiotensin II had no effect on the ability of the kidney to regulate glomerular filtration rate in response to these manoeuvres. It is possible that the lack of effect of this analogue on intrarenal regulation of renal haemodynamics reflects some aspect of this drug, such as its partial agonist activity, which makes it unreliable as a tool for investigating the physiological role of the renin-angiotensin system, particularly at an intra-renal site. This study emphasises the importance of using a wide variety of drugs if a specific function is to be ascribed to angiotensin II.

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