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THE RENAL RESPONSE TO ELECTRICAL STIMULATION OF RENAL EFFERENT SYMPATHETIC NERVES IN THE ANAESTHETIZED GREYHOUND

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SUMMARY

1. The effect of direct electrical stimulation of the renal efferent nerves upon renal haemodynamics and function was studied in greyhounds anaesthetized with chloralose and artificially ventilated. The left kidney was neurally and vascularly isolated, and perfused with blood from one of the femoral arteries at a constant pressure of 99 ± 1 mmHg. Renal blood flow was measured with a cannulating electromagnetic flow probe placed in the perfusion circuit, glomerular filtration rate by creatinine clearance, urinary sodium excretion by flame photometry and solute excretion by osmometry. β-Adrenergic receptor activation was blocked by the infusion of *dl*-propranolol (17 μg kg^{-1} min^{-1}). The peripheral ends of the ligated renal nerves were stimulated at 0·5, 1·0, 1·5 and 2·0 Hz.

2. At 0·5 Hz frequency only osmolar excretion was significantly reduced ($10{\cdot}3 \pm 3{\cdot}2$ %, $P < 0{\cdot}05$, $n = 6$). Reductions in sodium excretion ($53{\cdot}6 \pm 8{\cdot}5$ %, $P < 0{\cdot}01$, $n = 6$) and water excretion ($26{\cdot}9 \pm 8{\cdot}0$ %, $P < 0{\cdot}05$, $n = 6$) and further reductions of osmolar excretion ($20{\cdot}7 \pm 3{\cdot}7$ %, $P < 0{\cdot}01$, $n = 6$) were observed at 1·0 Hz; however, these were observed in the absence of significant changes in renal blood flow and glomerular filtration rate. Significant reductions were observed in glomerular filtration rate at 1·5 Hz ($16{\cdot}3 \pm 4{\cdot}1$ %, $P < 0{\cdot}02$, $n = 5$) and in renal blood flow at 2·0 Hz ($13{\cdot}1 \pm 4{\cdot}0$ %, $P < 0{\cdot}05$, $n = 5$). Further reductions in urine flow and sodium excretion were also observed at these higher frequencies.

3. These results clearly show that significant changes in renal tubular function can occur in the absence of changes in renal blood flow and glomerular filtration rate when the renal nerves are stimulated electrically from a zero baseline activity up to a frequency of 1·5 Hz. Higher frequencies caused significant changes in both renal haemodynamics and function.

INTRODUCTION

We have previously reported that the renal haemodynamics and function of dogs can be influenced by stimulation of baro- and chemoreceptors in the carotid sinus regions (Karim, Poucher & Summerill, 1984, 1987, 1989*b*) and atrial receptors

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(Karim, Majid & Summerill, 1989*b*). These responses were abolished following ligation of the renal nerves. The changes in urine output and sodium excretion were accompanied by changes in renal blood flow and glomerular filtration rate, even following small changes in carotid sinus pressure (Karim *et al.* 1989*b*). This suggests that the dominant pathway in the rapid adjustment of renal circulation and function from alterations in sensory receptor activity is through the renal nerves, and that the concomitant haemodynamic responses may account for a significant proportion of the changes in sodium and urine output (O'Connor & Summerill, 1979). However, some reports suggest that the renal nerves are able to influence renal function by a direct action upon the nephron: Slick, Aguilera, Zambraski, DiBona & Kaloyanides (1975) showed that low levels of renal nerve stimulation in anaesthetized dogs (0·5–2·0 Hz) resulted in decreases in urinary sodium excretion in the absence of significant changes in mean arterial pressure, renal perfusion pressure, glomerular filtration rate, renal blood flow (measured by *p*-aminohippurate (PAH) clearance) or intrarenal distribution of blood flow. Bello-Reuss, Trevino & Gottschalk (1976) also reported antinatriuretic and antidiuretic response to 1–2 Hz stimulation of the renal nerve without changes in renal plasma flow and glomerular filtration rate in the majority of their volume-expanded, anaesthetized rats. However, other investigations suggested that such low levels of renal nerve stimulation can also cause significant changes in renal haemodynamics. Significant reductions in renal blood flow at 0·5 Hz stimulation (Osborn, Francisco & DiBona, 1981) and at 0·9 Hz (range 0·5–1·4 Hz) stimulation (Kopp, Aurell, Nilsson & Ablad, 1980) have been reported in anaesthetized dogs. In their micropuncture study of single tubules DiBona & Sawin (1982) found that renal nerve stimulation below 0·9 Hz could reduce absolute and fractional excretion rates of sodium from the loop of Henle in hydropenic and volume-expanded rats, but the effects on water excretion were observed only when the whole kidney was studied. More recently, the same group (Osborn, Holdaas, Thames & DiBona, 1983) reported α-adrenoceptor-mediated antinatriuresis during 1 Hz renal nerve stimulation in the absence of changes in renal blood flow and glomerular filtration rate in anaesthetized dogs.

The above discrepancy may be related largely to methodological inadequacies. In the studies of direct renal nerve stimulation referred to above, neither was aortic pressure (renal perfusion pressure) controlled, nor was a perfusion circuit with a cannulating electromagnetic flow probe used for an accurate measurement of renal blood flow (see Discussion).

In view of the above discrepancy between the individual results and the findings of our reflex studies at which both renal haemodynamics and function changed significantly, the present investigation was undertaken. The objectives were first to determine whether there was a range of low-level frequencies which can cause significant changes in solute and water excretion without influencing renal blood flow and glomerular filtration rate in a well-controlled dog preparation similar to that used in cardiovascular reflex studies (*vide supra*), and secondly, to assess the frequencies required to produce changes similar to those seen in the reflex effects. The renal blood flow was measured at a constant aortic pressure using a perfusion circuit and a cannulating electromagnetic flow probe.

METHODS

The dorsal branch of the right lateral saphenous vein of six dogs (20·6–26·6 kg, greyhounds of either sex, Leeds University Animal Services) was cannulated under local anaesthesia (lignocaine hydrochloride, 2% Xylocaine, Astra Pharmaceuticals, UK) and the catheter was gently advanced until the tip reached the inferior vena cava. Thiopentone sodium (Intraval Sodium, May and Baker, UK) was then given (0·5 g), followed by a 1% solution of α-chloralose (0·1 g kg^{-1}, Rentokil Ltd, UK). The α-chloralose solution was made up in 0·9% saline and the solution kept at 65 °C in a water bath to maintain solubility. Before administration the solution was filtered to remove any undissolved chloralose. In all experiments, anaesthesia was maintained during surgery and throughout the experiment by a constant infusion of chloralose (approximately $0·42 \pm 0·03$ mg kg^{-1} min^{-1}) into the left femoral or cephalic vein.

Immediately after induction of anaesthesia the trachea was exposed through a mid-line incision and cannulated. The lungs were artificially ventilated with oxygen-enriched air (40% oxygen) at a rate of 18 strokes min^{-1}; the stroke of the pump was initially set at 15 ml kg^{-1} (Karim *et al.* 1989*b*). Periodically the blood gas status of the animal was checked using a Corning 161 pH/blood gas analyser (Corning Scientific Instruments, USA) and corrected when necessary (Karim *et al.* 1989*b*). Deep body temperature was monitored continuously and was maintained at $37·8 \pm 0·1$ °C by means of heating elements. Arterial blood pressure was measured from the right brachial artery by a cannula attached to a pressure transducer (Statham, model P23 ID).

Surgical procedure

The animal was turned onto its right side and the left kidney exposed retroperitoneally through a flank incision which was extended medially to facilitate dissection of the renal nerves and cannulation of the renal artery. The ureter was cannulated for collection of urine. The renal nerves were exposed distal to the aortico-renal ganglion and a strong tie placed around them to ligate the nerves. A bipolar silver wire stimulating electrode was placed around the renal nerves peripheral to the tie and connected to a square-wave pulse stimulator (Grass SD9). The nerves and stimulating electrodes were bathed in warm paraffin oil to prevent deterioration of the nerves. The stimulation voltage was chosen for each animal to produce a maximal renal vasoconstriction at a duration of 0·1 ms and frequency of 5·0 Hz. Under these circumstances the voltage required was 20–70 V.

The kidney was perfused with the animal's own blood through a perfusion circuit which contained a cannulating electromagnetic flow probe (4 mm i.d., Gould Statham, USA). The perfusion circuit was first connected to the left femoral artery and primed with blood. A metal cannula was connected to the other end of the circuit and inserted into the renal artery for free-flow perfusion of the kidney (cannulation time 70–150 s). Zero blood flow was determined by occlusion of the circuit distal to the flow probe with the clamp that was removed from the bypass, which allowed renal perfusion to be maintained during this procedure (Fig. 1). At the end of the experiment the flow probe was calibrated using timed collections of blood. Renal perfusion pressure was measured from the circuit as shown in Fig. 1 and maintained at a constant level as described previously (Karim *et al.* 1984). Patency of the perfusion circuit was maintained by administration of heparin (priming dose of 185 i.u. kg^{-1} followed by continuous infusion into the renal perfusion circuit at $0·65 \pm 0·04$ i.u. kg^{-1} min^{-1}). Propranolol was also infused at 17 μg kg^{-1} min^{-1} (I.V.) throughout the duration of the experiment to prevent the release of renin. Approximately 50 min prior to the first clearance period, a continuous infusion of creatinine (10 mmol in a solution of 50% dextran, Dextraven 150, Fisons Pharmaceuticals Ltd, and 50% isotonic saline, 0·9% w/v, Travenol) was started at 2 ml min^{-1} and maintained throughout the experiment for determination of glomerular filtration rate. Creatinine concentration was determined by an automatic analyser; the method was based upon the Jaffe reaction (Technicon II). Sodium concentration was determined by flame photometry (Corning-Eel 400) and osmolality was measured by freezing-point depression (Osmette, Precision Instruments, Inc., USA).

Experimental protocol

After ligation of the renal nerves two consecutive urine samples were collected, each of 10 min duration. At the third minute of each collection period an arterial blood sample was taken from the brachial artery for measurement of plasma creatinine concentration. Stimulation of the efferent

nerves was then commenced at frequencies of either 0·5, 1·0, 1·5 or 2·0 Hz selected in random order. When 2 ml of urine had been passed, to allow for wash-out of the urine in the dead space of the ureteral catheter, a further two urine collections were made. The stimulation was terminated and further post-stimulation control collections made. The mean values of the variables during two

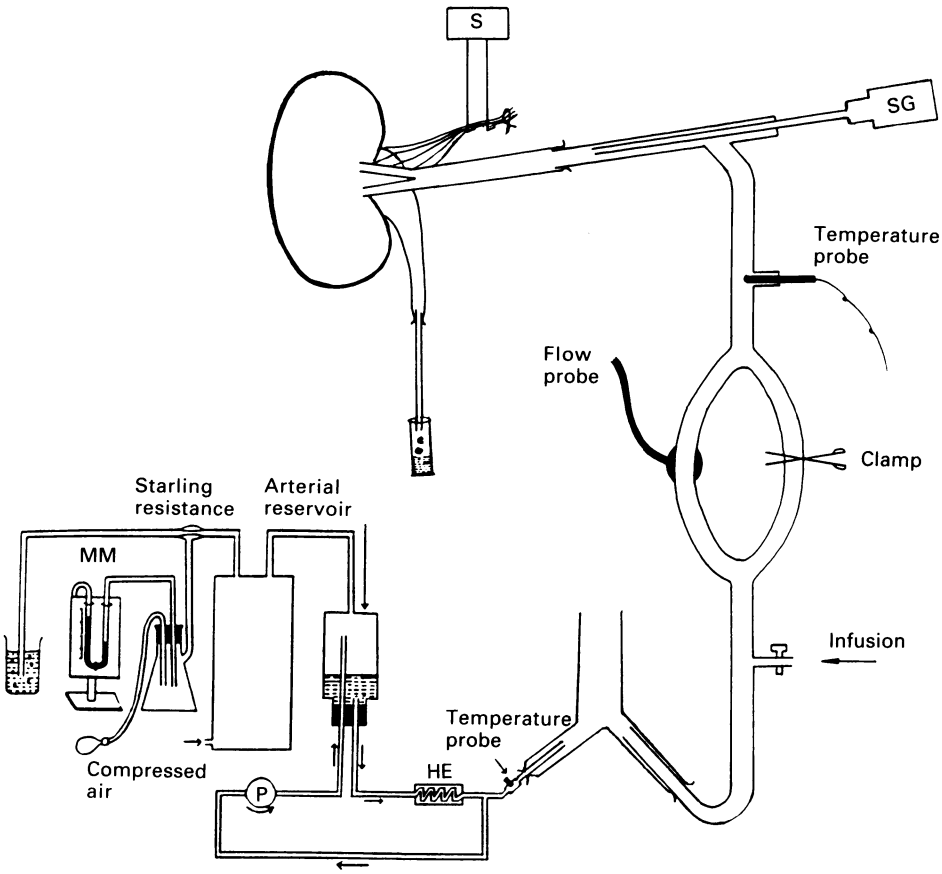
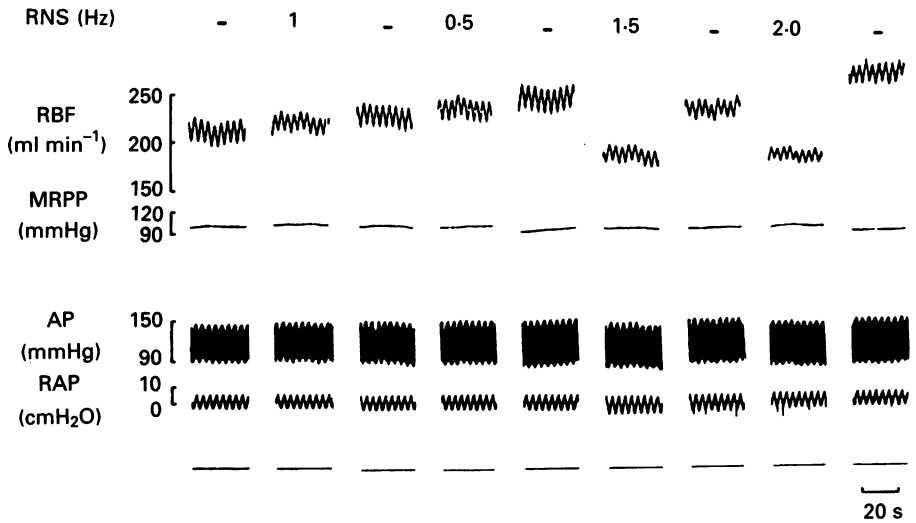


Fig. 1. Schematic diagram of the renal perfusion circuit. The kidney was perfused with blood taken from the cardiac end of one of the femoral arteries. Renal blood flow was measured with a cannulating electromagnetic flow probe situated in the circuit; zero blood flow was determined by removing the clamp from the bypass and occluding the main circuit distal to the flow probe. Renal perfusion pressure was measured using a pressure transducer (SG) connected to a catheter which was advanced in the circuit such that the tip lay close to the point of cannulation of the renal artery. The left renal nerves were exposed close to the aortico-renal plexus, ligated, and a bipolar silver wire stimulating electrode (S) placed on the peripheral segment and bathed in warm paraffin oil. The electrodes were connected to a stimulator (Grass SD9) set to give pulses at 0·5, 1·0, 1·5 or 2·0 Hz (0·1 ms pulse duration, 20–70 V). Renal perfusion pressure was maintained constant by connecting the descending aorta, via the other femoral artery, to a constant-pressure arterial blood reservoir. MM, mercury manometer.

10 min collections during renal nerve stimulation were compared with the averages of the values obtained during pre- and post-stimulation collection periods.

Statistical methods

All values are quoted as the mean ± standard error of the mean. Statistical analysis was performed using a *t* test for paired data. The results were considered to be statistically significant at $P < 0.05$.



GFR (ml min^{-1})	30·4	33·1	30·4	31·4	30·4	19·7	28·1	13·6	27·8
V (ml min^{-1})	0·68	0·51	0·77	0·65	0·83	0·42	1·10	0·38	1·10
$U_{Na}V$ (μmol min^{-1})	52·3	21·9	52·4	29·8	50·2	13·4	44·0	12·4	22·3
$U_{osm}V$ (μosmol min^{-1})	432	354	435	372	405	170	454	137	441

Fig. 2. Records and values showing an example of the renal responses to direct electrical stimulation (RNS) of the renal efferent nerves at frequencies of 0·5–2·0 Hz (0·1 ms duration, 20 V). Mean renal perfusion pressure (MRPP) was maintained constant throughout the whole of the experiment. Decreases in urine flow (V), sodium excretion ($U_{Na}V$) and solute excretion ($U_{osm}V$) were observed at 0·5 and 1·0 Hz, frequencies which did not cause changes in renal blood flow (RBF) or glomerular filtration rate (GFR). Arterial blood pressure (AP) and right atrial pressure (RAP) were unaltered throughout the study.

RESULTS

The mean arterial blood pressure was maintained at 112 ± 1 mmHg during all of the collection periods. The mean values of pH, P_{O_2}, P_{CO_2} and temperature were 7·38 ± 0·01, 155 ± 12, 37·5 ± 0·5 mmHg and 37·8 ± 0·2 °C respectively. Figure 2 shows the typical responses observed following stimulation of the renal nerves; summarized results are given in Fig. 3. Renal nerve stimulation decreased renal blood flow, and decreased urine flow, sodium excretion and solute excretion in a frequency-dependent manner. At the lowest stimulation frequency used (0·5 Hz) only osmolar excretion was significantly reduced (10·3 ± 3·2 %, $P < 0.05$, $n = 6$). Reductions in sodium excretion (53·6 ± 8·5 %, $P < 0.01$, $n = 6$) and water excretion (26·9 ± 8·0 %,

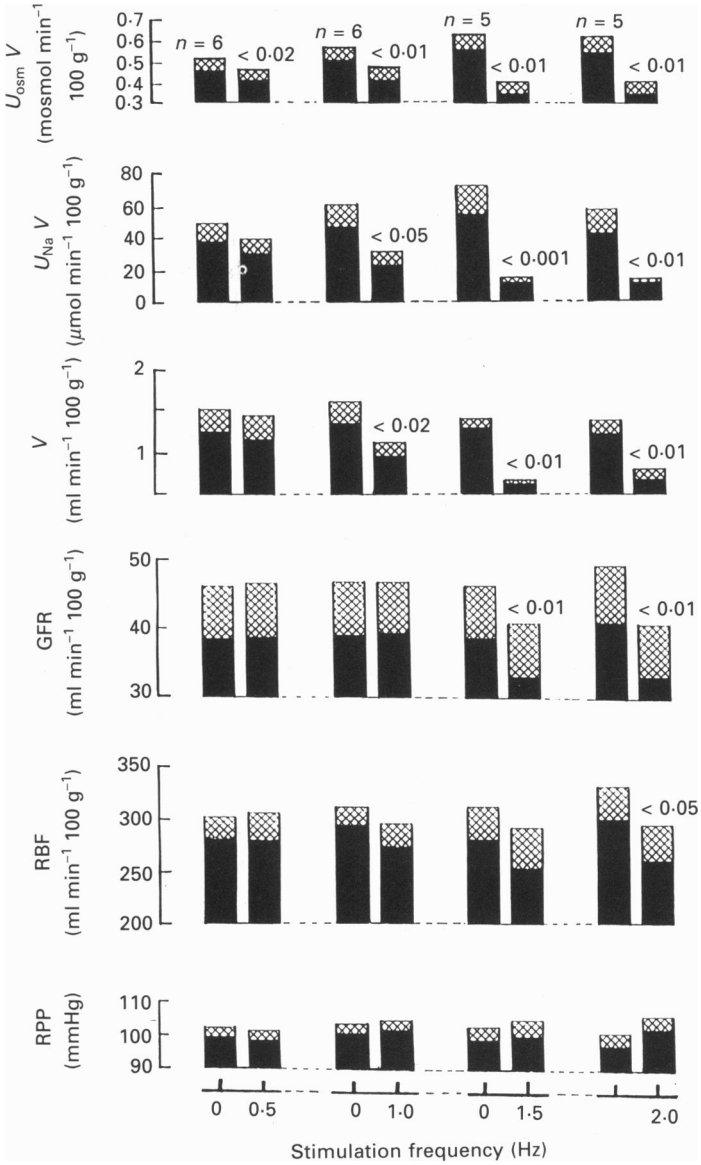


Fig. 3. The responses to electrical stimulation of the efferent nerves of the kidneys perfused at constant pressure. Propranolol was infused (17 μg kg^{-1} min^{-1}) to prevent renin release upon stimulation. Each column shows the mean values (filled part) with the standard error of the mean (hatched part). All values from each animal are the means of at least two consecutive 10 min stimulation periods. The values during electrical stimulation were compared statistically with the average of corresponding values during pre- and post-stimulation periods using Student's paired t test. All data are normalized and expressed per 100 g renal mass. RPP, renal perfusion pressure; other abbreviations as in Fig. 2.

$P < 0{\cdot}05$, $n = 6$) and further reductions of osmolar excretion ($20{\cdot}7 \pm 3{\cdot}7$ %, $P < 0{\cdot}01$, $n = 6$) were observed at 1·0 Hz; however, these were observed in the absence of significant changes in renal blood flow and glomerular filtration rate. Significant

reductions in glomerular filtration rate were observed at 1·5 Hz (16·3 ± 4·1 %, $P < 0·02$, $n = 5$) and in renal blood flow at 2·0 Hz (13·1 ± 4·0 %, $P < 0·05$, $n = 5$). Further reductions in urine flow and sodium were observed at these higher frequencies.

DISCUSSION

The results of the present experiments show that renal nerve stimulation at low frequencies (1 Hz and below) can cause significant changes in renal function in the absence of any change in renal blood flow or glomerular filtration rate (Figs 2 and 3). These changes in renal function in the absence of changes in renal blood flow and glomerular filtration rate can be used as evidence for a direction action of the nerves on the nephron and are consistent with a functional innervation of the nephron (Barajas & Muller, 1973). Significant decreases in glomerular filtration rate and renal blood flow occurred at 1·5 and 2 Hz (Fig. 3). Higher frequencies were not studied in the present investigation to demonstrate maximum changes in renal blood flow and glomerular filtration rate. Other groups have observed maximal reduction of renal blood flow at 10 Hz (DiSalvo & Fell, 1971; Hermansson, Larson, Kallskog & Wolgast, 1981; Osborn *et al.* 1981).

Although similar changes in some components of renal function (sodium excretion) at low frequencies have been reported previously in anaesthetized dogs and volume-expanded rats (Slick *et al.* 1975; Bello-Reuss *et al.* 1976; Zambraski, DiBona & Kaloyanides, 1976*a*; DiBona & Sawin, 1982; Osborn *et al.* 1983), the present study may be regarded as more complete and conclusive for several reasons: (1) a greater number of renal function variables (renal blood flow, glomerular filtration rate, sodium excretion, osmolar and water excretion) were studied; (2) the measurement of renal blood flow was made by means of a cannulating electromagnetic flow probe incorporated in a short perfusion circuit (see Fig. 1), whereas in all of the previous studies a less-accurate method (wrap-round electromagnetic probe) was used on the renal artery, which was within a very short distance of the stimulating electrodes on the renal nerves. We have observed serious disturbances in flow recording in preliminary experiments in which such a wrap-round flow probe was used; (3) the use of *p*-aminohippurate clearance technique for the measurement of renal plasma flow by some of the earlier workers (Slick *et al.* 1975; Bello-Reuss *et al.* 1976) is also not considered to be accurate or sensitive enough for this kind of study; (4) in some earlier investigations (e.g. Bello-Reuss *et al.* 1976; Hermasson *et al.* 1981) renal nerves were either incompletely sectioned or left intact during stimulation; under these circumstances changes in systemic blood (renal perfusion) pressure were likely through activation of renal afferent nerves, thus making it difficult for any valid interpretation of the results of these studies; we controlled the aortic pressure perfusing the kidney to eliminate any pressure effect during electrical stimulation of the peripheral ends of the ligated renal nerves (see Fig. 1); (5) in some of the previous studies (e.g. Osborn *et al.* 1983) only a single frequency (1 Hz) was used, whereas in the present study a range of low frequencies (0·5, 1, 1·5 and 2 Hz) were used.

The control values of the variables in the denervated kidneys in the present experiments were high and similar to those reported earlier in the reflex studies after denervation of the kidneys (Karim *et al.* 1984; Karim *et al.* 1989*a*, *b*). In these experiments the level of renal blood flow reached after denervation of the kidneys

was not higher than that seen at high carotid sinus pressure (at about 180 mmHg), but the levels of sodium and water excretion were higher (see Fig. 3, Karim *et al.* 1984). These results and those of the present experiments clearly indicate that at this level of high carotid sinus pressure the sympathetic nerve activity was likely to be as low as 1 Hz, removal of which, by denervation of the kidney, could produce renal functional changes without producing changes in renal blood flow and glomerular filtration rate. On the other hand, the values of both renal haemodynamic and functional variables after denervation at normal or low carotid sinus pressure were significantly higher than those seen at low (Karim *et al.* 1989*b*) and normal (Karim *et al.* 1989*a*) carotid sinus pressure; the differences of the functional values were much greater. Also, in our reflex studies of small and large changes in carotid sinus pressure (Karim *et al.* 1984, 1989*b*), both haemodynamic and functional variables changed significantly. This suggests that the magnitude of change in renal nerve activity that brought haemodynamic and functional changes was likely to be greater than 1·5 Hz. Thus, the changes in osmolar and water excretion in response to reflex activation of the renal nerves in our earlier studies were most likely to be caused by a combination of changes in renal blood flow and glomerular filtration rate and the direct action of the nerves to the renal tubules.

In the present series of experiments, as in some of those reported by other investigators (DiSalvo & Fell, 1971; Osborn *et al.* 1981, 1983; Ammons, Koyama & Manning, 1982), electrical stimulation always commenced from zero activity and was increased to 0·5, 1·0, 1·5 or 2·0 Hz. However, in our reflex studies with intact kidneys, initial carotid sinus pressure was set to high, medium or low levels within the baroreceptor sensitivity range (Karim *et al.* 1984, 1987, 1989*b*; Karim & Al-Obaidi, 1990; Karim & Majid, 1990) and thus the reflex alteration of the renal nerve activity commenced from some basal on-going activity (Kendrick, Oberg & Wennergren, 1972; Linden, Mary & Weatherill, 1981). Although few studies have measure renal nerve activity in response to changes in carotid baroreceptor and chemoreceptor activities (Kezdi & Geller, 1968; Karim, Kidd, Malpus & Penna, 1972; Linden *et al.* 1981), one has attempted to correlate sinus pressure (baroreceptor activity) with renal nerve activity and haemodynamics in the anaesthetized cat (Kendrick *et al.* 1972). However, these workers have shown that even small changes in carotid sinus pressure can produce large changes in renal nerve activity. Our results from anaesthetized dogs also support the earlier findings. Linden *et al.* (1981) showed in anaesthetized dogs that at a carotid sinus pressure of 72 mmHg (range 41–89) the renal nerve activity, measured from a few fibre strands, was 3·125 spikes s^{-1} (range 0·520–11·20), and at 132 mmHg (range 92–184) it was 1·836 spikes s^{-1} (range 0·45–6·52). Although their setting of carotid sinus pressure varied widely, the average carotid sinus pressure, 132 and 72 mmHg, may be comparable to decreasing carotid sinus pressure from 123 ± 5 to 78 ± 4 mmHg in one of our reflex studies (Karim *et al.* 1989*b*) in which both renal haemodynamic as well as functional changes occurred. We therefore assume that a change in renal nerve activity of about 1 Hz or greater produced these changes in renal variables. Linden *et al.* (1981) also observed that carotid chemoreceptor stimulation with venous blood caused changes in the renal nerve activity of about 1 Hz. However, in our study of the carotid chemoreflex (Karim *et al.* 1987), the changes in renal nerve activity must have been

greater, because both renal haemodynamics and function changed significantly, particularly when a natriuretic factor seemed to be working against the neural action.

The argument that changes in efferent renal nerve activity, induced by baro- or chemoreceptor stimulation, in our reflex studies were greater than 1–1·5 Hz is based on the following evidence and assumptions: (1) direct electrical stimulation in the present study and in those reported by DiBona (1977), Kopp *et al.* (1980) and Ammons *et al.* (1982), failed to modify renal haemodynamics until levels of 1·5–2 Hz were applied; (2) asynchronous, physiological reflex activation of the nerves from a baseline activity at the steep part of the renal function–renal activity curve and synchronous, non-physiological electrical activation of the nerves from zero activity produce similar effects on the kidney circulation and function. The latter can be tested by mimicking direct electrical stimulation of the nerves with reflex activation of the renal nerves; that is, to commence measurements of renal function at a carotid sinus pressure of greater than 250 mmHg, where renal nerve activity is likely to be close to zero (Kendrick *et al.* 1972), and reduce sinus pressure in a stepwise fashion to a level which activates the renal nerves to a degree that can cause significant changes in osmolar and water excretion in the absence of significant changes in renal blood flow and glomerular filtration rate.

The mode of action of renal nerves at low frequencies to produce changes in osmolar and water excretion is not yet definitely known. Their direct action on the tubular transport system via α-adrenoceptors has been suggested (Zambraski, DiBona & Kaloyanides, 1976*b*; Osborn *et al.* 1983). However, their indirect effect by releasing some intrarenal transmitters has not been elucidated, but it was unlikely that the renin–angiotensin system was involved in the present experiments since we minimized the release of renin by administration of *dl*-propranolol, as demonstrated previously (Ammons *et al.* 1982; Kopp & DiBona, 1983; Osborn *et al.* 1983).

In conclusion, the present investigation has clearly shown that direct low-frequency electrical stimulation of the renal nerves from a zero baseline activity can result in changes in osmolar and water excretion in the absence of changes in renal blood flow and glomerular filtration rate. The changes in renal function following stimulation of cardiovascular receptors are likely to be due to a combination of both changes in renal haemodynamics and a direct action of the renal nerves on the nephron. However, all these investigations can only give approximate information concerning the changes in impulse frequencies that occur during physiological stresses.

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