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Sympathetic Modulation of Renal Hemodynamics, Renin Release and Sodium Excretion

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Summary. In anesthetized animals it has been shown previously, that the influence of electrical stimulation of efferent renal nerves on renal function with increasing stimulation frequencies can be graded; renin release is affected at low, sodium excretion at intermediate and vascular resistance at high stimulation frequencies.

Experiments in conscious dogs are reviewed, which present evidence for a similar functional dissociation under physiological conditions.

Moderate activations of the renal sympathetic nerves, which do not change renal blood flow 1) decrease sodium excretion independent of changes in angiotensin II, 2) interact with the pressure-dependent mechanism of renin release by resetting its threshold pressure and 3) modulate autoregulation by increasing the lower limits of glomerular filtration rate and renal blood flow-autoregulation.

These findings may contribute to our understanding of the role of the renal nerves in the pathophysiology of congestive heart failure and hypertension.

Key words: Renal sympathetic nerves – Renin angiotension system – Autoregulation – Renal blood flow – Glomerular filtration rate – Sodium excretion – Baroreceptor reflexes

In an anesthetized dog which produced no urine Claude Bernard (1859) observed that urine started to flow when the splanchnic nerves were cut. This "denervation diuresis" probably resulted from the elimination of an excessively high vasomotor tone induced by anesthesia and preparative trauma (Berne 1952). Direct evidence for a vasomotor function of the renal nerves was not provided until Cohnheim and Roy had introduced their "oncometer" to measure kidney volume. It was shown that on electrical stimulation of the peripheral stump of the cut splanchnic nerves (Cohnheim and Roy 1883) or renal nerves (Bradford 1889) kidney volume decreased. For decades then the influence of the renal sympathetic nerves on kidney function was bedeviled by the fact that some workers performed their experiments on anesthetized animals, whereas others worked on conscious animals; not surprisingly they obtained different results. This led Homer Smith (1951) to state: "the history of renal physiology has been in too large measure a history of traumatic procedures which have in the end only misled investigation". Although a tonic effect of the renal nerves on excretory function under normal conditions is still a matter of controversy, more recent studies including clinical observations on patients with autonomic failure (Gottschalk et al. 1985) have encouraged us to propose an important role for the renal nerves in body fluid homeostasis and in blood pressure control.

The present paper reviews experiments mostly made in our laboratory during the last years concerned with the effect of the renal sympathetic nerves on autoregulation, renin release and sodium excretion.

Methods

The data from our laboratory were obtained in conscious chronically instrumented foxhounds (body weight around 23 kg) which received a standard diet (daily sodium intake: 4.5–6 mmol/kg b.w.). The experiments were made between the 10th day and the 12th week after implantation surgery. During the experiments which started between 8.00 and 11.00 o'clock a.m., the dogs were resting on a padded bench in a laboratory which

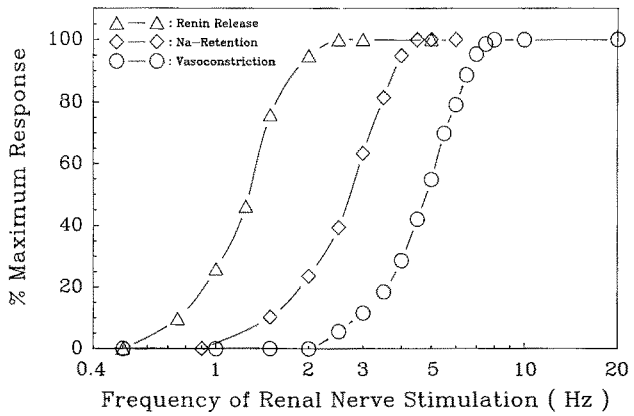

Fig. 1. Relationships between the frequency of electrical stimulation of the peripheral cut stump of renal nerves and the changes in renin release, sodium excretion and vasoconstriction (decrease of total renal blood flow). Data were collected from experiments made in anesthetized dogs, cats and rats (for detailed references see: DiBona 1982; Kirchheim 1983; Thames 1984; Gottschalk et al. 1985)

was strictly isolated from external disturbances; a technician familiar to the dog sat next to it and a curtain separated the experimenter from the dog. Renal blood flow was measured by an electro-magnetic flowmeter. Implanted catheters were used to measure blood pressure, collect blood samples and collect urine (standard clearance techniques). Renal perfusion pressure was reduced and maintained constant independent of aortic blood pressure using an implanted inflatable renal artery cuff and a pressure control system. Details of the applied methods have previously been published (see: Ehmke et al., Finke et al., Gross et al., Kirchheim et al., Persson et al.).

Dissociation of Responses by Graded Activation of the Renal Nerves in Anesthetized Animals

The curves in Fig. 1 were plotted using data from experiments in anesthetized dogs, cats and rats with a stimulus-strength of 8–10 V and durations of 0.5–1.0 ms (DiBona 1982; Thames 1984). Although the curves quantitatively strictly apply only to these conditions, they are of general importance, since a similar differential response to a graded activation of the renal nerves is also evident under physiological conditions in conscious dogs (see below). Between 0.5 and 1 Hz renin release is stimulated in the absence of changes in sodium excretion or vasomotor effects (Fig. 1). This response is blocked by a beta-1-selective antagonist and has been interpreted to be a direct effect on the granulated juxtaglomerular cells, while the stimulus to the pressure-dependent mechanism or to the macula densa seems to be negligible in this frequency range (for literature see: DiBona 1982; Kirchheim 1983; Thames 1984). The low discharge of the renal sympathetic nerves in a conscious dog at rest may also be located in this frequency range (Gross and Kirchheim 1980) thus mediating a "tonic" beta-adrenergic influence on renin release. Accordingly beta-blockade reduces resting renin release by one half in conscious dogs (Gross and Kirchheim 1980; Gross et al. 1981a). With stimulus-frequencies above 1 Hz sodium excretion is affected and a larger role of the macula densa mechanism for renin release can be suggested. The reduction in sodium reabsorption is independent of hemodynamic factors and is inhibited by alpha-blockade; possibly alpha-adrenoceptors located in epithelial cells especially of the proximal tubules are responsible for this effect (DiBona 1982). Decreases in renal blood flow are generally not observed at frequencies below 2 Hz, although it should be kept in mind, that this only applies to changes in total blood flow (Thames 1984).

Examples for a Dissociation of Responses with Physiological Activations of the Renal Nerves in Conscious Dogs

Figure 2 shows that bilateral carotid occlusion (B.C.O.) in conscious dogs (intact aortic baroreceptors) induces an increase of averaged renal sympathetic nerve discharge by 62%, while excitement (emotional stress) was associated with bursts of activation by as much as 500% of control. The high degree of sympathetic activation upon excitement caused a transient 40% reduction of renal blood flow. However, the moderate activation during B.C.O. had no influence on renal blood flow. The latter effect can also be observed when during B.C.O. renal perfusion pressure is kept constant (Gross et al. 1979; Gross et al. 1981a; Gross et al. 1981b; Kirchheim 1983). Nonhypotensive hemorrhage in conscious dogs also elicits an increase in renal nerve activity (Morita and Vatner 1985) but fails to induce a decrease of renal blood flow (Gross et al. 1979). However, these moderate activations of the renal sympathetic nerves do effectively influence renin release, sodium excretion and autoregulation (see below). In the experiments to be described below, B.C.O. will therefore be used as a model, to induce an increase of renal sympathetic nerve discharge, which does not induce major changes in total renal blood flow. It should be mentioned in this context that because of the well developed collateral circulation through the circle of Willis and other communications in the

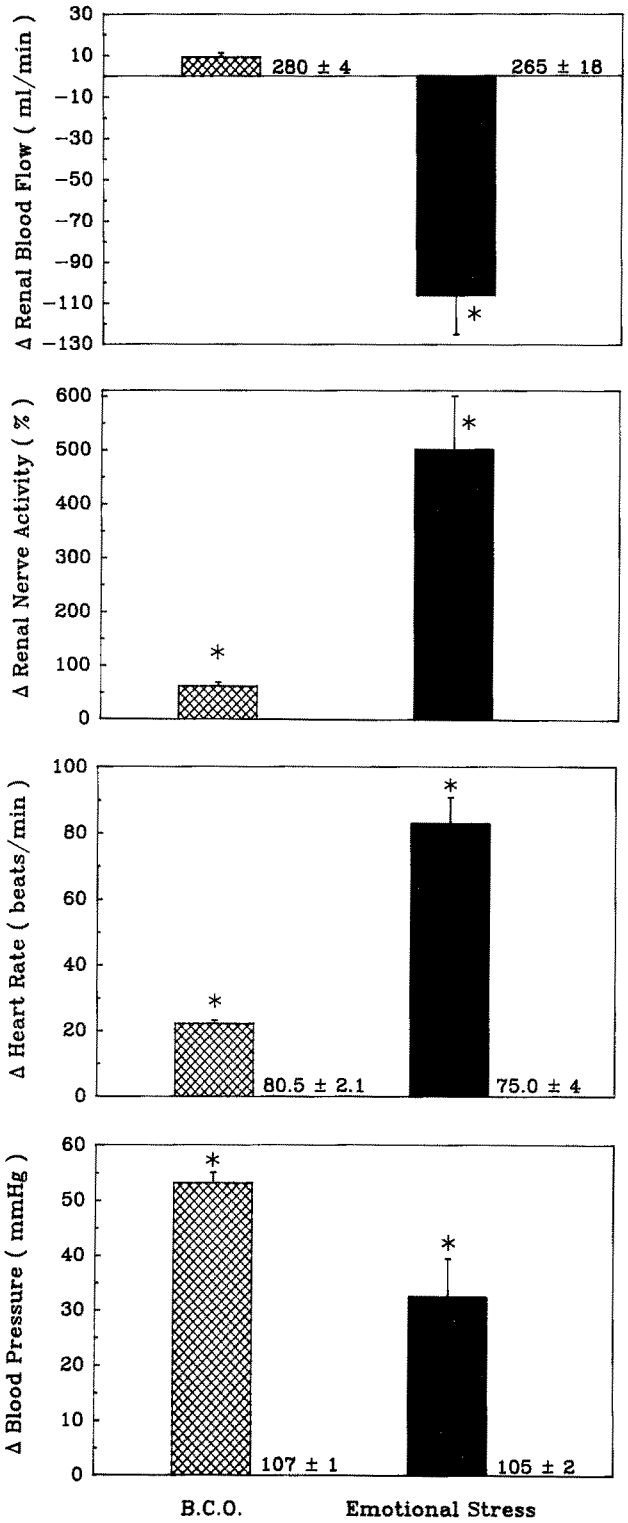

Fig. 2. Effect of bilateral carotid occlusion (B.C.O.: left cross-hatched bars) or emotional stress (right filled bars: auditory stimuli like handclapping, whistling or gun shot) on blood pressure, heart rate, averaged renal sympathetic nerve discharge and renal blood flow in conscious dogs. Numbers ± SE indicate controls. *: $P<0.05$ (Data taken from Gross and Kirchheim 1980)

dog intrasinusal mean blood pressure during the steady state of B.C.O. reaches a level only some 25% below control! (Kirchheim 1976).

Autoregulation of Renal Blood Flow, Glomerular Filtration Rate and Renin Release in Conscious Dogs

Autoregulation of renal blood flow (RBF), glomerular filtration rate (GFR) and renin release in resting conscious dogs is shown in Fig. 3. Renal artery pressure was reduced in steps of 5–10 minutes duration. Between 140 mmHg and the lower limit of RBF-autoregulation (83 mmHg) RBF and GFR remained perfectly constant. However, a significant difference was regularly observed between the lower limit of GFR-(83 mmHg) and of RBF-autoregulation (67 mmHg). The dissociation of GFR- and RBF-autoregulation suggests a further reduction of total resistance between 83 and 67 mmHg; this might be caused either by a dilatation of the efferent arteriole only or by a decrease of postglomerular resistance mediated by changes of tissue pressure due to the decrease of GFR. In conscious dogs receiving a normal sodium intake angiotensin II does not seem to play an essential role in autoregulation, as these curves are neither affected by the converting enzyme inhibitor Captopril nor by an intrarenal infusion of the angiotensin II antagonist saralasin (Persson et al. 1988a). The relationship between renal perfusion pressure and either renin release (Fig. 3) or the renal venous-arterial plasma renin activity (PRA)-difference (Fig. 4) according to AC Barger will be called "stimulus-response curve" for the pressure-dependent renin release (Farhi et al. 1982). The examples shown in Figs. 3 and 4 illustrate its characteristic pattern: a flat section or plateau level in the high pressure range, a very steep section in the low pressure range, and a well-defined threshold pressure (Farhi et al. 1982; Farhi et al. 1983; Finke et al. 1983; Gibbons et al. 1984; Kirchheim et al. 1985; Farhi et al. 1987; Kirchheim et al. 1987; Ehmke et al. 1987; Ehmke et al. 1989). Below the lower limit of RBF-autoregulation, when total renal vascular resistance has reached its minimal value, renin release levels off and shows no increase when blood pressure is further reduced (Fig. 3) (Eide et al. 1973; Finke et al. 1983).

Physiological Significance of the Renin Stimulus-Response Curve

Analyzing stimulus-response curves from 18 conscious dogs receiving a normal sodium diet we

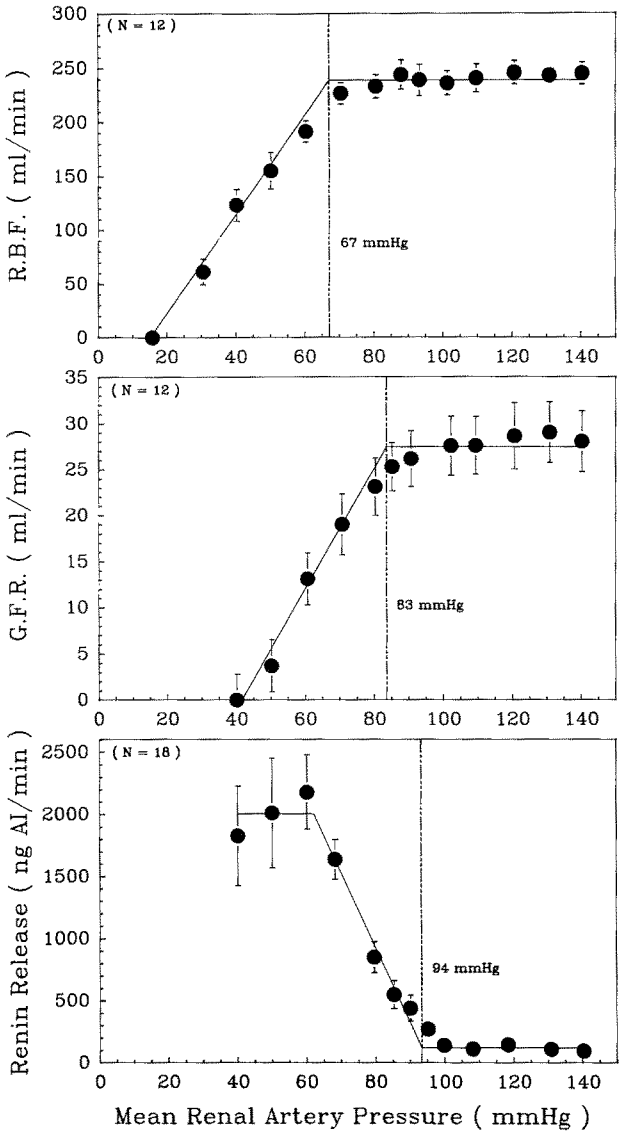

Fig. 3. Autoregulation of renal blood flow (RBF), glomerular filtration rate (GFR) and renin release in resting conscious dogs. Numbers and dashed-dotted lines indicate lower limits of autoregulation and threshold pressure for the pressure-dependent renin release. Data points above 110 mmHg were obtained during B.C.O. with an intrarenal alpha-blockade (0.2 µg/kg/min Prazosin). For points with missing error bars the standard error was smaller than the symbol size. *N*: Number of dogs. (Data taken from: Finke et al. 1983; Kirchheim et al. 1987 and Persson et al. 1988a)

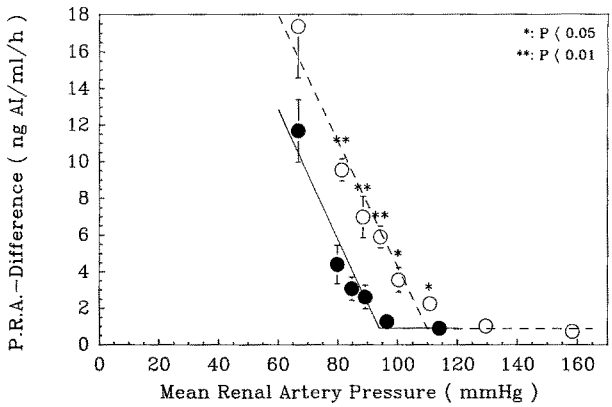

Fig. 4. Effect of bilateral carotid occlusion (B.C.O.) on the renin stimulus-response curve (difference in plasma renin activity between renal-venous and arterial blood as a function of mean renal artery pressure) in conscious dogs. Closed circles: Control ($N=7$ dogs); Open circles: During B.C.O. ($N=7$ dogs). For points with missing error bars the standard error was smaller than the symbol size. (Data taken from Kirchheim et al. 1985 and Ehmke et al. 1989)

found a marked long-term stability (2–6 weeks) in the individual animal. Since no other organ in the cardiovascular system needs a higher capillary filtration pressure than the kidney, it seems reasonable that the kidney induces the formation of a vasoconstrictor hormone before blood pressure reaches a level, which would compromise a normal glomerular filtration (Fig. 3). The high gain of this control system is illustrated by the fact, that below threshold pressure a fall of blood pressure by only 2 mmHg increases renin release by 100% of control. Recently we have quantitatively described the relationship between the stimulus-response curve and long-term blood pressure (Ehmke et al. 1987). A close relationship was found between the parameters of the pressure-dependent renin release and the height of long-term blood pressure. So the pressure-dependent renin release may participate in the long-term control of blood pressure by defending a minimum pressure level necessary for a normal renal function.

Sympatho-Adrenergic Modulation of the Pressure-Dependent Renin Release in Conscious Dogs

Although B.C.O. had no influence on renal blood flow it significantly increased the threshold pressure of the renin stimulus-response curve by on average 17 mmHg without inducing major changes in the slope (Figs. 4, 5) (Kirchheim et al. 1985; Ehmke et al. 1989). Systemic beta-blockade by propranolol in 4 dogs did not affect this response, i.e. B.C.O. still increased threshold pressure by 13 mmHg (Fig. 5). Because of the variability between dogs the slightly smaller increase in threshold during beta-blockade may simply depend on the small number of dogs in this group. In contrast intrarenal alpha-blockade completely abolished the threshold-shift induced by B.C.O. (Fig. 5). Finally we tested, whether a low dose intrarenal infusion of the alpha-1-adrenergic agonist Methoxa-

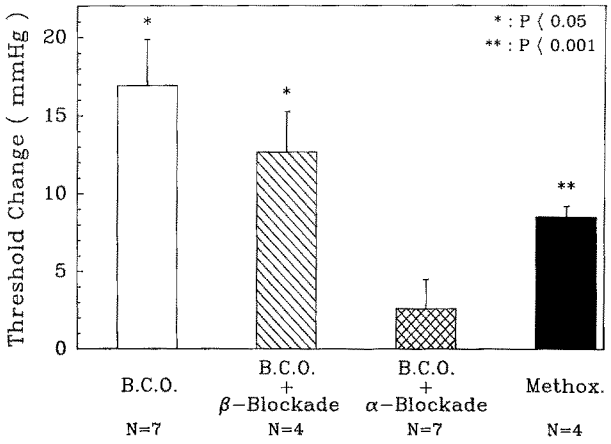

Fig. 5. Average (±SE) increases of threshold of the renin stimulus-response curve elicited by 1) bilateral carotid occlusion (B.C.O.), 2) B.C.O. during a systemic beta-blockade (0.5 mg/kg Propranolol i.v.), 3) B.C.O. during an intrarenal alpha-1-adrenoceptor blockade (0.2 µg/kg/min Prazosin i.a.ren.), and 4) a low dose intrarenal infusion of an alpha-1-adrenoceptor agonist (0.7 µg/kg/min Methoxamine i.a.ren.) in conscious dogs. *N*: Number of dogs. (Data taken from: Ehmke et al. 1989)

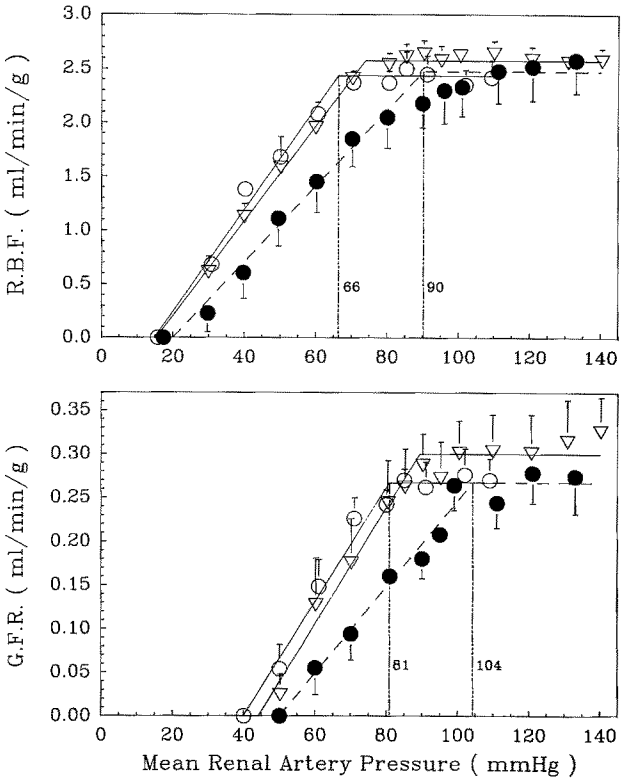

Fig. 6. Modulation of autoregulation of renal blood flow (RBF) and glomerular filtration rate (GFR) by bilateral carotid occlusion (B.C.O.). Open circles: Control ($N=6$ dogs); filled circles: During B.C.O. ($N=6$ dogs); open triangles: during B.C.O. and alpha-blockade (0.2 µg/kg/min Prazosin i.a.ren.) ($N=6$ dogs). Numbers and dashed-dotted lines indicate lower limits of autoregulation. For points with missing error bars the standard error was smaller than the symbol size. (Data taken from: Persson et al. 1988b)

mine, which is too small to induce major changes in total renal blood flow, would also be able to affect threshold pressure. The black column in Fig. 5 demonstrates that methoxamine induced a significant threshold-shift by 9 mmHg. Thus the neural control of renin release involves both, alpha- and beta-adrenoceptors. Beta-1-adrenoceptors located on the juxtaglomerular cells mediate renin release at any perfusion pressure and independent of the "renal baroreceptor" mechanism and macula densa signals. Intrarenal alpha-adrenoceptors, on the other hand, located either on smooth muscle cells of the larger preglomerular vessels or at the peritubular site of proximal tubular cells, are involved in the control of threshold pressure, thereby affecting the setpoint of the "renal baroreceptor" feedback system (see above) and/or the macula densa mechanism.

Sympathetic Modulation of Renal Blood Flow- and Glomerular Filtration Rate-Autoregulation in Conscious Dogs

Figure 6 shows that B.C.O. increases the lower limit of RBF-autoregulation by 24 mmHg and that of GFR-autoregulation by 23 mmHg. This shift is completely abolished by an intrarenal alpha-blockade (Persson et al. 1988b). These curves support the results mentioned above, since they indicate, that a moderate activation of the renal sympathetic nerves at a normal or an increased renal perfusion pressure causes little or no change in RBF and GFR. However, any reduction of blood pressure under these conditions reduces RBF and more importantly compromises renal function by reducing GFR. Although the parallel shift of RBF- and GFR-autoregulation suggests a vasomotor influence on preglomerular resistance vessels inducing a reduction of the "autoregulatory reserve" there are, of course, several other possibilities and it needs further work to explain the mechanism behind this shift in autoregulation.

Antinatriuretic Effect of a Moderate Activation of the Renal Nerves in Conscious Dogs

Figure 7 shows that B.C.O. in resting conscious dogs induces a reduction in sodium excretion. Because sodium excretion is a pressure-dependent phenomenon renal perfusion pressure was kept constant in these experiments. Since at a constant perfusion pressure of around 94 mmHg B.C.O. will increase renin release (see Fig. 4) and as angioten-

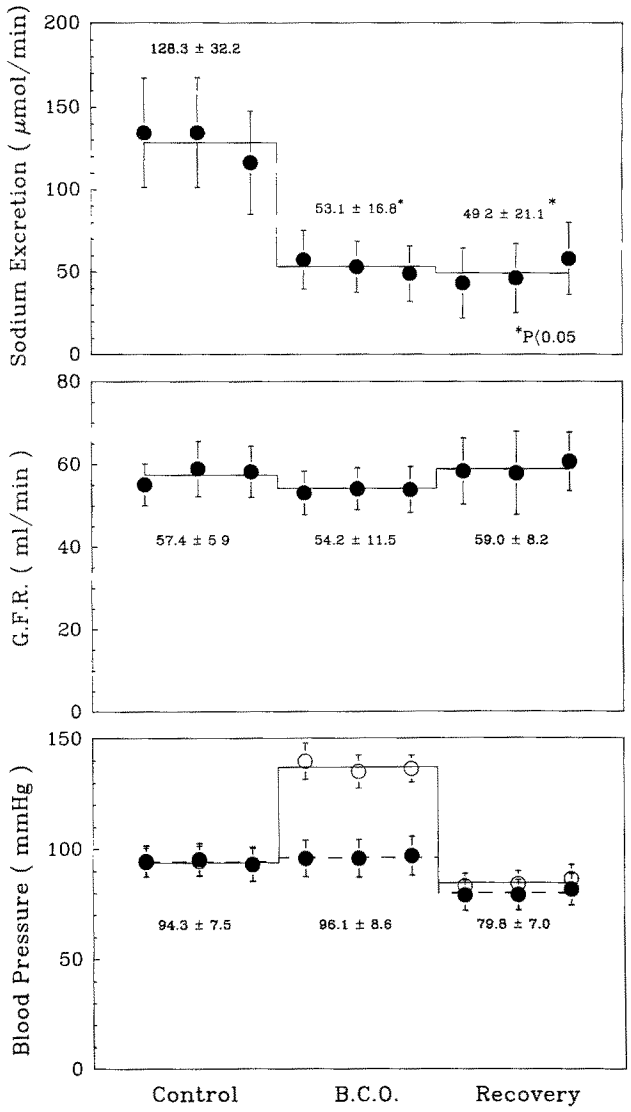

Fig. 7. Effect of bilateral carotid occlusion (B.C.O.) on sodium excretion, glomerular filtration rate (GFR), and blood pressure in 6 conscious dogs during converting enzyme inhibition (1 mg/kg Ramipril p.o.). Every data point depicts a 10 min collection period. During B.C.O. renal perfusion pressure was kept close to its control level. Numbers ± SE indicate the averages of the respective control-, B.C.O.- and recovery-phase. Bottom diagram: open circles: aortic blood pressure; filled circles: renal artery pressure. (Data taken from Persson et al. 1989)

sin II has antinatriuretic effects, the experiments were made after the formation of angiotensin II was blocked by a converting enzyme inhibitor. Sodium excretion during B.C.O. is reduced by 59% independent of changes in GFR (Persson et al. 1989). The failure of sodium excretion to return to the control in the recovery phase is explained by the fact that in the recovery phase renal perfusion pressure is 14 mmHg lower than in the control. The experiments thus clearly demonstrate a direct antinatriuretic effect by a moderate activation of the renal sympathetic nerves, which cannot be attributed to alterations in the GFR or in the level of circulating angiotensin II.

Pathophysiological Implications

Any state of a moderate activation of the renal sympathetic nerves can directly reduce sodium excretion and activate the renin-angiotensin system including all its physiological consequences without inducing major changes in renal blood flow and glomerular filtration rate. The high dynamic sensitivity of the arterial baroreceptors (Kirchheim 1976) will sense even slight decreases in stroke volume and/or pulse pressure, which can induce activations of the renal sympathetic nerves, i.e. a decrease in mean blood pressure is not a prerequisite. Activations elicited from the low pressure side of the circulation ("cardiopulmonary afferents") only need small changes in intrathoracic blood volume as a stimulus. During these moderate sympathetic stimuli the lower limit of GFR-autoregulation is now located at the resting arterial blood pressure (100 mmHg); thus under these conditions even slight decreases of blood pressure will seriously decrease GFR. The resetting of threshold pressure of the pressure-dependent renin release by the renal nerves shows that this potentiating interaction between the non-neural and the neural mechanisms of renin release efficiently defends blood pressure rendering normal renal function. These physiological mechanisms have important consequences for our understanding of the pathophysiology of congestive heart failure (Kirchheim et al. 1988) and hypertension (Guyton et al. 1984).

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