Renal Nerve Stimulation Causes \( \alpha_1 \)-Adrenoceptor-Mediated Sodium Retention but Not \( \alpha_2 \)-Adrenoceptor Antagonism of Vasopressin

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SUMMARY. Renal \( \alpha_2 \)-adrenoceptor stimulation by epinephrine infusion reverses cyclic adenosine monophosphate-mediated effects of vasopressin on sodium and water excretion. We used this response to determine whether renal nerve stimulation can activate renal \( \alpha_2 \)-adrenoceptors in the non-recirculating isolated perfused rat kidney (Krebs-Henseleit solution; 3.5 g/100 ml Ficoll; 1 g/100 ml albumin; 36°C; propranolol 100 nM). In the presence of \( \alpha_1 \)-adrenoceptor blockade with prazosin (30 nM) \( \alpha_2 \)-adrenoceptor stimulation with epinephrine reversed the cyclic adenosine monophosphate-mediated effects of vasopressin on sodium (\( P < 0.05 \)) and water (\( P < 0.05 \)) excretion. Subthreshold (for vasoconstriction) renal nerve stimulation (10 V; 1 msec; 0.65 ± 0.10 Hz) failed to alter the effect of vasopressin. Similarly, higher levels of renal nerve stimulation [plus prazosin (100 nM) or phenoxybenzamine (1.0 mg/kg per hr) to block \( \alpha_1 \)-adrenoceptors] did not activate renal \( \alpha_2 \)-adrenoceptors which are associated with the antagonism of the effects of vasopressin. The same level of subthreshold renal nerve stimulation (0.85 ± 0.14 Hz) in the absence of vasopressin, and without \( \alpha_1 \)- or \( \alpha_2 \)-adrenoceptor blockade, decreased (\( P < 0.05 \)) sodium and water excretion. The reversal of this effect by \( \alpha_1 \)-adrenoceptor blockade (prazosin 30 nM) but not \( \alpha_2 \)-adrenoceptor blockade (yohimbine 300 nM) indicates that this effect of renal nerve stimulation is mediated through \( \alpha_1 \)-adrenoceptors. Thus, subthreshold renal nerve stimulation in the rat kidney induces sodium and water retention through activation of \( \alpha_1 \)-adrenoceptors, as shown by others in the rabbit and dog. This and even higher levels of renal nerve stimulation failed to activate \( \alpha_2 \)-adrenoceptors associated with antagonism of vasopressin. These results are consistent with the theory that \( \alpha_1 \)-adrenoceptors—which mediate sodium and water retention—are located postjunctionally, and that \( \alpha_2 \)-adrenoceptors—which antagonize the renal actions of vasopressin—are located extrajunctionally. (Circ Res 57: 304-311, 1985)

RENA L sympathetic nerves play a tonal role in sodium retention (for reviews, see Kim et al., 1980; DiBona, 1982). This was initially shown as enhanced water and sodium excretion following renal denervation (Kris et al., 1948; Kaplan and Rapoport, 1951). Recent studies in conscious rats have confirmed these findings (Rogenes and Gottschalk, 1982; DiBona and Sawin, 1983). Also, subpressor threshold concentrations of catecholamines (Kim et al., 1980) or renal nerve stimulation (RNS) (Slick et al., 1975; DiBona and Sawin, 1982; Osborn et al., 1983) increase sodium retention.

The effects of renal sympathetic nerve stimulation and catecholamines on sodium and water excretion appear to be mediated through either \( \alpha_1 \)- or \( \alpha_2 \)-adrenoceptors. Tubular \( \alpha_1 \)-adrenoceptor activation by subpressor RNS in the dog (Osborn et al., 1983) and rabbit (Hesse and Johns, 1984a) increases sodium and water reabsorption. However, the reported effects of renal \( \alpha_2 \)-adrenoceptor activation have been variable. Recently, Hesse and Johns (1985) reported finding that \( \alpha_2 \)-adrenoceptor activation had no effect on sodium and water excretion. However, other investigations, including that of Hesse and Johns (1985), have reported an increase in sodium and water excretion. In these studies, infusion of \( \alpha_2 \)-adrenoceptor agonists in the dog (Strandhoy et al., 1982, 1983) and rabbit (Hesse and Johns, 1985) in vivo, in isolated rabbit cortical collecting-duct segments (Krothapalli et al., 1984), and in the isolated perfused rat kidney (Smyth et al., 1984a), increased sodium and/or water excretion. These observed effects of \( \alpha_2 \)-adrenoceptor activation were subsequently attributed to antagonism of vasopressin by inhibition of adenylate cyclase in a few of the studies (Krothapalli et al., 1983, 1984; Smyth et al., 1985). Conversely, in the isolated perfused rat kidney in the presence of furosemide, \( \alpha_2 \)-adrenoceptor activation decreased the elevated sodium, water, and cyclic adenosine monophosphate (cAMP) excretion (Smyth et al., 1984b). In these studies, it appears that the effects of \( \alpha_2 \)-adrenoceptor stimulation were through reversal of the specific effects of furosemide or vasopressin that were mediated by cAMP. These studies suggested that vasopressin and furosemide stimulated specific adenylate cyclases, whereas epinephrine, through \( \alpha_2 \)-adrenoceptors, was a nonspecific inhibitor of these stimulated adenylate cyclases.

The above observations suggest a possible exclu-
selective concentration of propranolol (100 nM) was added to the perfusion medium. Creatinine (50 mg/dl) was added for determination of the glomerular filtration rate (GFR). The solution was oxygenated by passing the perfusate through the hollow core fibers of a C-DAK 135 sce artificial kidney (Cordis Dow). Equilibration with 95% O2-5% CO2 was achieved by flowing this gas mixture through the dialysate chamber at a rate of 2 liters/min. The perfusate was prefiltred and filtered again (5.0 μm) just before entering the kidney. The temperature of the perfusate at the level of the kidney was 35–37°C with a pH of 7.30–7.40. A Harvard peristaltic pump (model 1210) was used to maintain a pulsatile flow.

**Experimental Protocol**

After a stabilization period of 15 minutes, four timed urine collections were obtained in preweighed collection tubes. Urine was collected 15–25, 30–40, 40–50, and 50–60 minutes after the start of perfusion. Urine flow rate was determined gravimetrically, and perfusate flow rate was determined volumetrically for each collection period. Experimental treatments were administered immediately before the second urine collection (30–40 minutes). Thus, the first collection period was used to verify adequate renal function of each individual preparation prior to the administration of the experimental interventions. The two major groups studied are listed below.

**Renal Nerve Stimulation and Urinary Electrolyte Excretion**

In control studies (no interventions) and those in which the effect of RNS was investigated, the area around the renal artery was cleaned of perirenal tissue once perfusion was begun. Two platinum electrodes were placed in contact with the renal artery as close as possible to the end of the cannulated portion. The renal nerves located in this area were then stimulated (Narco stimulator S1-10) at 10 V and 1.0 msec at a frequency which was below the threshold level required to induce an increase in perfusion pressure. This was determined by starting at 0.3 Hz and gradually increasing the frequency until a slight change in perfusion pressure was observed. Then the frequency was adjusted just below this level. Kidneys that failed to demonstrate an effect by 3.0 Hz were excluded. Similarly, the threshold level was established again at the end of the experiment. Kidneys that failed to demonstrate a threshold similar to that observed at the beginning of the experiment also were excluded.

The role of α1- and/or α2-adrenoceptors in mediating the effects of nerve stimulation on sodium excretion was established in two additional separate groups of rats with prazosin (30 nm) and yohimbine (300 nm), respectively. In these experiments, infusion of yohimbine or prazosin at the appropriate rate was started immediately before nerve stimulation and was continued throughout the experiment. In these experiments, the subthreshold level of nerve stimulation was established before the antagonist infusions.

**Renal Nerve Stimulation and Vasopressin-Induced Changes in Sodium and Water Excretion**

In these experiments, we attempted to activate, by RNS, renal α2-adrenoceptors associated with the antagonism of the effects of vasopressin (Smyth et al., 1984a). Propranolol and prazosin were used to block β- and α1-adrenoceptors, respectively, to ensure that only α2-adrenoceptors would be activated. Initially, prazosin (30 nm) was used.

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to block α₁-adrenoceptors. In these experiments, following the first urine collection, no intervention (control), vasopressin (10 μU/ml), or vasopressin and renal nerve stimulation (subpressor as above) was administered. The effect of higher levels of RNS on the action of vasopressin was studied in the presence of a higher dose of prazosin (100 nm) to prevent elevations in perfusion pressure, since changes in renal hemodynamics (i.e., perfusion pressure) may alter sodium excretion. Recent experiments in our laboratory have demonstrated that this dose of prazosin does not alter the α₂-adrenoceptor-mediated antagonism of vasopressin by epinephrine infusion in this preparation.

In another series of experiments, an α₁-adrenoceptor-selective infusion of phenoxybenzamine (Smyth et al., 1984a) was used to block α₁-adrenoceptors and allow a higher level of RNS before changes in perfusion pressure were observed. In these experiments, after the first urine collection, no intervention (control), vasopressin (10 μU/ml), vasopressin plus epinephrine (28 nM) and vasopressin, epinephrine, and RNS were administered to the study groups. In all groups studied, rats received an infusion of phenoxybenzamine (1.0 mg/kg per hr), in vivo, before preparation for perfusion was begun.

Perfusate and urine Na⁺ and K⁺ concentrations were determined with a Beckman Klina flame photometer. Creatinine concentrations were determined by a method described by Yatzidis (1974).

Drugs used and their sources are as follows: vasopressin (Sigma), yohimbine (Sigma), prazosin (Pfizer), dl-propranolol (Sigma), L-epinephrine (Sigma), and phenoxybenzamine (Smith, Kline and French).

An analysis of variance was used for statistical evaluation. Homogeneity of the variances of the groups studied was established with Bartlett's test (Zar, 1974). The level of significance between groups was determined with Newman-Keuls multiple comparison test (Zar, 1974).

**Results**

**Vascular Dynamics**

Perfusion pressure and flow were not altered by renal nerve stimulation, even though the GFR tended to decrease (Fig. 1). In the presence of yohimbine, this decrease in GFR became significant (P < 0.05) for all collection periods after the control period (30-40, 40-50, and 50-60 minutes). Similarly, RNS in the presence of prazosin depressed GFR, and this was significant (P < 0.05) during the last collection period.

**Renal Nerve Stimulation and Electrolyte Excretion**

Electrolyte and water excretion prior to any experimental treatments during the control collection period (15-25 minutes) were similar in all the groups...
Smyth et al. / Renal α₂- and α₁-Adrenoceptors

Table 1
Effect of α₂- and α₁-Adrenoceptor Blockade on Subthreshold Renal Nerve Stimulation-Induced Sodium Retention

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>RNS</th>
<th>RNS + Yoh</th>
<th>RNS + Prz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freq. (Hz)</td>
<td>0</td>
<td>0.85 ± 0.14</td>
<td>0.77 ± 0.17</td>
<td>0.84 ± 0.13</td>
</tr>
<tr>
<td>PP (mm Hg)</td>
<td>97.2 ± 1.7</td>
<td>93 ± 1.5</td>
<td>90.2 ± 0.72</td>
<td>94.1 ± 1.0</td>
</tr>
<tr>
<td>PF (ml/min)</td>
<td>20.1 ± 0.7</td>
<td>21.2 ± 0.4</td>
<td>19.8 ± 0.4</td>
<td>21.3 ± 0.81</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>0.76 ± 0.05</td>
<td>0.65 ± 0.06</td>
<td>0.51 ± 0.03</td>
<td>0.67 ± 0.06</td>
</tr>
<tr>
<td>V (μl/min)</td>
<td>87.2 ± 4.1</td>
<td>57.9 ± 3.9</td>
<td>59.2 ± 7.5</td>
<td>82.5 ± 3.3</td>
</tr>
<tr>
<td>[Na+] (mEq/liter)</td>
<td>51.5 ± 3.9</td>
<td>29.1 ± 3.4</td>
<td>32.1 ± 3.9</td>
<td>48.2 ± 3.4</td>
</tr>
<tr>
<td>[K⁺] (mEq/liter)</td>
<td>47.5 ± 3.0</td>
<td>57.6 ± 2.8</td>
<td>54.2 ± 2.1</td>
<td>54.5 ± 2.0</td>
</tr>
<tr>
<td>UNaV (μEq/min)</td>
<td>4.50 ± 0.42</td>
<td>1.71 ± 0.23</td>
<td>1.96 ± 0.37</td>
<td>3.98 ± 0.34</td>
</tr>
<tr>
<td>UNaV (μEq/min)</td>
<td>4.08 ± 0.22</td>
<td>3.20 ± 0.24</td>
<td>3.33 ± 0.28</td>
<td>4.47 ± 0.16</td>
</tr>
<tr>
<td>% FeNa</td>
<td>4.58 ± 0.41</td>
<td>1.91 ± 0.27</td>
<td>2.75 ± 0.40</td>
<td>4.69 ± 0.79</td>
</tr>
</tbody>
</table>

C = control; RNS = renal nerve stimulation; Yoh = yohimbine (300 nm); Prz = prazosin (30 nm).

Subthreshold RNS decreased (P < 0.05) urinary volume (87.2 ± 4.1 to 57.9 ± 3.9 μl/min), urinary sodium concentration (31.5 ± 3.9 to 29.1 ± 3.4 mEq/liter) and excretion (4.50 ± 4.2 to 1.71 ± 0.23 μEq/min), urinary potassium excretion (4.08 ± 0.22 to 3.30 ± 0.24 μEq/min), and the percent fractional excretion of sodium (4.58 ± 0.41% to 1.91 ± 0.27%). α₁-Adrenoceptor blockade with yohimbine (300 nm) had no effect on RNS, and the differences (P < 0.05) attenuated the magnitude of the spontaneous time-related increase in urine flow rate and the sodium and potassium excretion observed in the control group. Yohimbine and prazosin had no effect on RNS, and the differences (P < 0.05) observed between the control and RNS groups were obtained during the third (40-50 minute) urine collection period.

α₂-Adrenoceptor stimulation with epinephrine (in the presence of prazosin 30 nm) reversed (P < 0.05) the effects of RNS on urinary volume (87.2 ± 4.1 to 57.9 ± 3.9 μl/min), urinary sodium excretion (1.88 ± 0.40 to 5.01 ± 0.61 μEq/min), and the percent fractional excretion of sodium (2.75 ± 0.40% to 0.40 ± 0.27%). Thus, α₁-α₂-Adrenoceptor blockade with prazosin (30 nm) reversed the effect of RNS back to control levels by the third urine collection period (40-50 minutes).

Renal Nerve Stimulation and Vasopressin-Induced Changes in Sodium and Water Excretion

The above series of experiments demonstrate that α₁-Adrenoceptors mediate the attenuation of the time-related increases in sodium excretion following subthreshold renal nerve stimulation. The present experiments were conducted in the presence of β- and α₁-Adrenoceptor blockade to ensure that only α₂-Adrenoceptors were activated by epinephrine infusion or neurally released catecholamines. The data presented were obtained during the third urine collection period (40-50 minutes) in each group of rats. In the first urine collection period for data shown in Figures 3 and 4, no differences in renal hemodynamics or electrolyte and water excretion were demonstrated (data not shown). Similarly, no changes in perfusion pressure, perfusate flow, or glomerular filtration were observed during the third urine collection period (data not shown), the time during which the data shown in Figures 3 and 4 were collected.

Vasopressin (10 μU/ml) decreased (P < 0.05) urinary volume (87.2 ± 4.1 to 6.7 ± 4.8 μl/min), urinary sodium excretion (4.50 ± 0.42 to 1.88 ± 0.40 μEq/min), and the percent fractional excretion of sodium (4.58 ± 0.41% to 2.05 ± 0.50%) (Fig. 3). α₂-Adrenoceptor stimulation with epinephrine (in the presence of prazosin 30 nm) reversed (P < 0.05) vasopressin's effects on urinary volume (60.7 ± 4.8 to 87.2 ± 7.5 μl/min), urinary sodium excretion (1.88 ± 0.40 to 5.01 ± 0.61 μEq/min), and the percent fractional excretion of sodium (2.05 ± 0.50% to 4.38 ± 0.53%). Subthreshold renal nerve stimulation (0.65 ± 0.10 Hz) plus prazosin (30 nm), failed to activate α₂-Adrenoceptors and subsequently alter va-
FIGURE 3. The inability of renal nerve stimulation (RNS) to activate \( \alpha_2 \)-adrenoceptors as measured by the reversal of the effects of vasopressin on electrolyte excretion. The frequency of stimulation (Hz) at 10 V, 1 msec, was 0.65 ± 0.10 in the presence of 30 nM prazosin and 2.00 ± 0.71 in the presence of 100 nM prazosin. Vertical axis is as described in Figure 1. Values represent mean ± SEM. * Denotes \( P < 0.05 \). Data shown were collected during the third urine collection (40-50 minute) period for each group.

**Discussion**

Adrenergic nerves terminate in close proximity to basement membranes of proximal and distal tubules (Barajas and Muller, 1973), the loop of Henle (Barajas et al., 1981), renal blood vessels (Muller and Barajas, 1972), juxtaglomerular apparatus, and the afferent and efferent arterioles (Barajas and Muller, 1973). Alterations in renal adrenergic tone, in the absence of renal hemodynamic changes, alter renal sodium handling (Slick et al., 1975; Osbome et al., 1983). Thus, renal adrenergic nerves have access to the functional tubular units which regulate sodium homeostasis. Although \( \alpha_1 \)-adrenoceptors have been demonstrated to mediate nerve-stimulated sodium retention (Osborn et al., 1983; Hesse and Johns, 1984), the relationships between \( \alpha_1 \) and \( \alpha_2 \)-adrenoceptors are unclear.

Besarab et al. (1977) and Bello-Reuss (1980) suggested that catecholamines or renal adrenergic nerves may regulate electrolyte excretion through activation of \( \beta \)-adrenoceptors. However, their conclusion was based on studies using a very high concentration of propranolol (10^{-4} M) which has nonspecific membrane-stabilizing effects.

Most of the evidence indicates that the effects of renal nerve stimulation on sodium excretion are mediated by \( \alpha \)-adrenoceptors. Renal nerve stimulation, in the absence of changes in renal hemody-
namics, enhanced sodium reabsorption in the dog (DiBona, 1982). However, the reversal of this effect by relatively nonspecific adrenoceptor blockade with phenoxybenzamine (Zambraski et al., 1976), phentolamine (Sadowski and Portalska, 1982), or guanethidine (Slick et al., 1975) failed to identify the $\alpha_2$-adrenoceptor subtype(s) responsible. Recently, Osborn et al. (1983) demonstrated in the dog, and Hesse and Johns (1984a) in the rabbit, that suppressor levels of renal nerve stimulation induced an antinatriuresis through activation of renal $\alpha_1$-adrenoceptors.

The present study verifies this finding in the rat. $\alpha_1$-Adrenoceptor blockade with prazosin blocked the antinatriuretic action of subthreshold renal nerve stimulation. This ability of the neurotransmitter released by low levels of renal nerve stimulation to activate $\alpha_1$-adrenoceptors would suggest that these adrenoceptors were located postjuntionally but within the synaptic cleft area, as shown in Figure 5. In the presence of prazosin, no effects of RNS were observed. The failure to observe an effect of RNS when $\alpha_2$-adrenoceptors were unblocked would indicate that, under basal conditions, $\alpha_2$-adrenoceptors do not alter sodium, water, and potassium excretion. Alternatively, this may indicate that $\alpha_2$-adrenoceptors, at least those associated with sodium and water excretion, were located such that RNS-released neurotransmitter did not have contact with these receptors. Also, since yohimbine alone, an $\alpha_2$-selective blocker, did not alter the effect of RNS, it appears to be entirely an $\alpha_1$-adrenoceptor-mediated effect. We extended this study further by attempting to elucidate whether this same level of RNS mediated a well-documented $\alpha_2$-adrenoceptor effect.

The $\alpha_2$-adrenoceptor response studied was the antagonism of vasopressin-induced sodium and water retention (Strandhoy et al., 1983; Smyth et al., 1984a). These studies were done in the presence of prazosin to reverse the effect of RNS on $\alpha_1$-adrenoceptors back to control and ensure that only $\alpha_2$-adrenoceptors were activated. Sub- or supratherhold levels of RNS failed to alter the response to vasopressin, indicating that these $\alpha_2$-adrenoceptors were not activated by the released neurotransmitter.

There may be two reasons for the failure to observe an effect on RNS. First, the area of the nephron activated by vasopressin may not receive sympathetic innervation. Vasopressin activates adenylate cyclase in the ascending thin limb of Henle (Jacobson, 1981), medullary thick ascending limb of Henle (Culpepper and Andreoli, 1983), and in the medulary and cortical collecting tubules (Jacobson, 1981; Krothapalli and Suki, 1983, 1984). This activation of adenylate cyclase has been related to altered chloride absorption in mouse medullary thick ascending limbs of Henle (Culpepper and Andreoli, 1983) and altered water absorption in the rabbit cortical collecting tubule (Krothapalli and Suki, 1983, 1984). However, only the effect of vasopressin on adenylate cyclase and water absorption in the cortical collecting tubule has been shown to be attenuated by $\alpha_2$-adrenoceptor stimulation (Krothapalli and Suki, 1984). In accord with these findings, studies in our laboratory have demonstrated that vasopressin-stimulated adenylate cyclase is inhibited by $\alpha_2$-adrenoceptor stimulation in medullary and cortical collecting tubules and not in the medullary thick ascending limb of Henle in the rat (Umemura et al., 1985). These studies would indicate, although not conclusively, that $\alpha_2$-adrenoceptor stimulation antagonizes the effect of vasopressin stimulated adenylate cyclase predominantly in the cortical collecting tubule. This section of the kidney, as well as the other sites at which vasopressin activates adenylate cyclase, have demonstrated...
some sympathetic innervation (Kim et al., 1980; Barajas et al., 1984). Thus, the failure to activate α2-adrenoceptors and antagonize the effects of vasopressin could not be directly related to a lack of sympathetic innervation at vasopressin’s sites of action. However, whether the specific cell types with which vasopressin interacts were innervated has not been determined.

Thus, a favorable explanation would be that α2-adrenoceptors associated with antagonism of the effects of vasopressin (i.e., adenylate cyclase inhibition) were not activated by the neurotransmitter released following low levels of renal nerve stimulation because of their extrajunctional location (Fig. 5). In parallel to the present study, Yamaguchi and Kopin (1980) observed that the response (pressor) in pithed rats to infused catecholamines was insensitive to α1-antagonists but was selectively blocked by α2-antagonists, whereas the response (pressor) following nerve stimulation was selectively blocked by α1-antagonists. Similar findings have been reported by Willfert et al. (1982). These and similar findings in other species have led to the hypothesis that (at least in arterial tissue) α1-adrenoceptors are located postjunctionally, and α2-adrenoceptors, extrajunctionally (Timmermans and Van Zwieten, 1981, 1982; Langer and Shepperson, 1982; Langer and Hicks, 1984; Ruffolo, 1984). This proposed model in the vasculature of normal rats is consistent with that proposed in the present study (Fig. 5). The major differences are that the end-organ response in the vasculature is vasoconstriction, and, in this tissue, α2-adrenoceptors may be associated with calcium channels rather than the adenylate cyclase system (Timmermans and Van Zwieten, 1982). Thus, nerve stimulation would physiologically activate postjunctional α1-adrenoceptors. Circulating catecholamines, however, would predominantly activate extrasynaptic α2-adrenoceptors with the α1-adrenoceptor being activated only under pathological conditions when circulating catecholamine levels are high or if their affinity or number should increase.

In the original functional classification of α1- and α2-adrenoceptors, Berthelsen and Pettinger (1977) proposed a “postsynaptic” location for the multitudinous α2-adrenoceptors on plasma membranes of effector cells. According to this new evidence, the localization should now be more specifically defined as “extrajunctional site” of α2-adrenoceptors, as in Figure 5.

In the present study, subpressor levels of renal nerve stimulation and epinephrine infusion (with α1-adrenoceptor blockade) were administered to avoid changes in renal hemodynamics. In a number of nonrenal vascular beds in various species, catecholamines can induce vasoconstriction by activation of α1- and/or α2-adrenoceptors (Langer and Hicks, 1984). However, in the renal vasculature, the α1-adrenoceptor appears to be the predominant receptor mediating this effect in the dog (Horn et al., 1982), the cat (Drew and Whiting, 1979), and the rat (Schmitz et al., 1981; Wolff et al., 1985). At present, only studies in the rabbit have demonstrated that both α1- and α2-adrenoceptors mediated a considerable renovasconstriction (Hesse and Johns, 1985). Thus, in the present study, vascular α2-adrenoceptors need not be considered in the interpretation of the results.

Finally, α1-adrenoceptors have only recently been identified, and, subsequently, their physiological function(s) have yet to be described in detail. Another effect of α2-adrenoceptor stimulation not measured in the present study or elucidated at present may be reversed by RNS.

In conclusion, α1- and α2-adrenoceptor stimulation alters sodium and water excretion. Stimulation of α1-adrenoceptors increased basal sodium and water reabsorption (present study), whereas α2-adrenoceptor activation had no effect on basal (i.e., no furosemide or vasopressin) sodium and water excretion (Smyth et al., 1984b, 1985; Hesse and Johns, 1985). The effects of renal denervation and renal nerve stimulation on sodium retention previously documented are probably mediated by α1-adrenoceptors located postjunctionally (Osborn et al., 1983; Hesse and Johns, 1984a; present study). Qualitatively, α2-adrenoceptors (extrajunctional) may decrease (Smyth et al., 1984b), increase (Strandhoy et al., 1983; Smyth et al., 1984a; Hesse and Johns, 1985), or have no effect (Hesse and Johns, 1985) on sodium excretion. These effects appear to be dependent on the function specificity of the predominant adenylate cyclase-cAMP activated at any given moment (Smyth et al., 1984b) and may be dependent on blood-borne hormones (i.e., epinephrine), rather than on neurally released catecholamines (i.e., norepinephrine).

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References


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Renal nerve stimulation causes alpha 1-adrenoceptor-mediated sodium retention but not alpha 2-adrenoceptor antagonism of vasopressin.

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