Specific Supersensitivity of the Mesenteric Vascular Bed of Dahl Salt-Sensitive Rats


Dahl salt-sensitive (DS) and salt-resistant (DR) rats were maintained on a diet containing normal (0.45%) or high (7%) salt for 5 days. The DS rats had slightly higher systolic blood pressures than DR rats, although a high salt diet failed to significantly elevate pressure in either group when compared with their appropriate (low salt diet) controls. The sensitivity of the isolated, perfused mesenteric vasculature from DS rats fed a high salt diet to nerve stimulation was greater when compared with all other groups in the presence or absence of cocaine (1 μM). A similar difference in sensitivity between high salt DS rats and high salt DR rats to bolus injections of norepinephrine was observed only in the presence of cocaine. The change in sensitivity was characterized by a leftward shift of the dose–response curve without a change in maximum response. No difference in sensitivity between the high salt DS group and any other treatment group was observed in response to the pressor agents KCl, angiotensin II, 5-hydroxytryptamine or the depressor agent acetylcholine. These data indicate that DS rats on a short-term, high salt diet possess a significant and specific elevation in sensitivity to nerve stimulation and norepinephrine in the absence of an increase in blood pressure. Differences in the effectiveness of cocaine among the groups suggest that differences may exist in neuronal uptake (uptake 1). Although the greater neuronal uptake in preparations from high salt DS rats masks a greater sensitivity of the vascular smooth muscle to exogenous norepinephrine, supersensitivity of the smooth muscle may contribute to the enhanced responses to nerve stimulation since neuronal uptake has less influence on responses to neurally released norepinephrine. The specificity of the sensitivity difference suggests that the vascular smooth muscle of DS rats on high salt diets for 5 days possesses an abnormality either at the level of the α1-adrenoceptor or in the sequelae that develop after adrenoceptor occupation. This could be an early event in the induction of hypertension in the Dahl rat. (Hypertension 1991;17:349–356)
detected before the onset of an NaCl-induced elevation of arterial pressure. The perfused mesenteric bed includes a composite of resistance vessels, and its isolation removes in vivo variables such as neuronal activity and blood-borne vasoconstrictors. Particular attention is paid to controlling the disposition of norpinephrine in the tissues by neuronal and extraneuronal transport. The growing body of data with this preparation will allow a valuable comparison with other models of hypertension under uniform conditions.

Methods

Animals

Male DS and DR rats (outbred strains), 3–4 weeks of age, were purchased from Harlan Sprague Dawley, Indianapolis, Ind., and were maintained for approximately 5 days before any treatment. After the period of acclimation, the systolic blood pressures were measured with tail-cuff plethysmographic procedures. The rats were initially fed a low salt diet (0.18% NaCl), which was purchased from Teklad, Madison, Wis. One day after blood pressures were measured, both DS and DR rats were randomly assigned to either “normal” or “high salt” groups and were started on a diet in which NaCl was added to the regular lab chow to achieve a final content of 0.45% (normal salt) or 7% (high salt) NaCl. Animals were maintained on the respective diets for 5 days with systolic blood pressure measurements taken again 1 day before the rats were killed.

Preparation of Tissues

The preparation of the isolated, perfused mesenteric vasculature was made according to the method originally described by Castellucci et al with modifications previously established in our laboratory. This preparation involves the entire isolated mesenteric vascular bed with the intestinal tract intact. Preparations were obtained from four rats each day, one each from the DS normal salt, DS high salt, DR normal salt, and DR high salt groups. The rats were killed by cervical dislocation followed by decapitation. Heparin (10 units/100 g) was administered intravenously approximately 5 minutes before the rats were killed to reduce clotting in the fine resistance vessels of the mesenteric vasculature. Preliminary experiments indicated that this dose of heparin did not alter either the basal perfusion pressure or the responses to any agonist used in the experiments described below. After a "V" incision was made in the abdomen, the inferior mesenteric and superior pancreaticoduodenal artery were ligated, and the superior mesenteric artery was located. A cannula of PE-90 tubing was inserted into the superior mesenteric artery at its junction with the aorta and was tied firmly in place. The entire mesenteric vascular bed and intestinal tract were removed from the animal and the intestinal contents were flushed out with ice-cold Krebs' solution. The appendix was identified, ligated, and removed. The preparation was then mounted on a holding apparatus containing platinum stimulating electrodes. One ring electrode circled the proximal portion of the mesenteric artery. At a position 2.5 cm distal from the ring electrode, a hook electrode was embedded in the tissue fascia. The apparatus with the preparation attached was then placed into a 50 ml water-jacketed organ bath, and the preparation was perfused through the cannula with a modified Krebs-Henseleit solution of the following composition (mM): NaCl 117, KCl 4.7, CaCl2 2.5, KH2PO4 1.2, MgSO4 1.2, NaHCO3 25, and glucose 11.5. The Krebs-Henseleit solution was continuously bubbled with a 95% O2-5% CO2 mixture, was maintained at 37°C, and was delivered to the tissues at a constant flow of 4 ml/min by means of a Gilson Minipuls 2 peristaltic pump (Rainin Instrument Co., Woburn, Mass.). A "t"-tube was inserted between the preparation and the pump and connected to a Statham P23 AC pressure transducer (Statham Co., Hato Rey, Puerto Rico), which was used to monitor perfusion pressure. Changes in perfusion pressure were recorded on a Grass Model 79D polygraph (Grass Instrument Co., Quincy, Mass.).

Experimental Protocol

Noncumulative dose–response and frequency–response curves were constructed on individual preparations. Drugs were injected (in bolus doses) intraluminally into the perfusion fluid near the cannula. Frequency–response curves were obtained using a Grass Model S44 stimulator that produced square wave pulses of 0.5 msec duration and supramaximal voltage from the platinum electrodes around the superior mesenteric artery. Preparations were stimulated for 20 seconds using increasing frequencies, with 2 minutes allowed after each return to baseline between successive stimulation periods. Cocaine (1 µM), desoxycorticosterone acetate (DOCA, 30 µM), or phentolamine (3 µM) was added to the perfusion fluid 60 minutes, 30 minutes, or 15 minutes, respectively, before any subsequent dose–response curves were constructed. Preliminary studies showed that the responses of the preparations to nerve stimulation and norpinephrine remained unchanged for up to 5 hours after beginning the perfusion procedure. Multiple dose–response curves could be constructed on an individual preparation, which permitted comparisons of dose–response data among different agonists as well as to the same agonist before and after exposure to other agents (e.g., cocaine and phentolamine). Preliminary experiments suggested that multiple dose–response curves could be constructed without significant alteration in responsiveness.

Statistical Analysis

Body weight, systolic blood pressure, basal perfusion pressure, and changes in perfusion pressure were calculated as arithmetic mean values. The sensitivity of an individual preparation to a given stimulus was calculated by constructing full dose–response or frequency–response curves and determining the
TABLE 1. Body Weight and Systolic Pressure in Dahl Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Weight (g)</th>
<th>Systolic blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial</td>
</tr>
<tr>
<td>DS normal salt</td>
<td>30</td>
<td>187±4*</td>
<td>119±3f</td>
</tr>
<tr>
<td>DS high salt</td>
<td>30</td>
<td>172±4</td>
<td>118±3</td>
</tr>
<tr>
<td>DR normal salt</td>
<td>32</td>
<td>187±4*</td>
<td>110±3</td>
</tr>
<tr>
<td>DR high salt</td>
<td>30</td>
<td>176±4</td>
<td>116±3</td>
</tr>
</tbody>
</table>

Values given are mean±SEM. Body weights were measured on the day the rats were killed. Initial arterial pressure was determined on the day that salt diets were begun. Final arterial pressure was determined 24 hours before the rats were killed. DS, Dahl salt-sensitive rats; DR, Dahl salt-resistant rats.

*p<0.05 for DS normal salt and DR normal salt vs. DS high salt and DR high salt groups.

Statistical analysis was performed using an analysis of variance followed by Newman-Keuls test for comparisons among multiple groups. In a few instances, as appropriate, Student’s t test for paired samples was used. A value of p≤0.05 was considered to be significant.

Results

Body weight and arterial pressures of rats included in the experiments are presented in Table 1. The weight of the rats at the time they were killed varied only moderately among the groups but was least in the DS rats on the high salt diet. The mean systolic pressure was slightly higher in the DS compared with the DR rats, both before initiation of salt diets and after 5 days on the diets. However, consistent with our previous experience,9 systolic pressure in DS rats after 5 days on the 7% NaCl diet was not increased above that in DS rats on the normal salt diet.

The mean basal perfusion pressures, determined 1 hour after the perfusion was begun and before the administration of any drugs, were similar among the four groups (DS normal salt, 26±1 mm Hg; DS high salt, 25±1 mm Hg; DR normal salt, 28±1 mm Hg; DR high salt, 24±1 mm Hg). Basal perfusion pressures remained stable throughout the course of the experiments in all groups.

Figure 1 presents the mean frequency–response curves obtained with transmural nerve stimulation of the perfused mesenteric vascular bed. The curve obtained in the preparations from the DS high salt group lies to the left of the curves for the other three groups (p<0.05). There were no significant differences in mean maximum responses to nerve stimulation among the four groups. The greater sensitivity of the DS high salt group to nerve stimulation was also apparent in the presence of cocaine (1 μM), as shown in Figure 2. Although cocaine increased the maximum response to nerve stimulation by 30–40 mm Hg in each of the four experimental groups, there were no significant differences in maximum response among the groups in the presence of cocaine. Control responses were unchanged when repeated in the absence of cocaine.

In the absence of cocaine, the clearest difference among the four groups in response to bolus doses of norepinephrine was in maximum response (Figure 3, Table 2). Even in that regard, the DS high salt group was significantly greater than only one group, the DR normal salt group. Although there were some small but significant differences in sensitivity (as determined by the geometric mean ED50) among the groups, the mesenteric vasculature from DS high salt rats did not differ significantly in sensitivity to norepinephrine in comparison with any other group (Table 2).

Cocaine (1 μM) induced significant decreases in the ED50 and increases in maximum response to norepinephrine in all four experimental groups (Ta-
FIGURE 2. Line graph showing mean frequency-response curves obtained in mesenteric vascular beds by means of electrical stimulation of periarterial nerves. Experiments done in presence of cocaine (1.0 μM). Vertical bars represent SEM. *Significant difference (p<0.05) between responses of preparations from Dahl salt-sensitive (DS) rats fed a high salt diet vs. responses of preparations from each of the other groups. n=10–12 per group. DR, Dahl salt-resistant rats.

As with nerve stimulation, responses to norepinephrine were very repeatable in the absence of cocaine. The decrease in ED₅₀ values induced by cocaine was greatest for the DS high salt group (ratio of ED₅₀ before and after cocaine of 3.2) and least for the DR high and normal salt groups (ratios 1.7 and 1.5, respectively). Cocaine increased the maximum responses to both norepinephrine and nerve stimulation. However, the maximum responses to norepinephrine and nerve stimulation were similar to each other either in the absence or presence of cocaine (compare Figures 1 and 3 and 2 and 4).

In the presence of cocaine, the geometric mean ED₅₀ for norepinephrine in the DS high salt group was approximately one half of that value for any other group (Table 2). This difference was significant for the DS high salt group versus the DR high salt group (p<0.05) but not quite significant for DS high salt versus DS normal salt or DR normal salt (0.05<p<0.1). In terms of increases in perfusion pressure, the responses to norepinephrine in the DS high salt group were significantly greater than either the DR+ or the DR− group at doses of 0.3, 1.0, and 3.0 μg (p<0.05). The difference in sensitivity between the DS high salt and DR high salt groups in the presence of cocaine is particularly apparent from Figure 4 (data for DS and DR normal salt not shown). Also, in the presence of cocaine the maximum response to norepinephrine was significantly higher in either DS group than in the DR normal salt group (Table 2).

The enhanced sensitivity of the DS high salt group to nerve stimulation and exogenous norepinephrine was specific. There were no significant differences among the four groups in regard to geometric mean ED₅₀ values or maximum responses to either KCl or angiotensin II (Table 3). This was true of KCl either in the absence or presence of phentolamine, added to the perfusion fluid to antagonize the effects of any norepinephrine released by the KCl. The concentration of phentolamine used (3 μM) caused shifts of about 30-fold to the right in norepinephrine dose–response curves in the perfused mesenteric vascular bed (data not shown). Phentolamine did cause slight decreases in the maximum responses to KCl, indicating that higher doses of KCl probably were causing some release of norepinephrine. Phentolamine did not have any effect on the mean ED₅₀ values of KCl (Table 3).

There also were no significant differences among the four groups in sensitivity to 5-hydroxytryptamine (5-HT) as measured by ED₅₀ values (Table 3). The maximum response to 5-HT was significantly higher in the DS high salt group relative to the DR normal salt group but not to any other group (Table 3).
The maximum response to bolus administration of KCl to the vascular preparations was only about 40% of the maximum response to norepinephrine. Although angiotensin is a potent vasoconstrictor, with ED₅₀ values in the nanogram range, the maximum response was quite small, 10–15% of the maximum response to norepinephrine. Preliminary experiments had established that with the doses and intervals between doses used in these experiments, tachyphylaxis to angiotensin II was not a complicating factor and, therefore, is not the explanation for the low maximum response to that agonist. Maximum responses to 5-HT were also low, ranging from 20% to 30% of the maximum responses to norepinephrine. The responsiveness of the endothelial relaxation mechanism was assessed by dose–response curves for acetylcholine for the DS high salt group did not differ significantly from that of any other group. At the highest dose, 1.0 μg, the DS high salt group produced moderately less inhibition than the DR low salt group (p<0.05). This was the only significant difference at any dose among the four groups. The acetylcholine responses were repeated in each preparation 2 hours after the first dose–response curve. Sensitivity to acetylcholine had markedly declined in all four groups by a factor of fivefold to sevenfold (data not shown).

Experiments were carried out to be certain that differences in extraneuronal uptake of norepinephrine was not a factor in the supersensitivity to norepinephrine and nerve stimulation. Dose–response curves to norepinephrine were determined in the presence of cocaine (1 μM) without or with DOCA (30 μM). This concentration of DOCA has been

| Table 2. Responses of Perfused Mesenteric Vascular Beds of Dahl Rats to Norepinephrine |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Group                          | n   | KCl (mg)          | Max (mm Hg)     | KCI (ng)          | Max (mm Hg)     |
|                                |     | -Phent. (+Phent.) | -Phent. (+Phent.) | -Phent. (+Phent.) | -Phent. (+Phent.) |
| DR normal salt                 | 10  | 2.4* (1.8–3.3)    | 1.1† (0.7–1.6)  | 2.2              | 199±12           |
| DS high salt                   | 11  | 1.9 (1.4–2.5)     | 0.6†§ (0.4–1.0) | 3.2‖             | 211±8§           |
| DR normal salt                 | 12  | 1.5 (1.1–1.9)     | 1.0† (0.7–1.5)  | 1.7              | 173±6            |
| DR high salt                   | 10  | 2.2* (1.7–2.8)    | 1.3† (0.9–1.9)  | 1.7              | 196±7†           |

ED₅₀, geometric means with 95% confidence intervals; Max, maximum response; DS, Dahl salt-sensitive rats; DR, Dahl salt-resistant rats.

*p<0.05 in the absence of cocaine for DS normal salt and DR high salt vs. DR normal salt.

†p<0.05 for + cocaine group vs. paired - cocaine group.

‡p<0.05 in the presence of cocaine for DS normal salt and DS high salt vs. DR normal salt groups.

§p<0.05 in the presence of cocaine for DS high salt vs. DR high salt groups.

*p<0.05 in the absence of cocaine for DS normal salt and DS high salt vs. DR normal salt groups.

*p<0.05 vs. DR low salt.

†p<0.05 vs. max in absence of phenolamine, paired t test.

Table 3. Responses of Perfused Mesenteric Vascular Beds of Dahl Rats to KCI, Angiotensin II, and 5-Hydroxytryptamine

<table>
<thead>
<tr>
<th>Group</th>
<th>KCl (mg)</th>
<th>Ang II (ng)</th>
<th>5-HT (μg)</th>
<th>KCI (ng)</th>
<th>Max (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS low salt</td>
<td>2.9</td>
<td>3.3</td>
<td>146</td>
<td>1.95</td>
<td>72</td>
</tr>
<tr>
<td>(2.5–3.3)</td>
<td>(2.4–4.6)</td>
<td>(60–355)</td>
<td>(1.92–1.98)</td>
<td>(1.93–1.98)</td>
<td>(1.95–2.00)</td>
</tr>
<tr>
<td>DS high salt</td>
<td>3.4</td>
<td>3.3</td>
<td>123</td>
<td>1.95</td>
<td>59</td>
</tr>
<tr>
<td>(2.0–5.5)</td>
<td>(1.8–6.2)</td>
<td>(47–323)</td>
<td>(1.93–1.98)</td>
<td>(1.93–1.98)</td>
<td>(1.93–1.98)</td>
</tr>
<tr>
<td>DR low salt</td>
<td>2.7</td>
<td>2.6</td>
<td>84</td>
<td>1.98</td>
<td>78</td>
</tr>
<tr>
<td>(2.2–3.3)</td>
<td>(1.9–3.6)</td>
<td>(51–140)</td>
<td>(1.95–2.00)</td>
<td>(1.95–2.00)</td>
<td>(1.95–2.00)</td>
</tr>
<tr>
<td>DR high salt</td>
<td>3.0</td>
<td>3.0</td>
<td>80</td>
<td>2.01</td>
<td>80</td>
</tr>
<tr>
<td>(1.5–6.0)</td>
<td>(1.9–4.8)</td>
<td>(39–167)</td>
<td>(2.00–2.02)</td>
<td>(2.00–2.02)</td>
<td>(2.00–2.02)</td>
</tr>
</tbody>
</table>

ED₅₀, geometric means with 95% confidence intervals; Max, mean maximum response±SEM; n=4 for each group; Ang II, angiotensin II; Phent., phenolamine; 5-HT, 5-hydroxytryptamine.

*p<0.05 vs. DR low salt.

†p<0.05 vs. max in absence of phenolamine, paired t test.
Responses of preparations from Dahl salt-sensitive (DS) rats fed a high salt diet did not differ significantly from responses of preparations from any other group except the Dahl salt-resistant (DR) rats fed a normal salt diet at the 1.0 μg dose level approximately 100 mm Hg above basal perfusion pressure. Vertical bars represent SEM.

**FIGURE 5.** Line graph showing dose-response curves to the inhibitory effects of acetylcholine in perfused mesenteric vascular beds. Perfusion pressure was elevated to a steady-state level approximately 100 mm Hg above basal perfusion pressure with a constant infusion of norepinephrine (20 μM). Bolus injections of acetylcholine induced transient, dose-related decreases in perfusion pressure. Vertical bars represent SEM. Responses of preparations from Dahl salt-sensitive (DS) rats fed a high salt diet did not differ significantly from responses of preparations from any other group except the Dahl salt-resistant (DR) rats fed a normal salt diet at the 1.0 μg dose level. n=9 per group.

The preparations from the DS high salt rats were more sensitive to nerve stimulation than those from any of the other three groups. This was true regardless of whether the frequency–response curves in all four groups were determined in the presence or absence of cocaine to inhibit neuronal uptake. The mesenteric vascular bed from DS high salt rats was also more sensitive to norepinephrine. However, in contrast to nerve stimulation, the greater sensitivity of the DS high salt group to norepinephrine was demonstrable only in the presence of cocaine.

The reason for the importance of inhibition of neuronal uptake is clear from the effect of cocaine itself on norepinephrine dose–response curves in each of the four experimental groups. Cocaine induced a greater shift of the curve in the DS high salt group than any of the other groups. This suggests that neuronal uptake is greater in the mesenteric vascular bed of the DS high salt group. Thus, neuronal uptake masks the difference in vascular sensitivity to exogenous norepinephrine until it is inhibited.

Our findings of enhanced response to nerve stimulation and greater neuronal uptake in the mesenteric vascular beds from prehypertensive DS rats fed a high salt diet are consistent with existing evidence of altered adrenergic mechanisms in hypertensive Dahl rats. It is likely that the enhanced sensitivity to nerve stimulation in the mesenteric vascular bed is at least partially a reflection of the enhanced sensitivity of the vascular smooth muscle to norepinephrine. The supersensitivity to nerve stimulation was demonstrable both in the presence and absence of cocaine. The supersensitivity to intraluminal norepinephrine was apparent only after inhibition of neuronal uptake. This difference probably reflects the fact that neuronal uptake has less impact on responses to nerve stimulation than responses to exogenous norepinephrine. In all groups, cocaine caused only very small shifts (approximately 1.2-fold) in the frequency–response curves for nerve stimulation. Thus, uptake would be less able to mask an increase in postjunctional sensitivity to neurally released norepinephrine. It is possible, of course, that an enhanced neuronal release of the transmitter also contributes to the greater responsiveness to nerve stimulation in the DS high salt group.
From the lack of effect of DOCA on responses to norepinephrine, it is concluded that extraneuronal uptake is not a factor in sensitivity to norepinephrine in the mesenteric vascular bed of young Dahl rats. Since the greater sensitivity of the mesenteric vascular bed of DS high salt rats was specific for norepinephrine and not a function of extraneuronal uptake, it is likely that the supersensitivity is mediated specifically via the vascular adrenoceptor system. Enhanced sensitivity to norepinephrine has not been observed in the hindquarters or the mesenteric vasculature of DS rats on high salt diets after hypertension is established. It appears, therefore, that the early supersensitivity to norepinephrine may contribute to the development of salt-induced hypertension but is not maintained in the older animals and therefore does not contribute to sustaining the hypertension once it is established.

There are reports of increased density of $\alpha_2$-adrenoceptors in caudal arteries of spontaneously hypertensive rats (SHR) and of renal $\alpha_2$- and $\alpha_2$-adrenoceptors in both SHR and DS hypertensive rats. The absence of responses to clonidine in our experiments indicates an absence of functional $\alpha_2$-receptors in the mesenteric vascular bed of Dahl rats, at least at 5–6 weeks of age. A recent report by Eerdmans and DeMay also came to the conclusion that the smooth muscle and endothelium of mesenteric arteries of SHR lack functional $\alpha_2$-receptors. It is concluded that the mesenteric supersensitivity to norepinephrine in prehypertensive DS rats is mediated via $\alpha_1$-adrenoceptors or the second messenger systems or ion channels to which they are coupled.

Luscher et al. reported a decline in the responsiveness of the endothelial relaxing mechanisms of aortic rings in DS rats with established hypertension. That finding is consistent with morphological signs of endothelial damage in mesenteric arteries of DS rats with established hypertension. The supersensitivity to norepinephrine in the mesenteric vascular bed from the prehypertensive DS high salt group could, therefore, be due to the loss of a buffering effect of endothelium-mediated relaxation.

To investigate that possibility, relaxations induced by acetylcholine were investigated in the presence of infusion of norepinephrine to induce vasoconstriction. With the exception of the highest dose in the DR normal salt group, there were no differences in response to acetylcholine in the DS high salt group relative to any other group. It is concluded that the supersensitivity of the mesenteric vascular bed of prehypertensive DS rats fed a high salt diet is not the consequence of differences in endothelium-mediated relaxation among preparations from the four experimental groups of rats. It follows that the loss of endothelial structure and function in arteries from DS rats with established hypertension may be secondary to sustained hypertension. Interestingly, responses of the mesenteric vasculature to acetylcholine were markedly reduced in all four groups after perfusion for 3–4 hours. Thus, the relaxing mechanism mediated by the endothelium deteriorates with prolonged perfusion. In contrast, responses to norepinephrine are readily repeatable over the same span of time.

The supersensitivity to norepinephrine is not likely to be the result of structural differences between the DS high salt group and the other experimental groups. Three facts support this conclusion. 1) The rats used were prehypertensive, thus eliminating the possibility of hypertension-induced changes in the arterial wall. 2) The supersensitivity appears to be specific for agonists acting via adrenoceptors, specifically $\alpha_1$-receptors. 3) The supersensitivity is characterized by a parallel shift of the norepinephrine dose–response curve to the left without a change in maximum response. Compare these results, for example, with those of Longhurst et al. in the mesenteric vascular bed from SHR with established hypertension in which arteriolar wall thickening has been demonstrated. Longhurst et al. presented data indicating enhanced responses of preparations from SHR to both norepinephrine and KC1, characterized by dose–response curves with markedly increased slopes and maxima but little sign of lowered threshold or ED50 values. Follkow and Karlstrom have stressed the relation of nonspecific increases in maximal responses associated with increased vascular wall thickness and narrowing of the lumen.

For two agonists, norepinephrine and 5-HT, the maximum responses of the DS high salt group were significantly greater than the maximum responses of the DR normal salt group. The reason for this is unknown. However, it is probably not indicative of structural differences for two reasons. 1) The maximum responses did not differ for the other three agonists or for nerve stimulation. 2) There were no differences in maximum responses between the DS high salt and DR high salt groups. Because hypertension in Dahl rats is the consequence of a genetic difference in response to salt, the DR rat fed a high salt diet is probably the most meaningful control for DS rats fed a high salt diet.

In summary, the mesenteric vascular bed of prehypertensive DS rats, on high salt for 5 days, is supersensitive to norepinephrine and periarterial nerve stimulation. There is no supersensitivity to other vasoconstrictors, namely KCl, 5-HT, or angiotensin II. There also may be enhanced neuronal uptake in preparations from the DS high salt group, based on the greater effect of cocaine in these preparations. The supersensitivity to norepinephrine is demonstrable only when neuronal uptake is inhibited. The enhanced sensitivity does not involve $\alpha_2$-adrenoceptors, differences in extraneuronal uptake, or changes in endothelium-derived relaxation. It is probably the result of a change in vascular $\alpha_1$-receptors or their coupling to second messenger systems or ion channels. The supersensitivity to norepinephrine is reflected in supersensitivity to sympathetic nerve stimulation. Because the enhanced responses to nerve stimulation are not fully..
masked by neuronal uptake, an elevated neurally induced vasoconstriction may contribute to the development of hypertension.

References


KEY WORDS: mesenteric arteries • norepinephrine • potassium • angiotensin • cocaine • acetylcholine • Dahl rats
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