In accordance with this hypothesis, repeated daily experimental or behavioral challenges are enhanced (15). In the development of hypertension (22). The factor(s) pressure (BP) variability increases progressively with arterial blood pressure (BP) and sympathetic nerve activity (SNA) at rest and during a controlled behavioral stress at an early stage in the development of hypertension in borderline hypertensive rats (BHR). Ten rats were maintained on a high-salt diet (8% NaCl) while 14 were fed a low-salt diet (0.8% NaCl) for 8 wk. They were trained in a Pavlovian paradigm by following a conditional stimulus tone (CS+) with a 0.5-s shock. SNA and BP were measured by implanted electrodes around the left renal nerve and a catheter in the femoral artery, respectively. There were no detectable between-group differences in BP or in BP variability in the resting animal at the end of the 8-wk dietary treatment. Moreover, there were no significant between-group differences in the changes in SNA evoked by the CS+ tone. Conversely, the amplitude of the initial conditional increase in BP was significantly (P < 0.05) larger in the high-salt (6 ± 0.6 mmHg; mean ± SEM) compared with the low-salt (4 ± 0.4 mmHg) group. In addition, the BP excursion (peak/trough) during CS+ was larger in the high (18.2 ± 6.1 mmHg)- vs. low-salt (5.8 ± 0.4 mmHg) diet-fed subjects. The ratio of the average percent change in mean BP to the average percent change in SNA at the beginning of CS+ was 0.029 ± 0.004 for the low-salt group and 0.041 ± 0.006 for the high-salt group. We find that, before the development of overt hypertension, the enhanced conditional BP response in the high-salt BHR appears to reside at the interface between changes in SNA and the effector response and not within the central nervous system. These observations help explain the increasing BP variability typically observed with the development of hypertension in humans.

The effects of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

There is widespread agreement that arterial blood pressure (BP) variability increases progressively with the development of hypertension (22). The factor(s) responsible for this increased variability has not been clearly identified, but one intriguing possibility is that the pressor and depressor responses to acute environmental or behavioral challenges are enhanced (15). In accordance with this hypothesis, repeated daily exposure to such challenges in sensitive individuals accounts for the augmented BP fluctuations, perhaps even in otherwise normotensive people, and contributes to the ultimate development of sustained elevations in arterial BP via the autonomic nervous system.

In another vein, numerous epidemiological surveys and experimental studies imply that high dietary salt intake potentiates the development of high BP (16), although recently published findings do not support recommendations for routine dietary sodium restriction in the general population (1, 24). Moreover, the mechanism(s) relating dietary sodium consumption and the potential development of hypertension is not clear. Renal dysfunction (6), natriuretic hormone (29), and elevated sympathetic nervous activity (SNA) (10, 12) are thought to be involved in some way.

We have described a pattern of change in SNA in the Sprague-Dawley rat that is tightly coupled to stereotypic changes in BP during an acute behavioral stress (18, 26); autonomic ganglionic blockade eliminates the stress-induced changes in SNA and BP (26). These features of the paradigm have proven useful in demonstrating the existence of a lawful relationship between changes in SNA and BP (3–5, 11). This preparation would be very useful in clarifying the etiology of BP variability if a suitable animal model were available to study the phenomenon. In this regard, the borderline hypertensive rat (BHR), studied extensively by Sanders and Lawler and colleagues (30), mimics a number of features in the development of human hypertension. In particular, the BHR becomes hypertensive if subjected to repeated stress (15), and placing these animals on a high-salt diet for 8 wk or longer also reportedly causes their BP to increase (16). The salt diet interacts with chronic stress in altering central levels of norepinephrine in identified hypothalamic nuclei (17).

In the present experiment we exposed BHR to a low- or high-salt diet for 8 wk to determine whether there were significant between-group differences in the sympathetic control of BP variability during rest or in response to an acute stress. We found no group differences in resting BP or in BP variability in the undisturbed animal. Likewise, the changes in SNA evoked by the sudden behavioral challenge did not differ in the rats maintained on a high- vs. low-salt diet. However, the high-salt diet-fed animals responded to the stress with significantly larger changes in BP compared with the subjects on a low-salt diet. The apparent explanation for this difference in BP variability is an increased responsiveness of the vasculature to a given change in SNA in the rats chronically exposed to a high-salt diet.
METHODS

Subjects. Experiments were completed on 24 BHR purchased from Taconic Farms (Germantown, NY) at 4 wk of age. The animals were divided into low- vs. high-salt exposure groups and housed three rats per cage according to group. The high-salt group was fed an 8% NaCl diet for 8 wk. The low-salt group was fed a 0.8% NaCl diet for an equal period of time. All animals had ad libitum access to both chow and water. The protocol was approved by the University of Kentucky Animal Care Committee.

Behavioral training. Details of the behavioral conditioning paradigm have been published elsewhere (27). Briefly, the animals were adapted to restraint in a soft conical terrycloth sock starting at ~7 wk after being placed on the respective diets. The sock adaptation consisted of two daily 1-h sessions in which the rats were placed in the sock and repositioned if they emerged. The next day five trials each of a pulsed and a nonpulsed 15-s-long tone were presented in random order. Shock was never delivered during these habituation trials, and there was no demonstrable difference in the BP response to the two tones by the last presentations (D. Randall, unpublished observation). Finally, during the last 2 days of training, the conditional stimulus tone (CS+) was followed by a 0.5-s shock delivered between a pair of electrodes secured to the animal's tail. The minimum intensity of shock (0.2–0.4 mA) that caused the animal to flinch noticeably was used. The steady tone (CS−) was never followed by shock. An 80486-based personal computer controlled the presentation of the tones and shocks. Since previous reports (18, 26, 27) we determined that the pulsed tone always begins in the “off” state, so that an initial 45 ms of silence preceded the first audible pulse for CS+. Accordingly, in this report the timing of all physiological responses to the pulsed tone has been adjusted to take account of this initial tone off period. Training was complete by the end of the eighth week of dietary salt treatment.

Surgery. Procedures for implantation of the femoral arterial and venous catheters and for placing the renal bipolar nerve electrode have been described in detail elsewhere (3). Briefly, the animals were anesthetized (pentobarbital sodium, 65 mg/kg), and Teflon catheters were placed inside each vessel. A nerve coursing over the aorta and along the left renal artery toward the kidney was then identified through a flank incision. The nerve was freed from surrounding connective tissue to place a pair of fine, closely spaced gold electrodes around it. The electrodes were then encased in silicon gel (Wacker Chemia, Munich, Germany). The catheters and twisted-pair copper wires soldered to the electrodes were tunneled under the skin and exited at the nape of the rat’s neck; each was then lead through a protective, flexible spring. The rats were housed individually after surgery.

Protocol. Data recording started 24 h after surgery, but, to allow the animals 48 h to recover from the operation, only those trials on the second postoperative day are reported here. All tests were conducted inside a shielded wire cage to minimize electrical noise. First, BP was recorded, as described in Data acquisition and analysis, in a subset of the low (n = 9)- and high-salt (n = 8)-diet-fed animals while they were undisturbed in the restraining sock for 10 min. Then the responses of all animals in both groups to a minimum of five of each tone were recorded with at least 5 min between tones. The animals were returned to their home cages at the end of the test session. Sessions were continued each day until either the BP or SNA signal failed, but only the day 2 trials are reported here. The animals were killed at the end of the experiment with an overdose of pentobarbital IV.

Data acquisition and analysis. Arterial BP was recorded using a calibrated transducer (Cobe model CDX-i11) connected to a Grass polygraph (model 7). The nerve signal was amplified (>50,000) and band-pass filtered between 0.3 and 3 kHz using a Grass P511 differential amplifier. SNA and BP were digitally sampled at 10,000 Hz. To utilize these large files, programs were developed using Microsoft Foundation Class. The SNA recording was digitally full-wave rectified and integrated over 0.01-s intervals; likewise, the BP recording was digitally meaned. The result was a set of files of SNA and mean arterial BP for the 10-min rest recordings and for each behavioral trial. For the latter, each variable was compressed into a continuous sequence of 0.01-s intervals for a 9-s pretone control, the 15-s tone, and a 6-s posttone recovery. Likewise, a similar digital file of heart rate (HR) was computed from the pulsatile BP signal. An index of BP variability (i.e., the standard deviation/mean BP) and the power spectrum of mean BP for selected frequency ranges were computed to quantify variability over the 10-min sock-restraint sessions. The data files for four or more individual CS+ trials (and for 4 or more CS− trials) in a given rat were ensemble averaged to produce a “high-resolution” analysis of the behaviorally conditioned response pattern to the stress tone (and to the neutral tone) (26, 27). These data were evaluated using an ANOVA with a between-group factor for diet (high salt-low salt) and within-group factor for tone (stress-nonstress). ANOVAs were computed for each physiological variable [i.e., SNA, mean arterial pressure (MAP), HR] for selected aspects of the response pattern (see RESULTS). Posthoc t-tests were performed when appropriate. All data are given as means ± SE unless otherwise indicated. Statistical significance was accepted for P < 0.05.

RESULTS

Average SNA, HR, and MAP during the pretone control are given in Table 1. There were no significant differences in any of the three variables. In particular, the MAP did not differ between the low- and high-salt diet-fed groups.

The BP variance index (i.e., SD/mean) for the low (0.13 ± 0.006)- and high-salt (0.13 ± 0.005) diet-fed

<table>
<thead>
<tr>
<th>Table 1. Resting level for SNA, HR, and MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
</tr>
<tr>
<td>Low salt (n = 14)</td>
</tr>
<tr>
<td>High salt (n = 10)</td>
</tr>
<tr>
<td>ANOVA Results</td>
</tr>
<tr>
<td>Resting SNA, nV</td>
</tr>
<tr>
<td>27.4 ± 4.4</td>
</tr>
<tr>
<td>28.4 ± 4.4</td>
</tr>
<tr>
<td>CS−</td>
</tr>
<tr>
<td>27.4 ± 4.4</td>
</tr>
<tr>
<td>28.4 ± 4.4</td>
</tr>
<tr>
<td>CS+</td>
</tr>
<tr>
<td>25.4 ± 3.8</td>
</tr>
<tr>
<td>25.2 ± 3.6</td>
</tr>
<tr>
<td>Resting HR, beats/min</td>
</tr>
<tr>
<td>360 ± 96</td>
</tr>
<tr>
<td>362 ± 112</td>
</tr>
<tr>
<td>Resting MAP, mmHg</td>
</tr>
<tr>
<td>114 ± 1.0</td>
</tr>
<tr>
<td>114 ± 1.0</td>
</tr>
<tr>
<td>116 ± 1.6</td>
</tr>
<tr>
<td>115 ± 1.5</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td>W</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td>B × W</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. SNA, sympathetic nerve activity; HR, heart rate; MAP, mean arterial pressure; B, between group; W, within group; B × W, interaction; CS−, nonreinforced steady tone; CS+, reinforced, conditional stimulus tone; NS, not significant.
groups did not differ for the 10-min recordings in the animals at rest. Figure 1 shows the average BP power for the two groups derived from these same recordings. Data are shown within frequency bins centered around 0.4 Hz (i.e., 0.15–0.60 Hz; see Ref. 3), the respiratory rate (i.e., 0.60–3.0 Hz), and HR (i.e., 5.0–8.0 Hz). There were no significant between-group differences.

Figure 2 is a digital reconstruction of a portion of the pretone control (1 s) and the initial 5 s of a single CS+ trial for one rat maintained on the high-salt diet. The illustration was derived from a “raw” (i.e., 10,000 Hz) data file and shows the pulsatile arterial pressure and the bipolar nerve recording before rectification and integration. Here, as in the Sprague-Dawley (26) and spontaneously hypertensive rats (SHR) (18), the beginning of the tone was followed quickly by an intense sudden burst (SB) in nerve activity and then by an initial increase (C1) in arterial BP (BPc1). SNA was momentarily depressed after the opening burst; we referred to this brief decrease in nerve activity as the “quiet period” (QP). As is the case in the trial in Fig. 2, the QP is closely followed by a momentary drop in BP (18, 26). The “second component” (C2) of the BP conditional response is characterized by a modest increase in SNA and BP.

Figure 3 is a high-resolution analysis of the changes in MAP and SNA derived by ensemble averaging files from four individual CS+ trials in an animal on the high-salt diet. The tone was presented during the period indicated by the dark bar on the time axis. The amplifier used to record SNA was disabled during delivery of the shock at the end of the tone. The SB in SNA and the associated C1 component of the conditional pressor response are indicated. The QP was associated with a brief drop in BP to ~4 mmHg below baseline before rising for the rather sustained C2 BP increase. The between-group differences in the response pattern were evaluated in terms of each of these components of the response pattern. In particular, we compared the peak and average increase in BP during C1 and the average increase during C2. We also compared the BP “excursion” during the initial seconds of the stress response; the excursion is the difference in BP between the two short, dashed lines (top and bottom of C1 in Fig. 3).

Overall there were no significant between- or within-group differences in the latency from the beginning of either the CS+ or CS- tone to the onset of the SB in nerve activity or to the initial increase in mean BP (i.e., C3, Table 2). Likewise, there were no differences in the duration of the SB in SNA.

The average amplitude of the QP in SNA was virtually identical for both tones and for both groups (Fig. 4, top). Nevertheless, the drop in BP (Fig. 4, middle) after this depression in SNA was significantly larger for the rats
maintained on high-salt as opposed to low-salt diet. As is shown in Fig. 5, this combination of a larger BPc1 increase and larger QP BP decrease in the high-salt group resulted in a significantly larger overall excursion in BP in response to CS1 in the high-salt (18.2 ± 6.1 mmHg) compared with the low-salt (5.8 ± 0.4 mmHg) rats. The same tendency for increased BP fluctuation in the high-salt group was noted in response to CS2, although the between-group difference was not statistically significant for the nonreinforced tone.

Figure 3 indicates the time interval over which we evaluated the C 2 component of the BP and SNA response amplitudes. Note (Fig. 4) in this regard that both SNA and MAP were significantly elevated above baseline during this interval for the stressful tone. Also the change in nerve activity, BP, and HR (Fig. 4, bottom) during C2 showed discrimination between CS+ and CS− trials. There were no statistically significant between-group differences in any aspect of the conditional response during C2.

The SB in SNA is temporally related to C1 (4, 11, 26). Moreover, the BPc1 increase is due almost exclusively to an increase in peripheral resistance (19). These two facts allowed us to estimate the sensitivity of the peripheral vasculature to a change in sympathetic drive. More specifically, we computed the ratio of the average percent C1 change (vs. pretone control) in mean BP evoked by CS+ to the average percent change in SNA during the SB (BPc1%/SNA-SB%; see also Ref 18). For the low-salt diet-fed animals this ratio was 0.029 ± 0.004 and for the high-salt diet-fed group it was 0.041 ± 0.006 (P < 0.05, 1-tailed t-test).

DISCUSSION

We believe the differences in BP regulation that we report here in prehypertensive rats fed high- vs. low-NaCl diets contribute importantly to understanding the increased BP fluctuation that grows with the development of overt, salt-sensitive hypertension in humans (reviewed in Ref. 22). After 8 wk of high- vs. low-salt diet, there were no demonstrable differences in either resting BP or in the BP and SNA variability when the rats were undisturbed in the sock. This included the BP power centered ~0.4 Hz that is closely associated with changes in SNA (3). Moreover, virtually every component of the SNA response to the acute behavioral challenge was similar across diets. In contrast, the change in MAP associated with the given change in SNA, whether for the SB increase or the QP decrease, was larger in the animals fed the high-salt diet.

Table 2. Onset latency and duration for SNA and MAP responses

<table>
<thead>
<tr>
<th>Diet</th>
<th>Low salt (n = 14)</th>
<th>High salt (n = 10)</th>
<th>ANOVA Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CS−</td>
<td>CS+</td>
<td>CS−</td>
</tr>
<tr>
<td>SBOnset</td>
<td>0.12 ± 0.08</td>
<td>0.11 ± 0.01</td>
<td>0.11 ± 0.02</td>
</tr>
<tr>
<td>SBDur</td>
<td>0.49 ± 0.02</td>
<td>0.54 ± 0.03</td>
<td>0.57 ± 0.03</td>
</tr>
<tr>
<td>C1Onset</td>
<td>0.42 ± 0.08</td>
<td>0.42 ± 0.05</td>
<td>0.47 ± 0.05</td>
</tr>
<tr>
<td>C1Dur</td>
<td>1.93 ± 0.08</td>
<td>2.08 ± 0.05</td>
<td>1.81 ± 0.05</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. SBOnset, latency time of SNA sudden burst after tone onset; SBDur, duration of sudden burst; C1Onset, latency time of first conditional increase in MAP after tone onset; C1Dur, duration of first conditional MAP response. *P < 0.05.
diet. In short, an increase in BP variability at this stage of the development of the physiological responses to the high-salt diet was evident only when the animal was challenged by the behavioral stress.

Before we interpret these results it is worth noting that the two groups did not differ in two important ways: both their genetic background and their resting arterial pressure were the same. Therefore, both groups were equally prone genetically to develop high BP. Moreover, because their resting BP was the same, we did not have to make comparisons between groups in which the input to baroregulatory mechanisms differed markedly.

What do the subtle comparisons between groups described above tell us about the regulation of arterial BP in the prehypertensive state? First, our data indicate that the increase in BP reactivity to the acute stress in the BHR-high-salt group at this early, prehypertensive stage cannot be attributed to increased extremes of sympathetic activity originating within the central nervous system; the onset latency, duration, and average amplitude of the SB were virtually identical in the two groups. It appears, instead, that the explanation for the increased BP responsiveness must reside at the interface between the changes in sympathetic activity and the effector response, probably at the vascular smooth muscle.

Comparisons between the regulation of BP in the SHR and BHR are also very instructive. For example, we reported that the amplitude of both the renal SNA and BP responses to the behavioral stress was significantly larger in SHR compared with Wistar-Kyoto rats (WKY); likewise, the “gain” of the effector’s response (BPc%/SNA-SB%) was increased (18). This previous work led us to conclude that, in the SHR with well-established hypertension, the centrally mediated autonomic response to the stress is significantly greater than in the normotensive WKY. We believe our collective data indicate that the increased effector responsiveness to SNA seen in the prehypertensive state correlates with enhanced central reactivity as hypertension becomes established. Kirby et al. (14) found that, although resting BP was similarly elevated in BHR and SHR vs. WKY rats, the BP increased more in the SHR than in the BHR (or WKY) after being transferred from their home cage to a novel environment. Moreover, the SHRs showed greater increases in catecholamines in blood drawn 5 min after a period of intermittent foot shock than did the other two strains. They concluded that the sympathetic responsiveness of BHRs (on a standard diet) to acute stress is more similar to normotensive WKYs than it is to hypertensive SHRs. Finally, DiBona and Jones (8) exposed WKY, SHR, and BHR to air-jet stress while measuring renal SNA and BP. Their

Fig. 4. Average of renal SNA (top), change in MAP (middle) and change in heart rate (HR; bottom) for baseline, C1 (or SB for SNA), QP and C2 for high (n = 10)- and low (n = 14)-salt diet in CS+ and steady tone (CS−) trials. There were no between group differences in SNA data, but changes in BP did differ significantly in high- vs. low-salt animals. *Statistically significant difference between high- and low-salt groups; #difference between response to CS1 and CS2.

Fig. 5. BP excursion (difference between peak increase during C1 and trough after QP) during CS+ and CS− trials in high- and low-salt diet-fed groups. Excursion was significantly larger in response to CS+ for high-salt (n = 8) compared with low-salt (n = 14) diet-fed animals.
norepinephrine

lated that the QP in SNA is due to the action of the
developing and established hypertension. We specu-
the possibility that the baroreflex is depressed in
-agonists (e.g., Ref. 32), vascular structural changes
There is evidence for increased vasoconstriction to
patients are also difficult to delineate unequivocally (2).
reactivity to changes in SNA in borderline hypertensive
mediating the apparent increase in vascular resistance
however. For example, the relative changes in plasma
creases were achieved by different physiological mecha-
mmHg; resting plasma norepinephrine 186 ± 14 pg/ml)
to that of 15 borderline hypertensive patients (ages
37.1 ± 2.0 yr; mean BP = 103 ± 1.5 mmHg; plasma
norepinephrine = 232 ± 18 pg/ml) who had never
received antihypertensive medication. There were no
statistically significant differences either in the in-
creases in mean BP and HR or in the elevations in
plasma norepinephrine or epinephrine, but the in-
creases were achieved by different physiological mecha-
nisms. The pressor response in the normotensive sub-
jects was attributable primarily to augmented
myocardial contractility, whereas the borderline hyper-
tensive individuals relied primarily on increased vas-
cular resistance. The relationship between stress, SNA,
and cardiovascular function is not easily characterized
however. For example, the relative changes in plasma
catecholamines, cardiac output, and vascular resis-
tance appear to depend on the nature of the behavioral
challenge faced by the subject (31). The mechanisms
mediating the apparent increase in vascular resistance
reactivity to changes in SNA in borderline hypertensive
patients are also difficult to delineate unequivocally (2).
There is evidence for increased vasoconstriction to
α-agonists (e.g., Ref. 32), vascular structural changes
(e.g., Ref. 9), and alterations in responses to neuropep-
tide Y (e.g., Ref. 20).

There has been a great deal of discussion concerning
the possibility that the baroreflex is depressed in
developing and established hypertension. We specu-
lated that the QP in SNA is due to the action of the
baroreflex (18, 26). In that regard, SNA fell to virtually
an identical value during this interval in both groups
(Fig. 3). Conversely, the resulting depressor effect was
significantly greater in the high-salt diet-fed group.
This would seem to belie the possibility that the
baroreflex gain is depressed in these subjects with
developing hypertension.

Potential limitations of the experiment. We demon-
strated a tight temporal and quantitative coupling be-
tween the changes in renal and arterial BP (3–4, 11)
and believe that this neural signal is a reliable instru-
ment for the study of the sympathetic regulation of
vascular smooth muscle to a given change in SNA.

Our BHRs on the high-salt diet did not show a
chronic elevation in resting MAP (Table 1). This differs
from previous reports by Lawler et al. (16) and DiBona
and Jones (8). The experience of those (J. E. Lawler and
S.-G. Li) who were involved in studies in both Lexing-
don and Knoxville suggests that differences in proce-
dures may account for these conflicting BP findings.
In the Knoxville experiments, arterial BP was measured
by either tail cuff or in a prestress period. Both proce-
dures might elicit increased behavioral arousal com-
pared with that observed in the home cage. The studies
in Lexington utilized a “sock” into which the rat volun-
tarily entered. Rats are usually quiet in this restraint.
There is no apparent behavioral stress during the
period of baseline measurement or in the interval
between trials. It is thus possible that the differences in
BP levels in the two laboratories reflect differences in
cortical arousal, exactly as would be predicted by the
present results. That both groups in the present experi-
ment had the same resting BP was advantageous in
making between-group comparisons. However, we did
not demonstrate that the high-salt animals
would eventually have an increased resting BP, one
might challenge our data as a basis for describing the
events that lead to salt-sensitive hypertension. Even if
this were the case, we showed that the high-salt diet
produced physiologically interesting changes in the
relationship between changes in SNA and arterial BP.

Perspectives

A recent study stemming from a nationwide military
BP screening of 19-year-old Norwegian men (28) places

BHRs were placed on either 1 or 8% NaCl diets at 4 wk
of age and were maintained on the diet until 16 wk of
age (for 12 wk). With the longer salt exposure the
arterial BP in the high-salt diet-fed BHR group at the
time of study was significantly greater than in the 1%
group. Their results clearly show large, stress-induced
sympathoexcitation in the SHR that was not seen in
WKY or BHR on a 1% NaCl diet. However, with the
extended diet, the high-salt diet-fed BHRs also showed
stress-induced changes in SNA similar to that of the
SHR. In short, the existence of a powerful interaction
among genetic background, dietary salt, and stress is
apparent in all three studies.

It is important to consider our hypothesis regarding
increased vascular responsiveness to changes in SNA
in prehypertensive BHR in relation to previous work on
the etiology of the early stages of human hypertension.
In a recent review, Julius and Nesbitt (12) argued
strongly for a causative role for the sympathetic ner-
vous system overactivity in the etiology of a hyperki-
netic circulation in early hypertension, including an
inappropriately elevated vascular resistance. They fur-
ther posited that as vascular responsiveness to SNA
increases with the progression of hypertension the
brain can achieve the same (elevated) BP level with less
sympathetic firing. Numerous studies have tested the
hypothesis of elevated adrenergic vascular reactivity in
borderline hypertension. In particular, de Champlain
et al. (7) compared the physiological responses to
isometric exercise of 25 normotensive subjects [ages
36.5 ± 2.0 (SE) yr; resting mean BP = 86.6 ± 1.7
mmHg; resting plasma norepinephrine 186 ± 14 pg/ml]
to that of 15 borderline hypertensive patients (ages
37.1 ± 2.0 yr; mean BP = 103 ± 1.5 mmHg; plasma
norepinephrine = 232 ± 18 pg/ml) who had never
received antihypertensive medication. There were no
statistically significant differences either in the in-
creases in mean BP and HR or in the elevations in
plasma norepinephrine or epinephrine, but the in-
creases were achieved by different physiological mecha-
nisms. The pressor response in the normotensive sub-
jects was attributable primarily to augmented
myocardial contractility, whereas the borderline hyper-
tensive individuals relied primarily on increased vas-
cular resistance. The relationship between stress, SNA,
and cardiovascular function is not easily characterized
however. For example, the relative changes in plasma
catecholamines, cardiac output, and vascular resis-
tance appear to depend on the nature of the behavioral
challenge faced by the subject (31). The mechanisms
mediating the apparent increase in vascular resistance
reactivity to changes in SNA in borderline hypertensive
patients are also difficult to delineate unequivocally (2).
There is evidence for increased vasoconstriction to
α-agonists (e.g., Ref. 32), vascular structural changes
(e.g., Ref. 9), and alterations in responses to neuropep-
tide Y (e.g., Ref. 20).

There has been a great deal of discussion concerning
the possibility that the baroreflex is depressed in
developing and established hypertension. We specu-
lated that the QP in SNA is due to the action of the
baroreflex (18, 26). In that regard, SNA fell to virtually
an identical value during this interval in both groups
(Fig. 3). Conversely, the resulting depressor effect was
significantly greater in the high-salt diet-fed group.
This would seem to belie the possibility that the
baroreflex gain is depressed in these subjects with
developing hypertension.

Potential limitations of the experiment. We demon-
strated a tight temporal and quantitative coupling be-
tween the changes in renal and arterial BP (3–4, 11)
and believe that this neural signal is a reliable instru-
ment for the study of the sympathetic regulation of
vascular smooth muscle to a given change in SNA.

Our BHRs on the high-salt diet did not show a
chronic elevation in resting MAP (Table 1). This differs
from previous reports by Lawler et al. (16) and DiBona
and Jones (8). The experience of those (J. E. Lawler and
S.-G. Li) who were involved in studies in both Lexing-
don and Knoxville suggests that differences in proce-
dures may account for these conflicting BP findings.
In the Knoxville experiments, arterial BP was measured
by either tail cuff or in a prestress period. Both proce-
dures might elicit increased behavioral arousal com-
pared with that observed in the home cage. The studies
in Lexington utilized a “sock” into which the rat volun-
tarily entered. Rats are usually quiet in this restraint.
There is no apparent behavioral stress during the
period of baseline measurement or in the interval
between trials. It is thus possible that the differences in
BP levels in the two laboratories reflect differences in
cortical arousal, exactly as would be predicted by the
present results. That both groups in the present experi-
ment had the same resting BP was advantageous in
making between-group comparisons. However, we did
not demonstrate that the high-salt animals
would eventually have an increased resting BP, one
might challenge our data as a basis for describing the
events that lead to salt-sensitive hypertension. Even if
this were the case, we showed that the high-salt diet
produced physiologically interesting changes in the
relationship between changes in SNA and arterial BP.

Perspectives

A recent study stemming from a nationwide military
BP screening of 19-year-old Norwegian men (28) places
our findings in a wider clinical perspective. On the basis of their (auscultatory) BP at screening, men were recruited: those in the first percentile (group 1; n = 15; BP = 62 ± 2 mmHg, mean ± SE), the 50th percentile (group 50; n = 15; 90 ± 4 mmHg), and the 99th percentile (group 99; n = 14; 123 ± 5 mmHg). The subjects were kept ignorant of their BP. During the subsequent experiment, mean BPs (intra-arterial catheter) for men in groups 99 and 50 did not differ after 30 min supine rest (89 and 86 mmHg, respectively), suggesting that the latter group's high BP at screening was in itself an accentuated stress response. The increase in diastolic BP in group 99 to the announcement of an impending stress test (mental arithmetic) as well as to the test itself was significantly larger than for the other two groups. Conversely, there were no significant between-group differences in plasma epinephrine or norepinephrine responses. The authors suggest that increased sensitivity to arterial epinephrine played a role in the hyperreactivity of the men in group 99. With regard to the ultimate consequences of high-BP reactivity, Matthews et al. (23) measured the BP change to defined mental and physical challenges in middle-aged adults and their children. The subjects' resting BPs were measured 6.5 yr later. They found that larger pressor responses to the stress tests were associated with higher resting diastolic pressures during the follow-up tests in the adults. Among boys, but not girls, larger responses to the challenges were associated with higher subsequent resting BP. Their data indicate that people who have a higher BP reactivity to stress at a younger age may be at increased risk for the ultimate development of hypertension.

We are struck by the physiological similarities between our findings and those from the borderline hypertensive men with essentially normal BP at rest but highly reactive pressures even to the expectation of a stress. There are, of course, limitations in any animal model, but it seems not unreasonable to postulate that similar physiological mechanisms underlie the human situation as we observed in the BHR. Thus these data in the BHR may be relevant to human borderline hypertension in which it has frequently been noted that BP is normal during sleep or during relaxation but is elevated in the presence of a physician (“white-coat” hypertension).

In conclusion, the present study shows that the high-salt diet enhanced the pressor response to stress in BHR at an early, prehypertensive stage. The increased BP responsiveness probably resides at the interface between the changes in sympathetic activity and the effector response, probably at the vascular smooth muscle, rather than central sympathetic discharge. Therefore, the initial physiological changes ultimately leading to sustained hypertension may be due to an increased smooth muscle response to changes in SNA, rather than to some process within the central nervous system. As hypertension becomes established, as in the SHR (18), both the effector and central processes may be altered.

The authors thank Laura Brown for generous technical help. This research was supported by an American Heart Association (AHA) Kentucky Affiliate grant and a Kentucky Tobacco and Health Research Institute grant to D. R. Brown, an AHA Kentucky Affiliate fellowship to S.-G. Li, National Aeronautics and Space Administration Experimental Program to Stimulate Competitive Research grant WKU-522611, and by National Heart, Lung, and Blood Institute Grants HL-19680 to J. E. Lawler and HL-19343 to D. C. Randall. Address for reprint requests and other correspondence: D. R. Brown, Dept. of Physiology, Univ. of Kentucky College of Medicine, Lexington, Ky 40536-0084 (E-mail: randall@pop.uky.edu).

Received 20 October 1998; accepted in final form 10 May 1999.

REFERENCES


