Alterations in Autoregulatory and Myogenic Function in the Cerebrovasculature of Dahl Salt-Sensitive Rats

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Background and Purpose—Dahl salt-sensitive rats fed an 8.7% NaCl diet exhibited hypertensive encephalopathy and developed seizures associated with areas of blood-brain barrier (BBB) disruption without brain ischemia. The incidence of hemorrhagic stroke was low (7/47). We tested the hypothesis that a defect in cerebral blood flow (CBF) autoregulation under hypertensive conditions preceded hypertensive encephalopathy.

Methods—Brain ischemia and BBB disruption were assessed with the use of tetrazolium red staining and Evans blue dye extravasation, respectively. Myogenic constriction to pressure was measured in isolated middle cerebral arteries (MCAs) with a pressure myograph. CBF autoregulation was assessed with the use of laser-Doppler techniques.

Results—Asymptomatic rats fed 8.7% NaCl had MCAs that developed an age-related attenuation in their ability to constrict to pressure, which was amplified in rats exhibiting hypertensive encephalopathy. The MCAs of rats with hemorrhagic stroke lost this function and developed large degrees of basal tone. The majority (4/6) of asymptomatic rats fed high salt for longer than 3 weeks exhibited a linear relationship between CBF and blood pressure. The characteristics of CBF regulation were consistent with the possible absence of autoregulation coupled with cerebrovascular vasoconstriction.

Conclusions—Both MCA pressure-dependent constriction and CBF autoregulation in the MCA perfusion domain were lost before the development of hypertensive encephalopathy or hemorrhagic stroke. These defects could contribute to the development of BBB disruption during hypertension. Cerebrovascular vasoconstriction in the absence of CBF autoregulation may protect the brain from excessive overperfusion during hypertension and could account for the low incidence of cerebral hemorrhage in this model. (***Stroke***. 2003;34:1484-1490.)

Key Words: blood-brain barrier ■ cerebral blood flow ■ hypertensive encephalopathy ■ hypertension ■ middle cerebral artery ■ muscle, smooth, vascular ■ stroke, hemorrhagic

Hypertensive animals and humans have cerebrovasculatures that are capable of autoregulating blood flow at higher blood pressures (BPs) than those of their normotensive counterparts.[1,2] Elevating the upper BP limit of cerebral blood flow (CBF) autoregulation under hypertensive conditions is a beneficial feature in that it prevents overperfusion of the brain during hypertension. This protective effect can be demonstrated in normal animals. Elevations in sympathetic nerve stimulation to the cerebrovasculature increase the upper limit of CBF autoregulation.[1,3] Such manipulations reduce the disruption of the blood-brain barrier (BBB) in response to experimental elevations in BP,[1,3,4] while the inhibition of CBF autoregulation in rats (by the infusion of high levels of Ca^{2+} channel blockers) under conditions when BP is elevated enhances BBB disruption.[5]

Pressure-dependent constriction helps to promote CBF autoregulation.[1,6] Elevations in BP promote cerebrovascular constriction, which elevates vascular resistance to flow and counteracts the potential increase in CBF that might be

expected to occur. Thus, CBF remains constant despite the change in BP.

Dahl salt-sensitive (Dahl-SS) rats fed a high-NaCl diet develop hypertension, behavioral signs of stroke, and disruption of the BBB.[7,8] The present study tested the hypothesis that stroke development in Dahl-SS rats was preceded by a defect in the ability of the cerebrovasculature to autoregulate blood flow and that this defect was associated with an inability of the cerebral arteries to constrict in response to pressure (myogenic response).

Materials and Methods

The experiments were consistent with the guidelines set by the Canadian Council on Animal Care. Male Dahl-SS rats used in the study were bred at our institute and fed a normal or high-salt diet from weaning (5 weeks of age). The normal-salt diet consisted of a Prolab RMH 3000 formula (PMI Feeds Inc) that contained 0.7% NaCl (0.26% Na$^+$, 0.44% Cl$^-$), whereas the high-salt diet contained 8.7% NaCl (5.11% Na$^+$, 3.59% Cl$^-$). Rats were monitored daily for signs of hypertensive encephalopathy or stroke (seizures, head and forelimb repetitive twitching behavior, forelimb and hindlimb paral-

ysis, severe lethargy; signs are described in greater detail in Results). The systolic BP was measured by a tail cuff compression method (model 59, IITC).

Examination of Brains

The brains of 47 Dahl-SS rats exhibiting behavioral abnormalities were fixed in 10% PO_4-buffered formalin. Forty brains were sectioned in 1-mm-thick coronal sections with the use of a jig (REM-4000C, ASI Instruments) and examined by microscope for cerebral hemorrhages. Seven brains were imbedded in paraffin and histologically sectioned. The 5-μm-thick sections were stained with cresyl violet blue or hematoxylin and eosin or assessed for the presence of glial fibrillary acidic protein (which accumulates in astrocytes after ischemic damage[9]) and examined for ischemic alterations and the presence of hemorrhage.

The unfixed brains of 6 rats exhibiting abnormal behavioral symptoms were sliced with the use of a jig (REM-4000C) and assessed for ischemic lesions with a tetrazolium red technique.[10] Tetrazolium red is taken up by the brain cells, and dehydrogenases convert this compound to an impermeable red dye that remains within the cells. Ischemic damage of the brain inactivates cellular dehydrogenase, leading to a failure in staining.

## Measurements of Plasma Extravasation Across the BBB

Rats were anesthetized with sodium pentobarbital (65 mg/kg IP), and Evans blue dye (30 mg/mL of 0.9% saline) was infused (30 mg dye per kilogram) into the femoral vein. After 12 minutes, the chest cavity was opened, and a polyethylene catheter (PE-50) was inserted into the aorta and tied. The right and left ventricles were cut to allow free outflow, and saline (0.9%) was perfused into the aorta at a pressure of 200 mm Hg. This cleared the intravascular dye from the cerebral vasculature, leaving only extravascular dye that had crossed the BBB. Evans blue dye likely conjugates to plasma albumin, and studies have shown that a direct relationship occurs between the extravasation of dye and albumin during conditions of inflammation.[11]

Measurement of Pressure-Dependent Constriction in Middle Cerebral Arteries

The technique used to measure pressure-dependent constriction and pressure-independent tone in the middle cerebral arteries (MCAs) has been described in other publications.[7,12–14] A segment of the MCA spanning the rhinalis fissure of the brain was excised and mounted on a pipette in a pressure myograph. The lumen and exterior of the artery were filled and suffused with oxygenated (95% O_2/5% CO_2) Krebs' solution. With the use of videomicroscopy, the lumen diameter was measured at ×322 magnification. Changes in lumen diameter 1 second to 4 minutes after the application of a pressure step of 100 mm Hg, subsequent to a 6-minute equilibration at 0 mm Hg pressure, were used as a measure of pressure-dependent constriction (myogenic response). Pressure-independent tone (basal tone) was measured as the difference in lumen diameter present at 1 second after MCA pressurization to 100 mm Hg (before the significant engagement of pressure-dependent constriction) versus the diameter present at 100 mm Hg after maximal dilation (3 μmol/L nifedipine or Ca^{2+}-free/2.5 mmol/L EGTA Krebs' solution).

Measurement of CBF Autoregulation

The laser-Doppler techniques used to measure CBF are described elsewhere.[12] Relative CBF (rCBF) was measured in the perfusion domain of the MCA. Blood $PaCO_2$, pH, HCO_3, and O_2 saturation were measured from a femoral arterial blood sample. Norepinephrine (which cannot constrict the cerebrovasculature[1]) was infused into the rats (via the femoral vein) to slowly raise the BP (measured through a femoral catheter). The CBF signals from the laser-Doppler probe and the synchronized femoral BP readings were stored as digital data. The CBF present at a given mean arterial BP (MAP) was normalized to the CBF present at a MAP of 100 mm Hg to give the
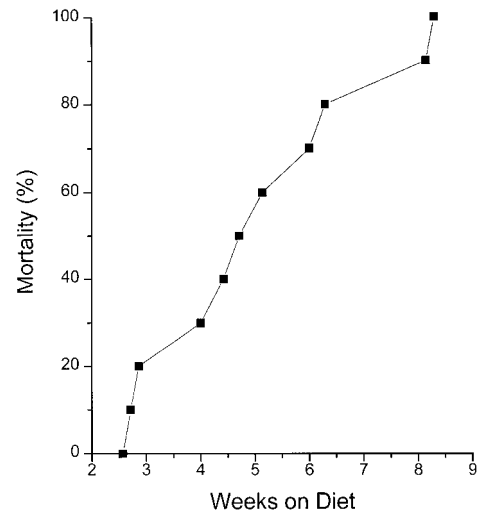
Figure 1. Mortality profile of Dahl-SS rats fed an 8.7% NaCl diet from weaning (5 weeks of age). Dahl-SS fed normal NaCl (0.7%) (n=10) remained healthy for the duration of the experiment (14 weeks of age).

rCBF value [ie, rCBF at a given MAP=(flux at MAP/flux at MAP of 100 mm Hg)]. rCBF was then plotted against MAP.

Statistical Analysis

A 1-way ANOVA and a Fisher post hoc test were used to determine group differences. A general linear model of MANOVA was used to analyze the CBF versus BP curve data. Changes in CBF with BP and the differential interactive effect of CBF with BP were assessed. Regression analysis (using the least squares standard deviation fit criterion) and the assessment of the Pearson correlation coefficient (r value) were used to determine whether significant relationships existed between parameters. Results were considered different at $P<0.05$. Data are represented as the mean±SE measurement; n values represent the number of rats used in the experiment.

Results

Hypertension and Mortality in Dahl-SS Rats

The onset of death started when Dahl-SS rats were fed 8.7% NaCl for periods >2.5 weeks, and 50% mortality was observed after 4.5 weeks of feeding (Figure 1). Before death, 70% of the animals exhibited seizures. The symptoms observed were the rhythmic, abrupt movements of the head in an up-and-down motion often associated with a lateral deflection or repetitive forearm flexion on the left or right side. The balance (30%) of the animals exhibited severe lethargy. Such animals were poorly groomed and remained huddled with urine-soaked bedding surrounding the posterior of the animal (indicating that the rat had not moved for a considerable time). Lethargy was not due to paralysis since the animals could be influenced to move. The rats often developed a persistent penile erection (only male rats were studied), suggesting autonomic dysfunction. Forelimb or hindlimb paralysis was rare (1/20 rats fed 8.7% NaCl for >4 weeks). Dahl-SS rats fed normal (0.7%) NaCl for 10 weeks remained asymptomatic and healthy.

In rats, a systolic BP of 150 mm Hg is considered the threshold for hypertension. Maximal systolic BPs were established at >200 mm Hg after 3 weeks of high-salt feeding (Figure 2). Dahl-SS rats fed 0.7% NaCl for 9
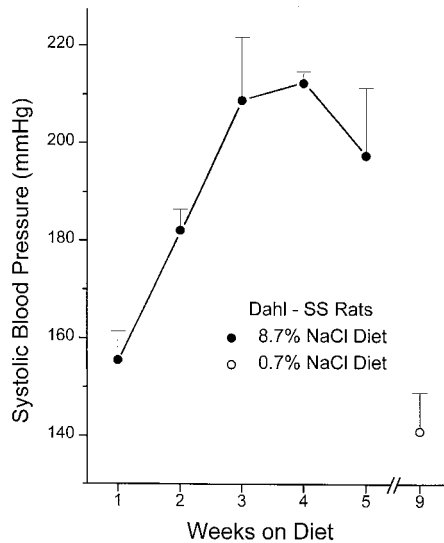
Figure 2. Systolic BP profile of Dahl-SS rats fed high-NaCl (8.7%) and normal-NaCl (0.7%) diets. Dahl-SS rats fed high salt after weaning (5 weeks of age) exhibited a rapid increase in BP, while those fed 0.7% NaCl for 9 weeks exhibited borderline hypertension (rats fed 8.7% NaCl: n=10 at 1, 2 weeks; n=8 at 3 weeks; n=7 at 4 weeks; n=4 at 5 weeks; rats fed 0.7% NaCl: n=5).

weeks exhibited borderline hypertension levels (systolic BPs near 150 mm Hg).

Cerebral Lesions in Dahl-SS Rats

The brains of 47 Dahl-SS rats exhibiting stroke-like symptoms were studied. Tetrazolium red staining (n=6) and histological examination (using cresyl violet blue or hematoxylin and eosin staining techniques or the assessment of the presence of glial fibrillary acidic protein[9]; n=7) failed to detect ischemic damage. The brains of 7 of 47 rats exhibited intracerebral hemorrhage in the cerebrum; 1 rat had hemorrhage in the cerebrum and brain stem. The brains of 6 rats were assessed by the Evans blue dye technique.[11] Five rats showed multiple sites of Evans blue dye extravasation, and 1 brain showed a diffuse extravasation of dye. Figure 3 represents the typical appearance of the brain from one of these rats. We concluded that the stroke-like behavioral dysfunctions (seizures, head and forelimb repetitive twitching behavior, forelimb and hindlimb paralysis, and severe lethargy) observed in Dahl-SS rats were more consistent with the presence of hypertensive encephalopathy than true stroke (discussed later). Hypertensive encephalopathy is a condition promoted by BBB disruption and cerebral edema secondary to hypertension, which can occur in the absence of cerebral ischemic or hemorrhagic lesions (true stroke).[15,16] Edema formation can be observed in the brain shown in Figure 3 as light-colored areas surrounding the Evans blue extravasation. We also observed that Dahl-SS rats exhibiting hypertensive encephalopathy have brains with higher tissue water contents than those in asymptomatic, younger Dahl-SS rats (G.W. Payne, MSc, unpublished data, 2002).
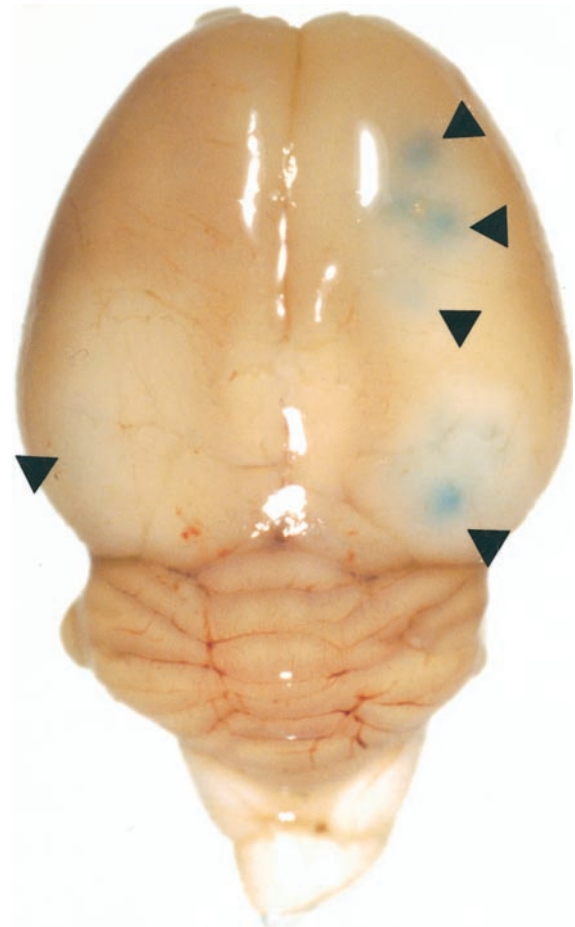

Figure 3. Evans blue dye extravasation in the brain of a Dahl-SS rat exhibiting seizures. Dahl-SS rats with behavioral abnormalities exhibited BBB disruption and the extravascular movement of Evans blue dye (arrows). Light-colored areas surrounding the extravasated dye correspond to areas of edema. Cerebral ischemia was absent, and hemorrhage rarely occurred (7/47 rats). On the basis of brain pathology, the behavioral dysfunctions observed best represent the occurrence of hypertensive encephalopathy.

Alterations in Cerebrovascular Pressure-Dependent Constriction in Dahl-SS Rats

Asymptomatic Dahl-SS rats fed 8.7% NaCl for 1 to 7 weeks (aged 6 to 12 weeks) had MCAs that exhibited an age-related decline in their ability to elicit pressure-dependent constriction (Figure 4A and Table 1; PDC, constriction observed from 1 second to 4 minutes after a pressure step of 100 mm Hg). Because of the attenuation of pressure-dependent constriction, the rats maintained progressively larger MCA lumen diameters with age at 100 mm Hg pressures (Figure 4B). This feature was particularly pronounced in rats with hypertensive encephalopathy (see data for 4 minutes at 100 mm Hg, Table 1). As shown in Figure 5 and Table 1, Dahl-SS rats fed 0.7% NaCl for 9 weeks (aged up to 14 weeks) had MCAs that maintained robust constriction to a pressure step of 100 mm Hg.

Dahl-SS rats with hypertensive encephalopathy (and no cerebral hemorrhage) had MCAs with attenuated pressure-dependent constriction compared with asymptomatic rats fed

A

B
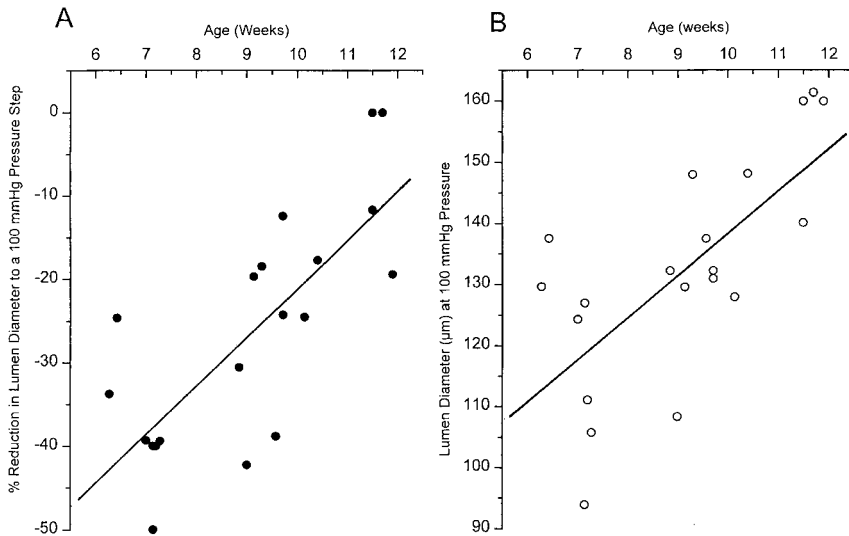
Figure 4. Age-related attenuation of pressure-dependent constriction (myogenic response) in MCAs of healthy asymptomatic Dahl-SS rats fed 8.7% NaCl from weaning (5 weeks of age). A, Lumen diameter constriction (%) in response to a pressure step of 100 mm Hg. As shown in B, a decrease in the ability of the MCAs to constrict to a pressure step of 100 mm Hg resulted in the maintenance of a larger MCA lumen diameter (at 100 mm Hg) with age. An age-related decline in pressure-dependent constriction was not observed in MCAs sampled from Dahl-SS rats fed 0.7% NaCl for 9 weeks (14 weeks of age; see Figure 5). In A, percent MCA pressure-dependent constriction=5.86×age (weeks)−79.3; n=20, r=0.761, $P<0.001$. In B, MCA lumen diameter (μm)=6.97×age (weeks)+69.3; n=20, r=0.702, $P<0.01$.

high salt for 1 to 3 weeks or rats fed low salt. Pressure-dependent constriction was abolished in the MCAs of Dahl-SS rats with cerebral hemorrhage (Figure 5 and Table 1). The average age of rats exhibiting hypertensive encephalopathy and cerebral hemorrhage was 9.3±0.1 and 10.3±0.1 weeks, respectively (fed high salt for 4.3±0.1 and 5.3±0.1 weeks, respectively). We attempted to determine whether the attenuated pressure-dependent constriction in the MCAs could be accounted for by the age-related decline in this function. In Figure 4A, asymptomatic Dahl-SS rats fed high salt exhibited the following relationship between pressure-dependent constriction and age: percent pressure-dependent constriction=5.86×age (weeks)−79.3 (r=0.761, $P<0.001$; n=20). On the basis of age, the latter equation predicted a −24.8% pressure-dependent constriction response in the MCAs of rats with hypertensive encephalopathy and −19%

in rats with cerebral hemorrhage. These predicted values were greater ($P<0.05$) than the actual pressure-dependent constriction responses measured in rats with hypertensive encephalopathy (−11.3±3.8%) or cerebral hemorrhage (−2.2±2.1%). We also selected age-matched asymptomatic Dahl-SS rats fed high salt and compared them with the rats with hypertensive encephalopathy and cerebral hemorrhage. The chosen asymptomatic rats had group ages of 9.3±0.1 weeks (n=7) and 10.3±0.3 weeks (n=5) and exhibited −26.6±0.1% and −15.8±0.3% MCA pressure-dependent constriction responses, respectively, which were greater ($P<0.05$) than those in rats with hypertensive encephalopathy (−11.3±3.8%) or cerebral hemorrhage (−2.2±2.1%).

Despite the absence of pressure-dependent constriction, rats with cerebral hemorrhage maintained substantial MCA pressure-independent tone. This is demonstrated by the high

TABLE 1.   Alterations in MCA Lumen Diameter in Response to a 100 mm Hg Pressure Step

	Dietary NaCl, %	Weeks on Diet	n	Status	Pressure Step — 1 Second at 100 mm Hg	Pressure Step — 4 Minutes at 100 mm Hg	At 100 mm Hg+ Maximal Vasodilation	PDC, μm	PIT, μm
A	8.7	1 to 3	7	Asymptomatic	192±4.9	118±5.8	200±5.7	73.3±5.9	7.9±2.8
B	8.7	3 to 5	7	Asymptomatic	181±9.1	131±4.5	198±10.1	50.1±9.7	16.5±7.9
C	8.7	5 to 7	6	Asymptomatic	172±8.1	150±5.5	206±2.9	22.1±7.6	34.0±8.4
D	8.7	4.3±0.1	6	Hypertensive encephalopathic	182±5.1	161±9.1	192±4.1	20.5±7.1	10.3±5.5
E	8.7	5.3±0.1	3	Intracerebral hemorrhage	149±16.5	145±13	199±4.5	4.0±4.0	49.4±12.2
F	0.7	9	5	Asymptomatic	190±14.5	127±9.1	213±8.6	63.8±9.8	23.6±8.7
					$P<0.05$	$P<0.05$	No significant differences between groups	$P<0.05$	$P<0.05$
					E vs A, B, D, F	A vs C, D, E		A vs B, C, D, E	B vs C, E
						B vs D		B vs C, D, E	C vs A, D
						F vs C, D		F vs C, D, E	E vs A, B, D

PDC indicates pressure-dependent constriction, difference in lumen diameter between 1 second and 4 minutes after pressurization to 100 mm Hg; PIT, pressure independent tone, difference in lumen diameter between maximal vasodilation (with 3 μm of nifedipine) and the diameter at 1 second after pressurization to 100 mm Hg.

Statistics: ANOVA plus Fisher post hoc test.
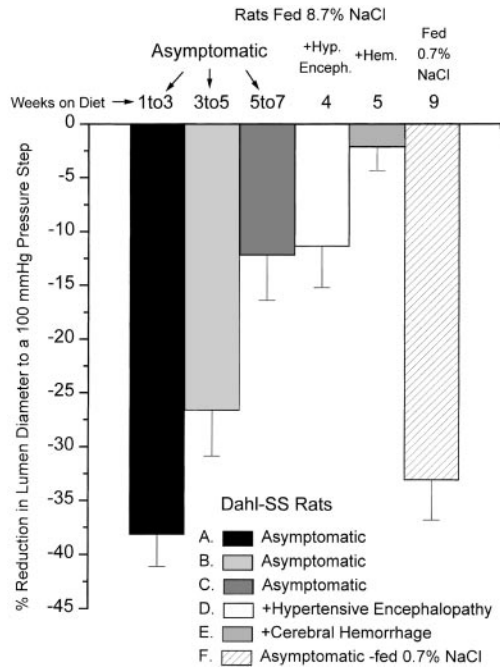
Figure 5. Pressure-dependent constriction (myogenic response) in MCAs of Dahl-SS rats before and after the development of hypertensive encephalopathy or hemorrhagic stroke. The percent decrease in lumen diameter after the application of a pressure step of 100 mm Hg is shown. Asymptomatic Dahl-SS rats fed 8.7% NaCl for 1 to 3 weeks (n=7; aged 6.9±0.2 weeks), 3 to 5 weeks (n=7; aged 9.3±0.1 weeks), and 5 to 7 weeks (n=6; aged 11.2±0.3 weeks) after weaning (5 weeks of age) had MCAs that progressively developed an attenuated ability to elicit pressure-dependent constriction. Pressure-dependent constriction was further attenuated in rats with hypertensive encephalopathy (+Hyp. Enceph.; n=6; aged 9.3±0.1 weeks) and was abolished in rats with cerebral hemorrhage (+Hem.; n=3; aged 10.3±0.01 weeks). Dahl-SS rats fed 0.7% NaCl diet for 9 weeks after weaning (n=5) had MCAs that maintained pressure-dependent constriction. $P<0.05$, A vs B, C, D, E; B vs C, D, E; F vs C, D, E (ANOVA and Fisher post hoc test).

level of constriction present at 1 second after equilibration to 100 mm Hg in comparison to maximal dilation (see pressure-independent tone data in Table 1). This suggested that cerebral hemorrhage is associated with the development of intrinsic tone in the isolated MCAs.

The MCAs of asymptomatic rats and rats with hypertensive encephalopathy or cerebral hemorrhage had comparable lumen diameters under conditions of maximum dilation (see Maximal Vasodilation at 100 mm Hg pressure data in Table 1). The ability of 3 μmol/L nifedipine to produce maximal vasodilation was validated. After administration of nifedipine, no further vasodilation occurred in Ca^{2+}-free/ 2.5 mmol/L EGTA Krebs' solution (mean percent difference in lumen diameter, nifedipine versus EGTA Krebs' solution: asymptomatic rats, 0.44±1.17%, n=5; rats with hypertensive encephalopathy, 0.01±0.93%, n=5). We also observed no differences in dilatory sensitivity to nifedipine (ie, comparable ED_{50} values for dose-response curves from 10^{-9} mol/L [subthreshold] to 3×10^{-6} mol/L [maximal vasodilation]) when MCAs sampled from asymptomatic Dahl-SS rats (young, n=5; old, n=8) or rats with hypertensive encephalopathy (n=5) or cerebral hemorrhage (n=3) were compared (data not shown).
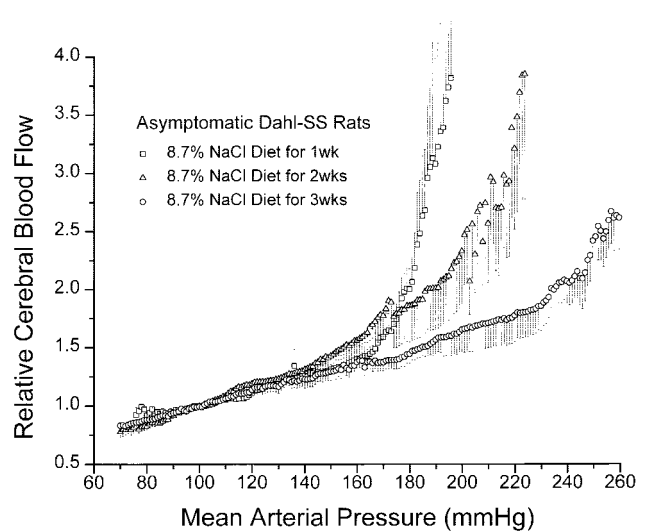
Figure 6. Alterations in CBF autoregulation in asymptomatic Dahl-SS rats fed 8.7% NaCl for varying durations. Before the development of hypertensive encephalopathy, most rats (4/6) fed high salt for 3 weeks exhibited a linear relationship between CBF and BP and the absence of a distinct inflection point (such as that observed in rats fed high salt for 1 or 2 weeks), representing an upper BP limit to CBF regulation. Such an alteration is consistent with a loss in CBF autoregulation. Dahl-SS rats fed 0.7% NaCl for 9 weeks maintained CBF autoregulation (Table 2). The CBF autoregulatory curve representing this group was identical to that of rats fed high salt for 2 weeks. These data were removed from the figure to decrease congestion. Each curve is significantly ($P<0.05$) different from all other curves in absolute levels over common BPs and in terms of the interactive effect of rCBF with BP ($P<0.001$ in all cases) (MANOVA on curves); n=6 rats in each group.

Alterations in CBF Autoregulation in Dahl-SS Rats

CBF autoregulation was assessed in asymptomatic Dahl-SS rats fed 8.7% NaCl for 1 to 3 weeks or 0.7% NaCl for 9 weeks after weaning. Through the control of respiratory rates and the administration of oxygen, blood Pa_{CO_2} (40±2 mm Hg), pH (7.40±0.01), and HCO_3 levels (25.3±0.8 mmol/L) were normal, and oxygen saturation was always >99.6% (n=25 rats).

Dahl-SS rats fed 8.7% NaCl for 1 week or 0.7% NaCl for 9 weeks autoregulated blood flow to an upper mean BP limit of 168±6 and 204±12 mm Hg, respectively (Figure 6 and Table 2). One of 6 rats fed 8.7% NaCl for 2 weeks and 4 of 6 rats fed the diet for 3 weeks exhibited linear increases in CBF with BP and the absence of an upper BP limit to CBF regulation (Figure 6 and Table 2). These characteristics are consistent with the loss of CBF autoregulation. Dahl-SS rats fed 0.7% NaCl for 9 weeks maintained CBF autoregulation (Table 2). The CBF autoregulatory curve representing this group was identical to that of rats fed high salt for 2 weeks and was removed from Figure 6 to decrease congestion.

The relative change in CBF between BPs of 90 to 120 mm Hg was comparable between the groups of rats (Table 2; discussed later). The upper BP limit of regulation shifted to higher pressures with the duration of salt feeding in Dahl-SS rats fed 8.7% NaCl and was remarkably high (204±12 mm Hg) in rats fed low salt that exhibited borderline hypertension (approximately 150 mm Hg).

TABLE 2. Characteristics of CBF Autoregulation in Asymptomatic Dahl-SS Rats

Dietary NaCl, %	Weeks on Diet	n	Rats Exhibiting CBF Regulation	Upper BP Limit of CBF Regulation	ΔrCBF/Δmm Hg
8.7	1	6	6/6	168±6†	4.73±1.17
8.7	2	6	5/6	181±9	9.2±1.13‡
8.7	3	6	2/6	NA*	7.12±0.94
0.7	9	7	7/7	204±12	5.41±0.85

ΔrCBF/Δmm Hg indicates change in relative CBF between BPs of 90 to 120 mm Hg ($\times 10^{-3}$).

*The 2 of 6 rats exhibiting CBF autoregulation had upper BP limits of 227 and 185 mm Hg.

Statistics (ANOVA): †$P<0.05$ vs 0.7% NaCl diet; ‡$P<0.05$ vs 8.7% NaCl diet for 1 week and 0.7% NaCl diet.

We attempted to measure CBF autoregulation in Dahl-SS rats exhibiting hypertensive encephalopathy. Unfortunately, these rats were highly susceptible to death within 1 hour of anesthesia. This prevented us from completing the experiments. However, since most asymptomatic Dahl-SS rats fed 8.7% NaCl for 3 weeks lost their ability to autoregulate CBF before hypertensive encephalopathy or hemorrhagic stroke (Figure 6 and Table 2), this function most likely remained defective after hypertensive encephalopathy.

Discussion

Dahl-SS rats fed 8.7% NaCl exhibited stroke-like behavior (seizures, head and forelimb repetitive twitching behavior, forelimb and hindlimb paralysis, severe lethargy). The brains of these rats indicated plasma extravasation and edema in the cerebrum. Ischemia was absent, and the incidence of cerebral hemorrhage was low (7/47). The rats best represented a model of hypertensive encephalopathy as opposed to true stroke. In humans, hypertensive encephalopathy is produced by BBB disruption.[16] The development of brain edema secondary to hypertension applies pressure to the neural tissue and promotes neurological dysfunction. Hypertensive encephalopathy is associated with confusion, stupor, and convulsions, symptoms similar to those observed in our rats, and is distinguished from stroke in that it can occur in the absence of cerebral ischemia or hemorrhage.[16]

Myogenic dysfunctions preceded the onset of hypertensive encephalopathy. Pressure-dependent constriction was attenuated in the MCAs of asymptomatic Dahl-SS rats in relation to the duration of high-salt feeding. As a result of the loss of pressure-dependent constriction, the MCAs maintain progressively larger lumen diameters at 100 mm Hg pressure. In the presence of hypertension, this alteration could increase downstream flow and pressure to the microvasculature and facilitate the formation of brain edema and hypertensive encephalopathy. The MCAs of rats with hypertensive encephalopathy or cerebral hemorrhage exhibited a greater attenuation of pressure-dependent constriction than that which could be accounted for by an age-related decline in this function. This added dysfunction could be promoted by secondary alterations after hypertensive encephalopathy or cerebral hemorrhage. Alternatively, hypertensive encephalopathy and cerebral hemorrhage could be favored in rats with cerebrovasculatures that exhibit a low capacity to elicit pressure-dependent constriction.

There was a linear increase in rCBF with BP and the absence of an upper limit to CBF autoregulation in most Dahl-SS fed high salt for >3 weeks. This is consistent with the absence of CBF autoregulation; however, the changes in rCBF with BP (ie, ΔrCBF/Δmm Hg BP; Table 2) were comparable to those present in rats capable of autoregulating CBF. We believe that higher ΔCBF/Δmm Hg BP ratios would have occurred if CBF autoregulation was lost under conditions of cerebrovascular vasodilation. However, if the loss of CBF autoregulation in Dahl-SS rats fed high salt was associated with cerebrovascular vasoconstriction, an increase in the slope of ΔrCBF/Δmm Hg BP could have been blunted to a point where it was comparable to that observed in rats capable of autoregulating CBF, despite the loss of autoregulation. An alternative possibility also exists. Our experiments were limited by the fact that the maximal mean BPs that could be achieved by the intravenous infusion of norepinephrine into Dahl-SS rats were approximately 260 mm Hg. If the upper limit of CBF autoregulation was >260 mm Hg, the inability to surpass this point would have produced a linear CBF versus BP curve with the absence of an upper BP limit to autoregulation. This could have resulted in the mistaken impression that no upper BP limit existed and that CBF autoregulation was lost. In our view, this would require an unprecedented large shift in the upper BP limit of autoregulation far above that observed in any other study involving hypertensive rats. Although our experiments cannot disprove the latter scenario, we believe that it is the less plausible of the 2 hypotheses presented.

The cerebrovascular alterations occurring in the Dahl-SS rats exhibit similarities and contrasts to the types of changes present in stroke-prone spontaneously hypertensive rats (SHRSP).[12,13,17] Unlike the SHRSP we have studied,[17] Dahl-SS rats developed a lower incidence of cerebral hemorrhage. We believe that seizures observed in Dahl-SS rats were associated with hypertensive encephalopathy. In this regard, the Dahl-SS model and the present study are unique because few studies have assessed cerebrovascular alterations preceding and following the development of hypertensive encephalopathy. Both SHRSP and Dahl-SS rats lose their ability to autoregulate CBF and develop defects in pressure-dependent constriction within the MCAs before the development of hemorrhagic stroke or hypertensive encephalopathy.[12,13] However, unlike Dahl-SS rats, the loss of autoregulation in SHRSP is associated with an increase in ΔCBF/Δmm Hg BP.[12] This type of change would facilitate overperfusion to a greater

degree than if (as predicted in Dahl-SS rats) regulation was lost under conditions of cerebrovascular vasoconstriction. This could account for the higher incidence of cerebral hemorrhage observed in SHRSP[17] versus Dahl-SS rats in the present study. Dahl-SS rats exhibiting seizures and hypertensive encephalopathy were also highly susceptible to death and survived for only a few days. It is possible that cerebral hemorrhage might have developed after hypertensive encephalopathy in Dahl-SS rats if the animals survived for a longer time in the presence of defective CBF autoregulation.

Acknowledgments

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