Proteinuria Precedes Cerebral Edema in Stroke-Prone Rats
A Magnetic Resonance Imaging Study

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Background and Purpose—Stroke-prone spontaneously hypertensive rats (SHRSP) subjected to high sodium intake develop severe hypertension, cerebral edema, and proteinuria, culminating in organ damage and early death. MRI, which can be applied serially, provides the unique opportunity to study temporal and quantitative relations between these changes and whether diminution of sodium intake can attenuate established cerebral edema.

Methods—SHRSP were subjected to 1% NaCl in drinking water. Cerebral MRI, proteinuria and systolic blood pressure (SBP) were measured serially. After detection of cerebral edema (T2-weighted MRI), 6 rats were killed for histology, to confirm the diagnosis of cerebral edema. The others were followed up for 7 more days while salt loading was continued (n=10, group 1) or after sodium intake was normalized (n=7, group 2).

Results—SHRSP invariably developed cerebral edema in 30 days (range, 8 to 54 days). At this point neurological signs were absent in 16 of 23 rats. SBP rose until 1 week before detection of cerebral edema, and then stabilized at approximately 265 mm Hg. Proteinuria invariably preceded cerebral edema, with a concentration exceeding 40 mg/d predicting development of cerebral edema in 9 days (range, 3 to 15 days). There was linear correlation (R=.62, P<.0001) between proteinuria and cerebral edema (pixels with an intensity above a defined threshold). Rats in group 1 showed an increase in cerebral edema (from 5.8±1.1% to 12.5±2.8%; P<.05), and proteinuria remained high (from 305±44 to 338±29 mg/d); and 2 died spontaneously. Rats in group 2 showed no significant change in edema (from 4.9±0.5% to 6.9±1.3%) but a marked fall in proteinuria (from 294±24 to 119±10 mg/d; P<.05), both significantly different from group 1 (P<.05); all survived. SBP remained unaltered in both groups.

Conclusions—Our data establish MRI as a sensitive method for detection of cerebral edema, often prior to neurological signs, in SHRSP. Proteinuria predicts cerebral edema, and these two variables, both obtained noninvasively, are quantitatively related. Moreover, in SHRSP normalizing sodium intake after salt loading attenuates development of cerebral edema and reduces proteinuria. (Stroke. 1998;29:167-174.)

Key Words: brain edema ■ magnetic resonance imaging ■ proteinuria ■ sodium, dietary ■ rats

Sodium intake plays a crucial role in determining hyperten-
sion2,3 and the occurrence of stroke.3–5 Dietary salt restriction reduces the risk and mortality of stroke.4 The SHRSP is an experimental model of malignant hypertension and has a high incidence (80%) of cerebrovascular disease.7 Elevation of sodium intake from 8 weeks of age onward accelerates the increase of blood pressure and the appearance of cerebral vasogenic edema in SHRSP.8 Thus, the young SHRSP is an appropriate model for studies of sodium intake–related development of malignant hypertension and cerebrovascular disease. In addition to cerebral vasogenic edema the SHRSP develops proteinuria,4 which is recognized as being an important prognostic marker for the occurrence of stroke.9

T2-weighted MRI (T2W MRI) is a noninvasive technique that is uniquely suited to the assessment of the development, progression, and regression of brain edema and intracerebral hemorrhage in vivo. It can define the number spatial distribution and quantitate the size of brain lesions better than any other imaging modality.10–14 This technique offers a novel possibility to do repeated measurements and thus monitor the development of cerebral lesions as well as the effect of therapeutic measures at different stages of developing cerebral injury. The first aim of our study was to describe the development of cerebral lesions in relation to neurological symptoms in young SHRSP during high salt intake with use of repeat T2W MRI. If a certain level of proteinuria inevitably precedes the development of cerebral edema, this level of proteinuria could be used as a starting point for prophylactic

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selected Abbreviations and Acronyms

SBP = systolic blood pressure
SHRSP = stroke-prone spontaneously hypertensive rats
SIIS = standard individual image set
T2W MRI = T2-weighted magnetic resonance imaging

interventions. Hence, the second goal was to study the relation between proteinuria and cerebral edema in salt-loaded SHRSP to ascertain whether proteinuria precedes cerebral edema in this model, and if so, to define a level of proteinuria that predicts the appearance of cerebral edema. Low salt intake reduced the incidence of stroke in humans\(^5\) and effectively prevented proteinuria in uninephrectomized SHR.\(^3\) Thus, the third goal was to study the effects of normalized salt intake in SHRSP, after the initial appearance of cerebral edema, on the subsequent evolution of proteinuria and cerebral edema.

Materials and Methods

Animals

Male SHRSP (n=23), age 6 weeks, were obtained from IFFA Credo, L’Arbresle, France. They were housed in constant conditions (day/night: 12/12; humidity, 55%; temperature, 22° C), given free access to a standard rat chow (RMH-TM rat chow: protein 22.2%; fat 4.8%; potassium 0.85%; sodium 0.40%; Hope-Farms), and allowed water ad libitum. The protocol was approved by the Utrecht University Board for study in experimental animals.

Protocol

Baseline measurements were collected in all rats at 7 weeks of age to determine the standardized threshold of brain edema in each individual rat (see below). Subsequently, at the age of 8 weeks all rats were switched to a high salt intake by 1% NaCl (170 mmol/L) in drinking water in order to accelerate the appearance of cerebral edema.\(^8\) The rats were observed daily for overt neurological symptoms and undergone weekly blood pressure measurements, T2W MRI of the brain, and metabolic studies, the latter to assess sodium intake, renal function, and proteinuria (see below). This was continued until the detection of cerebral abnormalities with T2W MRI (defined as day 0). If a rat showed behavioral dysfunction, intercurrent imaging was determined. To determine plasma creatinine, blood from the tail was collected (via page 6) and immediately followed by perfusion fixation with 4% formaldehyde in 0.1 mmol/L phosphate buffer at a pressure two thirds that of the last systolic blood pressure measured by the plethysmography tail-cuff method. Ten-μm sections of the brain (10 sections at 500-μm intervals) were stained with hematoxylin/eosin and Luxol fast blue. Brains of rats that had died spontaneously were collected in formaldehyde for histology.

T2W MRI

After inducing anesthesia with 1% halothane in N\(_2\)O/O\(_2\) (70/30), rats were intubated and mechanically ventilated during the MRI session with the same mixture. Expiratory CO\(_2\) was monitored, and body temperature was maintained at 37° C with use of a heated water pad. To prevent movement, the rats were fastened in a stereotactic holder and positioned in a 4.7-T, 200- to 400-NMR spectrometer (SiS Co). A 120-mm Helmholz coil was used for both transmission and signal reception. After a sagittal scout image, coronal multicoil spin-echo T2W MRI, covering the whole brain (25 slices of 1 mm; TE/TR, 60/3000; matrix, 128×128; field of view, 40×40 mm; two transitions) was performed.

T2W MRI Evaluation

The brain was segmented from the surrounding image by autocontouring, an analysis that automatically generates contours by edge tracking on a binary mask set by an upper and lower threshold of intensity values. From each animal a baseline SIIS was collected before salt loading. In this SIIS, 25 coronal T2W images (40×40×1 mm) rostral from the cerebellum were collected in such a way that the rostral/caudal, left/right, and dorsal/ventral axes of the brain were positioned parallel to the z, x, and y axes of the magnet of the NMR spectrometer, respectively. The four slices caudal to the cerebellum/cerebral hemispheres were considered a reference area where edema never occurred (REFerence area). This was confirmed (see "Results"). The remaining part of the brain rostral to this line until the last slice with a cortical area was analyzed for the appearance of brain edema. From this brain area and from the reference area the mean intensity (mi) of the pixels was computed (\(p_{BRAIN}^{SIIS mi}\) and \(p_{REF}^{SIIS mi}\), respectively). The standard deviation (\(σ\)) of the baseline \(p_{BRAIN}^{SIIS mi}\) was also calculated. The standardized threshold, \(p_{BRAIN}^{standardized threshold}\), of edema in the brain is unique for an individual animal and is defined as:

\[
p_{BRAIN}^{standardized threshold} = \frac{p_{BRAIN}^{SIIS mi} + 2σ_{BRAIN}^{SIIS mi}}{p_{REF}^{SIIS mi}}
\]

In every succeeding MRI experiment, the mean pixel intensity in the reference area, \(p_{BRAIN}^{SIIS mi}\), was calculated. Multiplying the \(p_{BRAIN}^{SIIS mi}\) with \(p_{BRAIN}^{standardized threshold}\) gives us the threshold of the experiment, \(p_{BRAIN}^{SIIS mi}\). If an individual pixel intensity in the brain was higher than \(p_{BRAIN}^{SIIS mi}\), it was considered to be edematous. Cerebral edema formation is associated with \(T_2\) prolongation.\(^9\) Spatial evaluation of the progression/regression of edema, we identified on day 0 the slice with the primary lesion site from where edema would eventually progress or regress. The percentage of edematous pixels was evaluated in ten slices that always fell within the cortex: five caudal and four rostral to the central slice.

Statistics

Data were evaluated by two-way ANOVA for repeated measurements, followed by a pairwise multiple comparison procedure (Student-Newman-Keuls method). Data are presented as mean±SEM. \(P<.05\) was considered statistically significant.
Results

Development of Cerebral Lesions

Neurological Symptoms and Mortality
The majority of the rats (16/23) did not show overt behavioral dysfunction at the time when first lesions on T2W MRI were observed, although some reduction of activity and ruffling of the fur was usually present. However, seven had a unilateral intermittent myoclonic deviation of the head. All animals developed lesions within 30 days (median) after starting 1% NaCl in the drinking water (range, 8 to 54 days).

T2W MRI
By definition, all 23 rats showed areas of high signal intensity on T2W MRI on day 0, and some also showed areas with low signal intensity (3 of 23). With this scanning modality it is known that edema is hyperintense (resulting from T2 prolongation), whereas hemorrhagic patches are hypointense (resulting from the T2 shortening effect of iron). This was confirmed histologically in the rats sacrificed at day 0 (Fig 1).

Fig 2 shows typical consecutive T2W MRI made in one rat, illustrating the temporal development of cerebral damage in the salt-loaded SHRSP. All primary lesions, and therefore the definition of the central slice (see below), occurred in the grey matter, mainly in the frontal or forelimb area of the cortex or in the caudate putamen within a 4-mm window (from bregma -1.80 to bregma 2.20). From there the edema invariably progressed to the ipsilateral white matter. In some cases edema spread via the corpus callosum to the contralateral white matter. Edema was never observed in the cerebellum. In sites with vasogenic edema secondary hemorrhagic patches occasionally occurred.

Fig 3 shows the percentage edematous pixels in the cerebrum, which spanned 13 to 14 slices, and included those slices rostral to the line cerebellum/cerebrum until the first slice without cortical area. Edema was determined in each rat in relation to an individual threshold, defined as the mean pixel intensity ± twice the standard deviation at baseline. Consequently, 5% of the pixels lie outside this range, by definition 2.5% above and 2.5% below this range. The pixels above this

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<td>210±4</td>
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<td>196±7</td>
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<td>Group 2</td>
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<td>17.6±0.9*</td>
<td>12.1±1.9</td>
<td>7.9±1.5*†</td>
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<td>534±45</td>
<td>459±45</td>
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<td>547±62</td>
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<td>10.6±0.7*</td>
<td>11.5±1.3*</td>
<td>16.1±1.4</td>
<td>16.3±1.4†</td>
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<td>Group 2</td>
<td>2.5±0.1*</td>
<td>9.2±1.1*</td>
<td>11.7±0.9*</td>
<td>12.5±0.8</td>
<td>2.8±0.3*</td>
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<th>Sodium excretion, mmol/d</th>
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<td>8.7±0.7*</td>
<td>10.1±1.4*</td>
<td>15.2±1.7</td>
<td>15.8±1.2†</td>
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<td>Group 2</td>
<td>1.4±0.1*</td>
<td>7.6±0.9*</td>
<td>9.3±1.0*</td>
<td>11.6±0.8</td>
<td>2.1±0.3*</td>
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Day 0 indicates cerebral lesion first detected on T2W MRI; group 1, rats that stayed on a high salt diet after day 0; group 2, rats switched from a 1% NaCl solution to normal drinking water on day 0; and baseline, time before salt loading started. Values are mean±SEM.

*P<.05 vs day 0; †P<.05 vs normalized salt intake.
range are therefore (by definition) “edematous” at baseline. At day 0, 5.8±1.1% of the pixels in the examined part of the brain of the rats in group 1 and 4.9±0.5% of the pixels in the rats in group 2 were edematous. These numbers were not different, but both differed significantly from the preceding time points (day -3 and baseline; \( P<.05 \) versus day 0). Fig 4 shows the distribution of the percentage of edematous pixels in the slice that showed the primary lesion site on day 0 and its surrounding slices.

**Physiological Parameters**

At baseline SHRSP had a systolic blood pressure of \(~200\) mm Hg, which rose to \(~245\) mm Hg at day 0 during salt loading (\( P<.05 \)) (Table). Body weight increased from baseline to day -7. However, from day -7 to day 0 growth was stunted, and some rats lost weight. Food intake increased until day -7, but from day -7 to day 0 food intake decreased. Water intake and urine production increased from baseline to day 0 (\( P<.05 \)). The glomerular filtration rate increased slightly from baseline to day -14 and then stabilized to day 0. Sodium intake, both from water (1% Na/l) and food (0.4% Na/kg food), increased significantly from baseline to day 0. Sodium excretion followed sodium intake closely (Table). There were no differences between groups 1 and 2 in this stage.

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Coronal T2W MRI (pixel resolution 0.31×0.31 mm, slice thickness 1 mm) of a rat sampled at day 0. a, Bregma -2.0. Hyperintensity is seen in the right frontal cortex, right cingulum, and corpus callosum. The right lateral ventricle is larger. b, In the histological section of the hyperintense right frontal cortex, multiple extracellular vacuoles give the tissue a “spongy” appearance, pointing to the presence of edema. (Magnification, ×300.) c, In the histological section of the ipsilateral frontal cortex, where hyperintense pixels are absent, no signs of damage were observed. (Magnification, ×300.) d, Bregma -0.92. Hyperintensity is seen in the right capsula externa, left and right cingulum, corpus callosum, and the left and right fimbria hippocampus. e, In the histological section of the hyperintense right capsula externa, the fibrous white matter is distended, indicating volume expansion as a result of edema. (Magnification, ×300.) f, In the histological section of the ipsilateral (not affected) left capsula externa, the white matter is not rarefied. (Magnification, ×300.)

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Typical MR images of the temporal development of chronic cerebral lesions in the salt-loaded SHRSP (group 1). Cerebral slices (1 mm thickness) positioned to the stereotaxic reference point bregma (row) at successive time points (column). Day 0: first lesion detected on T2W MRI. The first cerebral lesions normally occurred in the grey matter of the occipital cortex, thalamus, and striatum. In this case the first lesion was in the frontal cortex of the right hemisphere (bregma 2.20). The edema then progressed to the ipsilateral white matter and finally via the corpus callosum to the ipsilateral white matter. A small hemorrhage was observed in the frontal cortex on day +7. The lateral ventricles were enlarged.

![Figure 3](http://stroke.ahajournals.org/)

**Figure 3.** Changes of the percentage of cerebral edema in the rats that stayed on high salt intake (●) and the rats switched to normal salt intake (before switch ▲, after switch ▲ ). Values are mean±SEM. \( +P<.05 \) vs day 0; \#\( P<.06 \) vs normalized salt intake.
Development of Proteinuria and Its Relation to Cerebral Edema

From baseline to day 0, proteinuria (UpV, Fig 5) showed a steep increase and at day 0 UpV was 300±28 mg/d (n=17), and differed significantly from all preceding days in both groups 1 and 2. All rats developed cerebral vasogenic edema within a median of 9 days (range: 3–15 days) after reaching a UpV-level of 40 mg/d. The lowest level of proteinuria at which a rat showed cerebral edema was 169 mg/d. A linear relation was found between UpV and the percentage of edematous pixels in the whole brain. This evaluation included data points from all the rats before and on day 0, as well as those maintained on the high salt diet between day 0 and day 17 (group 1). Linear regression led to the following relationship:

percentage cerebral edema = 2.02 + (0.0196 x proteinuria in mg/d) (R=0.619; P<.0001) implying that for approximately every 50 mg/d increase in proteinuria there was an increase of 1% edematous pixels in the brain. The intercept of approximately 2% was mainly due to the high intensity of the fluid-filled ventricles. Free fluid has a long T₂-relaxation time.

Effect of Normalizing Salt Intake after Appearance of Cerebral Edema

Neurological Symptoms and Mortality

Of the 10 rats in group 1 maintained on the high salt diet, two died spontaneously within a week. Switching back to a normal salt intake in group 2 tended to ameliorate the condition of the rats. Three out of four rats that showed unilateral intermittent myoclonic deviations of the head at day 0 showed regression of this behavior. No mortality occurred and all rats in group 2 (n=7) could be sacrificed for histology as scheduled.

T₂W MRI

Rats in group 1 showed a progressive increase of the percentage of edematous pixels (day 0: 5.8±1.1%; day +3: 10.8±1.8%; day +7: 12.5±2.8%, both P<.05 versus day 0; Fig 3). In group 2 brain edema showed a dynamic pattern of reduction (3 out of 7), reappearance, stabilization or even progression (Fig 6). The net result was a slight, but not significant, increase in edematous pixels (day 0: 4.9±0.5%; day +3: 6.0±1.9%; day +7: 6.9±1.3%. At days +3 and +7 the mean percentage edematous pixels in group 2 differed significantly from that observed in group 1 (P<.05). Only 2 out of 10 rats which stayed on a high salt intake showed a transient reduction of lesion size compared to a previous MRI session. Histological verification at day +7 in group 2 showed that areas with a normalization in T₂W-pixel intensity, compared to the preceding MRI session, showed no edema. In group 2 cerebral hemorrhage stabilized, whereas in group 1 it tended to progress.

In group 1 it is apparent that continued excessive salt intake increased the percentage of edematous pixels per slice both in the central slice as well as in the slices surrounding this centrally affected slice. In group 2 the distribution of edematous pixels...
in the central slice, and the nine surrounding slices did not change (Fig 4) at day +3. At day +7 there is an increase of the percentage of edematous pixels in the central slice and the directly surrounding slices. This analysis revealed that in this model increases or decreases in brain edema are due to increased or decreased leakage or spreading from within one affected area, and not from widespread multiple foci.

**Physiological Parameters** At day +7 blood pressure in group 1 was not different from that found at day 0. Even though the salt intake was normalized in group 2, blood pressure did not change significantly (Table). After day 0 body weight continued to decrease in both groups 1 and 2, reflecting the poor physical condition of the animals. In group 1 food intake continued to decrease, but in group 2 food intake increased again to the level found at day –7 and differed from the rats in group 1 (P<.05). In group 2 water intake and urine production were reduced at day +7 as compared to day 0, and differed significantly from the high salt intake group at day +7 (P<.05). In group 1 glomerular filtration rate decreased from day 0 to day +7 (P<.05), but in group 2 glomerular filtration rate remained stable from day 0 to day +7 and differed significantly from group 1 (P<.05, Table). In group 1 sodium intake stabilized at day +7, whereas in group 2 sodium intake and excretion decreased significantly from day 0 to day +7 as a result of the absence of sodium in the drinking water (Table).

**Proteinuria (UpV)** UpV tended to increase from day 0 to day +7 in group 1 (from 305±44 to 338±29 mg/dl; NS). However, in group 2 UpV decreased markedly at day +7 (from 294±24 to 119±10 mg/dl; P<.05) and differed significantly from group 1 (P<.05, Fig 5).

**Discussion**

In this study cerebral edema in SHRSP was quantitated by semi-automatic segmentation of images collected by T2W MRI. This novel analysis clearly illustrates that in this model variation in brain edema is due to increased or decreased leakage or spreading within one affected area, and not from widely-scattered multiple primary foci. Cerebral edema was positively correlated with proteinuria during salt loading, and an excretion exceeding 40 mg/d preceded cerebral edema by 3 to 15 days. Furthermore, salt restriction stabilized cerebral edema and reduced proteinuria without an effect on blood pressure.

MRI allows the longitudinal, noninvasive examination of the brain, and is the most powerful tool available to assess the progression and effect of therapeutic measures can be related. The SHRSP developed cerebral edema at an age of about three months, that is at a median of 30 days (range: 8 to 54) after the start of salt loading. The lesions on T2W MRI were characterized by hyperintense pixels as a result of T2 prolongation. T2 prolongation, a sensitive MRI indicator of cerebral injury, is associated with edema. Occasionally, hyperintense pixels were combined with hypointense pixels, the latter resulting from T2 reduction, indicating hemorrhage. T2 reduction is consistent with the paramagnetic effects of deoxyhemoglobin. Extensive cerebral hemorrhage at day 0 was uncommon (3/23 rats). At later times hemorrhage sometimes did appear, both in the originally affected area or in more recently affected areas.

Repeated cerebral MRI measurements in our model revealed two important points. First, approximately 70% of rats developed changes in T2W MRI before they showed neurologic symptoms. Either the affected brain areas were not involved in motor function or they were not large enough to cause disorders in behavior. Thus, T2W MRI is a powerful tool in the temporal definition of the onset of cerebral lesions. Second, we observed that the spreading of edema was from a single focus. Initially, local spreading of edema occurred in gray matter of the cortex or in the striatum. Then, via the white matter, edema spread through the whole hemisphere, sometimes even reaching the contralateral hemisphere via the corpus callosum. The focal origin of cerebral edema was in contrast to the multifocal leakage sites found in SHRSP by Fredriksson et al. through use of histological techniques. However, the spreading pattern we observed concurs with their findings. The SHRSP in their studies were considerably older (5 to 9 months of age) than those in our study (2 to 4 months) and therefore will probably have had edema for a considerably longer period. This may explain why they did not observe a unifocal origin of edema. Persistent high NaCl intake after the initial appearance of cerebral edema resulted in a more than twofold increase in the amount of edema in 1 week. This was the result of an increase of edema both in the slice that was primarily affected and in the slices surrounding this central slice. This could mean either that the primary lesion increases in size or that vascular leakage occurs at multiple sites in close proximity (within 1 mm) to the original lesion. This could not be differentiated due to the chosen slice thickness of the MRI sequence. Alternatively, the capacity to remove extravasated plasma proteins and fluid may gradually become a limiting factor. This sequence of early pathological changes in the cerebrum of SHRSP provides a template to which the timing and effect of therapeutic measures can be related.

The steep increase of proteinuria in the last 2 weeks before the appearance of cerebral lesions is probably due to intrarenal changes rather than to the hypertension per se because blood pressure did not increase over this period. The precedence of proteinuria to cerebral edema has been recognized in SHRSP, but in the absence of noninvasive visualization of the brain the time scale could not be defined. Glomerular filtration rate was not a marker of incipient cerebral damage because it
showed a significant decrease only after day 0. In humans, the magnitude of proteinuria is a valuable prognostic marker for progression of malignant hypertension and renal glomerular disease. Both in nondiabetic and in non–insulin-dependent diabetic subjects proteinuria also independently predicted stroke. However, because of the insidious progression of cerebral damage leading to stroke, it has not been possible to determine the interval between the initial occurrence of proteinuria and the appearance of stroke. In the present study we were able to define the appearance of the first lesion accurately and thereby identified a proteinuria level of 40 mg/d above which the SHRSP develops brain edema within a median of 9 days (range, 3 to 15 days). It should be emphasized that part of the variability in the time for the development of cerebral edema following proteinuria is linked to the protocol, particularly at the lower end of the range. Because urine was collected at weekly intervals and MRI was performed at intervals of 3 to 4 days, it is quite feasible that an interval between proteinuria and cerebral edema was underestimated. Every rat showed proteinuria exceeding 100 mg/d prior to the first appearance of cerebral edema on T2W MRI. To the best of our knowledge, such intervals and thresholds have not been described previously in this model. Even though in patients with severe hypertension the interval will be much longer, it may be feasible, by combining these two noninvasive measurements (proteinuria and cerebral T2W MRI), to define a threshold of proteinuria and the time-span between the moment of exceeding this threshold and the appearance of cerebral edema.

It is known that sodium intake plays a crucial role in determining hypertension and that it is positively correlated with a high incidence of stroke. Benstein et al and Lax et al showed that in uninephrectomized SHR reduced salt intake blunted the increase in proteinuria and the severity of glomerulosclerosis, without resulting in a reduction in hypertension. The present study shows for the first time that reduction of salt intake stabilizes the amount of edema. Cerebral areas which showed a reduction in cerebral edema from day 0 to day 7 did not show any histological sign of damaged neurons, pointing to improved viability of the tissue. As others found in SHR, normalization of salt intake did not decrease blood pressure in SHRSP. In fact, systolic blood pressure tended to increase, as has been observed in a number of other rat models after reduction of dietary salt. Although tail-cuff pressure cannot be used to accurately measure small changes in blood pressure, the latter finding makes it unlikely that a change in arterial pressure contributed to the stabilization of the amount of cerebral edema. We have no direct evidence, but speculate that following blood-brain barrier disruption salt intake in relation to excretion by the diseased kidney determines the development of cerebral edema, as is the case in peripheral tissues. Another explanation could be that the blood–brain barrier, which has been shown to be disrupted in the malignant phase of hypertension, was restored.

While the rats were on a high salt diet, cerebral edema correlated well with proteinuria, pointing to a parallel variation in the permeability of cerebral vasculature and renal glomerular capillaries. Of course, this does not imply a causal relation between proteinuria and cerebral edema. Indeed, stabilization of cerebral edema, due to normalization of sodium intake, was accompanied by a marked reduction in proteinuria. Possibly, once sodium intake is normalized, the SHRSP is able to achieve sodium balance with restitution of preglomerular vascular resistance. Maintenance of preglomerular vascular resistance prevents glomerular hypertension, and glomerular hypertension is a prerequisite for proteinuria in hypertensive renal disease.

In conclusion, identifying cerebral edema by repeatedly performing T2W MRI in salt-loaded SHRSP revealed that in this model proteinuria invariably precedes cerebral edema and that cerebral edema often precedes neurological symptoms. Quantitative assessment of the percentage of the cerebrum that contained edema enabled us to correlate cerebral edema with proteinuria. In addition, normalizing sodium intake prevented progression of cerebral edema and decreased proteinuria. These effects, which were not due to a decrease of the blood pressure, may be related to restoration of the extracellular fluid volume so that in the cerebrum extravasation of fluid through the damaged blood–brain barrier is balanced by removal and in the kidney glomerular capillary pressure is normalized by restoration of the upstream vascular resistance. These mechanistic hypotheses await further study.

Acknowledgments

For T2W MRI evaluation the brain image was automatically segmented from that of surrounding tissue with use of an autocontouring program kindly supplied by Max A. Viergever, PhD, and J.B. Twan Mantz, PhD, Image Sciences Institute, University Hospital Utrecht. The MRI studies were performed at the Netherlands in vivo NMR facility (Bijvoet Center, Utrecht University), which is financially supported by the Netherlands Organization for Scientific Research (NWO). This study was supported by NWO grant 902–18-264 and by grant 93.174 from the Dutch Heart Foundation.

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Several studies have suggested that sodium intake contributes to the pathogenesis of chronic hypertension and stroke. Chronically hypertensive rats fed a diet high in sodium develop severe hypertension, cerebral edema, and proteinuria. However, the temporal relation between the development of these symptoms and sodium intake remains unclear. The purpose of the preceding study was to determine (1) the development of cerebral lesions in relation to neurological symptoms in rats fed a high-salt diet, (2) the relation between proteinuria and the development of cerebral edema, and (3) whether normalization of salt intake attenuates the development of cerebral edema.


**MRI of Cerebral Edema in SHRSP**


**Editorial Comment**

Several studies have suggested that sodium intake contributes to the pathogenesis of chronic hypertension and stroke. Chronically hypertensive rats fed a diet high in sodium develop severe hypertension, cerebral edema, and proteinuria. However, the temporal relation between the development of these symptoms and sodium intake remains unclear. The purpose of the preceding study was to determine (1) the development of cerebral lesions in relation to neurological symptoms in rats fed a high-salt diet, (2) the relation between proteinuria and the development of cerebral edema, and (3) whether normalization of salt intake affects the progression of proteinuria and cerebral edema.

Using MRI, the investigators examined the development of cerebral edema in rats. In fact, MRI often predicts the development of cerebral edema prior to neurological dysfunction. Second, there is a positive correlation between proteinuria and cerebral edema. Thus, a relatively noninvasive method can be used as a predictor for the development of cerebral edema during chronic hypertension. Third, normalization of salt intake attenuates the development of cerebral edema and reduces proteinuria. Thus, changes in salt intake in high-risk individuals may have important consequences for the pathogenesis of cerebral edema and perhaps stroke.

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