Brain Tissue Sodium Is a Ticking Clock Telling Time After Arterial Occlusion in Rat Focal Cerebral Ischemia

Yang Wang, MS; Weixing Hu, MD; Alejandro D. Perez-Trepichio, MD; Thian C. Ng, PhD; Anthony J. Furlan, MD; Anthony W. Majors, PhD; Stephen C. Jones, PhD

Background and Purpose—Many patients with acute stroke are excluded from receiving thrombolysis agents within the necessary time limit (3 or 6 hours from stroke onset) because they or their family members are unable provide the time of stroke onset. Brain tissue sodium concentration ([Na\(^+\)]) increases gradually and incessantly during the initial hours of experimental focal cerebral ischemia but only in severely damaged brain regions. We propose that this steady increase in [Na\(^+\)] can be used to estimate the time after arterial occlusion in the rat middle cerebral artery occlusion model of ischemic stroke.

Methods—Sixteen anesthetized Sprague-Dawley rats underwent permanent middle cerebral artery occlusion combined with bilateral common artery occlusion. After 100 to 450 minutes, diffusion-weighted MRI was used to generate apparent diffusion coefficient (ADC) maps, cerebral blood flow (CBF) was determined with \(^{13}\)C-iodoantipyrine (in a subset of 7 animals), and the brain was frozen. Autoradiographic CBF sections and punch samples for Na\(^+\) analysis were obtained from the brain at the same level of the MR image. Severe at risk regions were identified with an ADC of <520 \(\mu\)m\(^2\)/s and, in the subset, with both ADC of <520 \(\mu\)m\(^2\)/s and CBF of <40 mL \cdot 100 g \(^{-1}\) \cdot min\(^{-1}\).

Results—Both CBF and the ADC dropped quickly and remained stable in the initial hours after ischemic onset. Linear regression revealed strong linearity between [Na\(^+\)] and time after onset, with a slope of 0.95 or 1.00 (mEq/kg DW)/min, with both ADC and ADC-plus-CBF criteria, respectively. The 95% CIs at 180 and 360 minutes were between 41 and 52 minutes.

Conclusions—The time after ischemic onset can be estimated with this 2-step process. First, ADC and CBF are used to identify severely endangered regions. Second, the [Na\(^+\)] in these regions is used to estimate time after onset. The favorable 95% CIs at the time limits for thrombolytic therapy and the availability of measurements of ADC, CBF, and [Na\(^+\)] in humans through the use of MRI suggest that this time-estimation scheme could be used to assess the appropriateness of thrombolytic therapy for patients who do not know when the stroke occurred. (Stroke. 2000;31:1386-1392.)

Key Words: cerebral blood flow ■ cerebral ischemia ■ magnetic resonance imaging, diffusion-weighted ■ middle cerebral artery occlusion ■ sodium ■ stroke ■ rats

Several thrombolytic treatments for acute ischemic stroke have been shown to be efficacious.\(^1\)\(^-\)\(^3\) These treatments require administration during the hyperacute period within 6 hours of stroke onset. For example, if intravenous tissue plasminogen activator (tPA) administration is delayed past 3 hours, the risk of cerebral hemorrhage outweighs the benefit of thrombolysis.\(^4\) However, one fifth to one half of potential subjects cannot be treated with these agents because they or a family member were not aware or were asleep when the stroke occurred and the time of stroke onset could not be determined accurately or at all.\(^5\)\(^-\)\(^7\)

Brain tissue sodium concentration ([Na\(^+\)]) in these regions is used to estimate time after onset. The favorable 95% CIs at the time limits for thrombolytic therapy and the availability of measurements of ADC, CBF, and [Na\(^+\)] in humans through the use of MRI suggest that this time-estimation scheme could be used to estimate the appropriateness of thrombolytic therapy for patients who do not know when the stroke occurred. (Stroke. 2000;31:1386-1392.)

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advocated as possessing a threshold that, if exceeded, indicates irreversible tissue damage.\(^8\) In contrast to the persistent increase in [Na\(^+\)], cerebral blood flow (CBF) and the apparent diffusion coefficient (ADC) of water drop very quickly and remain relatively constant during this same several-hour period.\(^10\) We propose that by measuring several physiological and biochemical parameters, an objective estimate of the time after onset can be determined. By using the initial drop in ADC or in ADC and CBF to select endangered brain tissue, we hypothesize that [Na\(^+\)] in these selected regions can be used to estimate the time after arterial occlusion. Although we use an experimental model of ischemic stroke in the rat and brain tissue sampling, all of the crucial measurements can be

Received December 9, 1999; final revision received February 29, 1999; accepted February 29, 2000.

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made in humans with MRI, which suggests that this scheme for estimation of time after onset could be used to make an inclusion decision for thrombolytic therapy.

Materials and Methods

Sixteen Sprague-Dawley rats weighing 307 ± 7 g (mean ± SEM) were prepared with anesthesia of 1% to 2% isoflurane and 70% N2O (balance O2) administered via an endotracheal tube and artificial respiration (model 681; Harvard Apparatus). Rectal temperature was maintained at 37°C with a servo-controlled heat lamp (YSI 74; Yellow Springs). Femoral arterial and venous catheters were inserted bilaterally. Gallamine triethiodide (Davis-Geck) in normal saline was infused intravenously at 10 mg·kg⁻¹·h⁻¹. The head of the animal was then placed in a frame adapted for temporal exposure and underwent permanent direct occlusion of the right middle cerebral artery, with bipolar electrocautery followed by transection, and both common carotid arteries, with previously placed ligatures. The time between the occlusion of the middle cerebral artery and that of the common carotid arteries was 10±1.3 minutes. The time at which the common carotid arteries were ligated was used as time zero to calculate the time from onset to decapitation (Ta). We used the time of occlusion of both common carotid arteries as time zero because at this time, the flow is reduced to ischemic levels; the subsequent persistence of ischemia and consequent infarction then follows. Isoflurane was reduced to a maintenance level of 0.8% through monitoring of the blood pressure response to tail pinch. These procedures were in accordance with the institutional guidelines for studies with animals.

Arterial blood gases (PaO2, PaCO2, and pH) and hemoglobin concentration [Hb] were determined with a blood gas analyzer (model ABL3; Radiometer America). Arterial blood pressure was continuously monitored from a femoral artery with a strain gauge transducer (model DT-XX; Viggo-Spectramed). Mean arterial blood pressure (MBP) and end-tidal CO2 were recorded on a polygraph (Gould, Inc). MBP and blood gases were recorded just after the arterial occlusion, at the end of the MRI, and just before CBF determination or death.

MRI Studies

MRI experiments were performed with a 4.7-T General Electric CSI-II 40-cm horizontal-bore imaging spectrometer that was equipped with GE Acustar self-shielded gradient coils (maximum 200 mT/m). A revised saddle coil with a diameter of 35 mm and a window length of 40 mm was used for both transmittal and receipt. The B1 homogeneity of the revised saddle coil is similar to that of a birdcage coil. The coil was mounted on a plastic cradle, and the anesthetized rat was placed in the supine position with the head centered in the coil. Body temperature was maintained throughout the MRI scanning period with circulating temperature-controlled water under the rats.

A sagittal gradient recalled echo image through the midline of the brain was acquired to position the coronal images for the study. Two slices, each 2 mm thick and 1 approximately at the level of bregma and the other 3 mm posterior, were selected for acquisition of coronal diffusion-weighted images. A spin echo sequence with interleaved b values was used. The field of view was 32.67 mm, the matrix size was 128×128 (zero filled to 128×128 before Fourier transformation), and voxel sizes were 0.255×0.255×2 mm. ADC maps were obtained from the diffusion-weighted MR images (spin warp; TR = 1500 ms/TE = 35 ms; b = 0, 261, 586, and 1042 s²/mm², 12.5 ms diffusion time, Δ = 15 ms, δ = 7.5 ms) with a total acquisition time of 20 minutes. The time between the start of the ADC determination and decapitation was 52±3.7 minutes.

CBF Determination

In 7 of the 16 animals, after 100 to 450 minutes from occlusion, quantitative CBF was determined with 14C-iodoantipyrine autoradiography. A background arterial blood sample was taken, and 14C-iodoantipyrine (100 μCi/kg) was infused into the femoral vein continuously for 45 seconds. Multiple arterial blood samples were collected and analyzed for 14C with liquid scintillation counting. After 45 seconds, the anesthetized animal was decapitated. To preserve the spatial characteristics of the brain so the MR and CBF images could be digitally superimposed and aligned, the head was frozen immediately in dry ice and stored in a freezer (−80°C). In this subset of 7 animals, the time between the start of the ADC determination and decapitation was 54±5.9 minutes.

Brain Processing

The brain was chilled out of the skull in a −20°C cold box and aligned in the cryostat (−20°C) to the same coordinates as for MRI. A 20-μm CBF autoradiographic section was taken at the rostral face of the 2-mm ADC image, and 2-mm-deep samples were punched between the rostral and caudal ADC image boundaries. Punch sampling was directed in relation to low ADC from an ADC guide image. After cutting to a smooth surface, a second CBF autoradiographic section was taken. The brain sections were dried on a 60°C hot plate and exposed for 4 days to x-ray film (Kodak SB5) together with 8 precalibrated 14C-methyl-methacrylate standards.

Flame Photometry

The samples were placed in predried and preweighed vials. Wet tissue samples were weighed on a microbalance (ATI Cahn model C-44; Analytical Technology, Inc) to obtain the wet weight with 0.001-mg precision. The average sample weight was 1.935±0.331 mg. Tissue samples were dried in an oven at 90°C for 3 days and then placed in a desiccating chamber for 1 hour before measurement of the dry weight. Samples were turned into ash by heating at 400°C for 24 hours, and [Na⁺], expressed as milliequivalents per kilogram of dry weight (mEq/kg DW), were determined with flame photometry (IL943 Automatic Flame Photometer; Instrumentation Laboratory).

Data Processing and Analysis

CBF autoradiograms were digitized with a quantitative image analysis system (MCID model M1; Imaging Research). CBF images were produced by first converting optical density to 14C concentration with use of the 14C-methyl-methacrylate standards and then to CBF with use of the 14C concentration-versus-time arterial curve.

The MR data were postprocessed with a SUN SPARC I workstation (SUN Microsystems). The ADC map was obtained by fitting the 4 diffusion-weighted images, pixel by pixel, with a linear least-squares calculation, as the slope of the fits. ADC images were further converted into the digital format of the MCID image analysis system.

Image Alignment

CBF and ADC images and the digitized photographic slides of the brain in the cryostat were aligned so that CBF and ADC values were from the same regions that were punch-sampled for Na⁺, as shown in Figure 1. The physiological image (CBF) and the position of the punches for the biochemical parameter [Na⁺] were coregistered to the MR image (ADC). Photographs of the brain surface both before and after the punch sampling were used to locate the punches in the CBF and ADC images. Because the punching process distorted the dorsal surface of the brain, the ventral surface of the brain from the prepunch image (Figure 1A) was used as an intermediary to align the position of the punch samples in the postpunch image (Figure 1B) with the CBF (Figure 1C) and ADC (Figure 1D) images. The CBF image was aligned with the ADC image by positioning the autoradiographic film to coincide with the ADC image during digitization. CBF values were averaged from the rostral and caudal autoradiographic sections from both faces of the 2-mm-thick ADC image, and [Na⁺] in the punch samples was determined with flame photometry. These alignment procedures ensured that the values of CBF, ADC, and [Na⁺] were directly comparable.

Region Selection

Threshold CBF and ADC values were used to select the regions that fulfilled the characteristics of ischemic core. Two strategies were used: the first used only an ADC threshold in all 16 animals, and the
TABLE 1. Physiological Variables

<table>
<thead>
<tr>
<th></th>
<th>MAP, mm Hg</th>
<th>Paco2, mm Hg</th>
<th>Paco2, mm Hg</th>
<th>pH</th>
<th>[Hb], g/dL</th>
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<tr>
<td>After MCAO and biCCAO</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All</td>
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<td>End of MR</td>
<td></td>
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<tr>
<td>All</td>
<td>103±2.9*</td>
<td>38.4±1.9</td>
<td>118±5*</td>
<td>7.362±0.017*</td>
<td>17.0±0.4*</td>
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<tr>
<td>Subset</td>
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<td>37.3±2.8</td>
<td>118±8</td>
<td>7.344±0.023*</td>
<td>17.0±0.8*</td>
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<td></td>
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<td></td>
</tr>
<tr>
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<td>35.1±0.4</td>
<td>166±11</td>
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<td>16.5±0.5*</td>
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</tbody>
</table>

MCAO indicates middle cerebral artery occlusion; biCCAO, bilateral common carotid artery occlusion. Values are mean±SEM, n=16 (7 for the subset group in which CBF was determined). For statistical analysis, see text.

*Mean values differ over time from the values at MCAO and biCCAO (P<0.01).
†Mean values differ over time from the values at MCAO and biCCAO (P<0.05).
sured with the MRI method, the estimated time after onset for the rate of Na⁺ was 41 minutes. The animal contributing the point in Figure 3 at the relationship with brain tissue [Na⁺] was 360 minutes.

95% CIs (dotted lines) demonstrated a strong (R² = 0.93) linear correlation with a slope of 0.93 min/(mEq/kg DW). The solid vertical line is the CI at 360 minutes.

This example, if a subject arrives at the hospital with an ischemic stroke and has his or her brain tissue [Na⁺] measured with the MRI method, the estimated time after onset would have to be <180–51 = 129 minutes for tPA to be administered with 95% confidence that his or her ischemic stroke occurred within the previous 180 minutes. If the subject arrived at 360–51 = 309 minutes after onset, pro-UK could be administered with 95% confidence that the insult occurred within 360 minutes.

After we used only the ADC threshold to choose regions for analysis for all 16 animals, Tₐ showed a significant linear relationship with brain tissue [Na⁺] (R² = 0.68%, slope = 0.72 min/(mEq/kg DW), P < 0.0001, Table 2, Figure 3). The 95% CIs of Tₐ at 180 and 360 minutes after occlusion were 52 and 41 minutes. The animal contributing the point in Figure 3 at a [Na⁺] of 641 mEq/g DW at Tₐ = 177 minutes had a high [Na⁺] in normal cortex of 337 mEq/kg DW. This value is just >2 SDs above the normal cortex value of 248 mEq/kg DW (248 ± 2σ = 336 mEq/kg DW). If this point is excluded from the linear regression, R² and the slope approach the result with both ADC and CBF thresholds (R² = 80%, slope = 0.77 versus R² = 93%, slope = 0.93 min/(mEq/kg DW), and the 95% CIs at 180 and 360 minutes become 42 and 39 minutes.

The rate of [Na⁺] increase was 0.95 and 1.00 (mEq/kg DW)/min for the data with just ADC criteria and the data with both ADC and CBF criteria, respectively. Note that the units for the rate of Na⁺ increase are the inverse of the slope used to estimate time after onset.

Discussion

We were able to determine 3 biochemical and physiological variables in multiple brain regions. Using this information, we showed that the time after arterial occlusion in the rat could be estimated within 41 to 52 minutes at the established time limits for the administration of tPA or pro-UK as therapeutic agents for acute ischemic stroke in humans (180 and 360 minutes, respectively). Although we used an experimental model of ischemic stroke in the rat, we suggest that the same strategy could be used to estimate time after onset of ischemic stroke in patients, with several caveats: the time for performing the noninvasive MRI measurement must not be excessive, [Na⁺] must be determined with sufficient accuracy, and this scheme must be validated in the clinical setting of acute stroke.

Clearly, minimal variability of the estimate of time is crucial for this scheme to function properly. One factor that affects this variability is the choice of the thresholds of ADC and CBF and whether just ADC or both ADC and CBF are used. These decisions can be based on the fidelity of the regression obtained. The use of a higher threshold might be possible if both ADC and CBF are used to choose the regions that exhibit a steady Na⁺ increase. In initial explorations of which threshold to use, we showed that the R² and slope stabilized at ~0.70 and 0.7 min/(mEq/g DW), respectively, when the threshold was between 480 and 540 μm²/s. Thus, the rate of Na⁺ increase in these regions was independent of the ADC threshold level. The higher variability of the time estimate with only the ADC criteria might be reduced by using values of ADC, CBF, and [Na⁺] normalized to the normal cortex as a method of reducing animal-to-animal variability. Another strategy to reduce the variability of the estimate of time after onset would be to increase the number of measurements.

The slow process of Na⁺ accumulation in ischemic regions is based on residual blood flow that delivers Na⁺ from plasma and is based primarily on the increase in Na⁺ influx mediated by the stimulation of Na⁺/K⁺-ATPase in ischemic cortex. The abluminal location of Na⁺/K⁺-ATPase contributes to the lack of Na⁺ transport from brain to blood.

Other measurements of brain tissue [Na⁺] in experimental cerebral ischemia at various times after arterial occlusion are presented in Table 3. The rates of Na⁺ increase vary between 0.71 and 1.10 (mEq/kg DW)/min. Our rates are slightly higher than the mean of these estimates: the other studies used larger brain tissue samples, which would possibly include nonischemic tissue with lower, more normal [Na⁺].
Figure 3. Forty-nine regions were selected and used to estimate $T_a$, with just the criteria that ADC must be $<520 \mu m^2/s$ to select regions from all 16 animals. Each of the data points was composed of 1 to 5 punches from ischemic cortex. The variability of $[Na^+]$ averaged 13%, expressed as the coefficient of variation. Linear regression and 95% CIs for the time after occlusion, $T_a$, were determined from the brain tissue $[Na^+]$. The 95% CIs at 180 and 360 minutes after occlusion are both 51 minutes. The solid vertical line is the CI at 360 minutes.

lowering the estimate of $[Na^+]$ in ischemic cortex. Another factor that contributed to our higher rates is our guided sampling procedure. Our sampling was directed at areas with low ADC, minimizing admixture of the ischemic cortex with normal cortex.

Using $Na^+$ MRI, Thulborn et al.\(^9\) determined the time course of $[Na^+]$ in 1 monkey after ischemia caused by an autologous blood clot introduced into the right internal carotid artery. After a delay of $\approx 2$ hours, $Na^+$ increased at a rate of 0.46 (mEq/kg DW)/min in the MCA territory. The delay in the beginning of the $Na^+$ increase ($\approx 2$ hours) compared with that obtained through models with direct arterial occlusion, as presented in Table 3, could be because the occlusion was originally incomplete or the clot partially lysed and redistributed downstream. The partial volume effect could have produced lower ischemic cortex $[Na^+]$ in this MRI study\(^{9}\) and could in part explain their low rate of $Na^+$ accumulation in ischemic brain tissue (approximately half the rate we observed).

Thulborn et al.\(^9\) maintain that there is a threshold of brain tissue $[Na^+]$ above which the restoration of blood flow will no longer be beneficial. This concept would imply that brain tissue $Na^+$ is the integral of the time-CBF relationship of cerebral vulnerability proposed by Morawetz et al.\(^{23}\) This concept could be applied to individual brain regions with imaging methods. At the time of the transition to irreversible damage at 3 hours usually reported with the direct occlusion models, $[Na^+]$ is 430 to 455 mEq/kg DW based on the data from this study.

The determination of ADC with MRI is well established and is considered a surrogate measure of therapeutic effectiveness in clinical trials.\(^{24}\) However, the MRI methods for determination of CBF\(^{25}\) and especially $[Na^+]$ are still evolving. Perfusion indices are currently monitored with MRI with spin-tag\(^{26,27}\) and bolus tracking\(^{28-30}\) methods. The lack of quantification and the inaccuracy at low flows could be overcome with the use of the ratio of ischemic to normal cortex.

$[Na^+]$ determinations with MRI that supply acceptable spatial resolution in humans with imaging times of 10 minutes can be performed in sequence with standard proton imaging for diffusion and perfusion.\(^{31}\) In humans with stroke, these $Na^+$ MRI methods have been combined with perfusion and diffusion imaging,\(^9\) and quantification has been documented in a rat model.\(^{32}\) At this stage, however, these MRI $Na^+$ measurements are not generally available, because they require much attention to MRI hardware and software. The additional time required for $Na^+$ imaging would be justified in cases in which the onset of stroke symptoms cannot be determined.

This proposed scheme to estimate time after occlusion is a 2-step process. First, the identification of severely endangered tissue with both CBF and ADC or just ADC is needed to choose only the regions in which brain tissue $[Na^+]$ increases. Both CBF and ADC drop quickly after occlusion and stay relatively constant during the initial hours, so they can be used without regard to the time after occlusion. Second, the pattern of slow and constant change in $[Na^+]$ is used as a stopwatch that is started at the moment of arterial occlusion. This general scheme could have potential for estimation of the time after ischemic onset in humans because all of these parameters, including ADC, CBF, and $[Na^+]$, can be estimated with MRI.

**Acknowledgments**

The support of the US Public Health Service (NIH grant NS-30839) is gratefully acknowledged. The statistical services of Kirk Easley

<table>
<thead>
<tr>
<th>Reference</th>
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<th>Model</th>
<th>Time After Occlusion, h</th>
<th>Normal Brain Tissue $[Na^+]$, mEq/kg DW</th>
<th>Rate of $[Na^+]$ Increase, mEq/kg DW/min</th>
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<td>Rat</td>
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</table>

MCAO indicates middle cerebral artery occlusion; CCAO, common carotid artery occlusion; biCCAO, bilateral common carotid artery occlusion.
are greatly appreciated. We thank Keith Thulborn, Fernando Boada, and Thomas Kent for thoughtful criticism and suggestions.

References


Of all of the issues that confront clinicians in the quest for improved acute stroke treatment, one of the most vexing has been the time from onset of brain ischemia to the time of treatment initiation. Although results in animal experimental models had long suggested that successful intervention into the process of ischemic stroke was time limited, this fact was not fully appreciated by clinicians until the past 15 years. Undoubtedly, the rapidity with which treatment was brought to bear on patients with ischemic stroke treated with intravenous rtPA greatly influenced the positive outcome from those trials showing benefit, and later delivery likely influenced the neutral outcomes from other studies.

One problem that persistently arises in the clinical context of acute stroke treatment is the accurate assignment of the time of onset of ischemia. In most circumstances, the onset of definite focal symptoms (eg, hemiparesis, speech disturbance) is taken as a surrogate for the onset of brain ischemia. Nonspecific symptoms such as headache and general malaise are customarily disregarded in these settings, although there is no guarantee that brain ischemia was not actually occurring during these symptoms. In patients who have onset of symptoms while asleep or those who have unwitnessed onsets but are unable to communicate or are unaware of their deficits, timing the onset becomes problematic, and these patients are usually excluded from treatment. It is now clear that the presence or absence of early signs of ischemia on initial head CT scans is not a reliable measure of the duration of ischemia, because these signs have now been clearly recognized in patients scanned within 90 minutes of onset, whereas some patients with a much longer durations of symptoms may still have negative scans.

In the present article, Wang and colleagues present evidence that in a rat model of focal cerebral ischemia, brain tissue sodium concentrations varied linearly with time in tissues at risk of infarction defined by cerebral blood flow and apparent diffusion coefficient criteria. They suggest that because brain tissue sodium concentrations can be measured in humans with the use of MRI, this work could lead to a method of timing the onset of stroke in patients in whom the clinical information is not adequate. Although considerable work remains to confirm this hypothesis in humans, if the measurements proved to be accurate predictors and the data could be obtained expeditiously, then it might expand the number of patients who could be considered for treatment. Future research in this regard seems warranted.

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Brain Tissue Sodium Is a Ticking Clock Telling Time After Arterial Occlusion in Rat Focal Cerebral Ischemia

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Stroke. 2000;31:1386-1392
doi: 10.1161/01.STR.31.6.1386

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