Diffusion and extracellular space volume in the rat somatosensory cortex during recovery from transient global ischemia/hypoxia

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Introduction: The extracellular space (ECS) of the brain represents the microenvironment of neuronal and glial elements and enables the diffusion of neuroactive substances among neurons, axons and glial cells. It also serves as an important communication channel; the movement of substances in this microenvironment by diffusion is essential for extrasynaptic or "volume" transmission [1]. Diffusion is also necessary for the delivery of oxygen and glucose from the vascular system to brain cells. Changes in the ECS diffusion parameters during ischemia are well known [2], but information about changes in ECS diffusion in the postischemic period is lacking.

Subjects and methods: We studied postischemic diffusion changes in the rat somatosensory cortex. Extracellular volume fraction (α) and tortuosity (λ) were determined from concentration-time profiles of the extracellular marker tetramethylammonium (TMA^+) applied by iontophoresis [3], and diffusion-weighted magnetic resonance was used to determine the apparent diffusion coefficient of water (ADC_w) in the tissue. The data were correlated with the results of DC-potential recordings and measurements of extracellular potassium levels - $[K^+]_e$. Transient ischemia was induced in anaesthetised adult male Wistar rats by bilateral common carotid artery clamping for 10 or 15 min and concomitant ventilation with 6% O_2 in nitrogen. Prior to and after ischemia, animals were ventilated with pure oxygen.

Results: The extracellular diffusion parameters during normoxia were α=0.19±0.01 (n=12), λ=1.55±0.01 (n=12) and ADC_w= 596 ± 13 $\mu m^2 s^{-1}$ (mean ± SEM). After ischemia of 10 minutes duration, normal values of α = 0.20±0.01 and λ=1.55±0.01 were registered within 5-10 minutes of reperfusion, and no measurable deviations from normoxic values of ADC_w were found. In animals subjected to 15 minutes ischemia, α increased within 40-50 minutes to 0.29±0.03 and remained at this level until the end of the experiment (Fig. 1). ADC_w increased within 60 minutes after ischemia to 665±15 $\mu m^2 s^{-1}$ and stayed at this level until the end of the measurement period (Fig. 2). No significant changes in tortuosity λ were observed during the postischemic period in either group compared to preischemic values. Ischemia caused a quick $[K^+]_e$ increase from 3 mM up to 70 mM and a negative DC-potential was registered. After reoxygenation, $[K^+]_e$ and DC-potential recovered within 2-3 minutes to preischemic levels (Fig. 3).

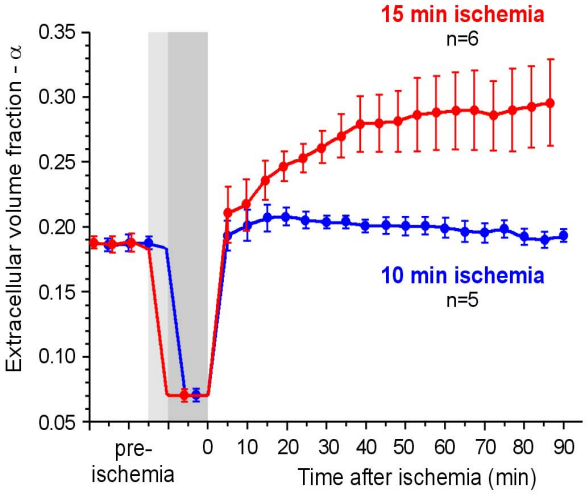

Figure 1: Time course of changes in ECS volume fraction (α) in the cortex after ischemia of 10 or 15 minutes duration. After 10 minutes ischemia, α quickly recovers and remains stable at this level. After 15 minutes ischemia, α increases extremely significantly above starting values after 40 minutes of reperfusion ($p<0.001$) and remains at this level until the end of the measurement period.

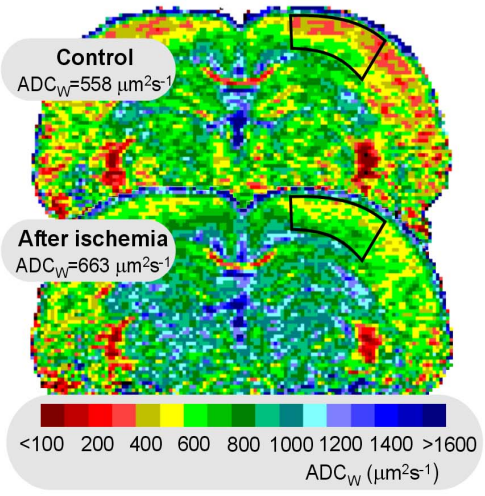

Figure 2: Typical ADC_W maps of a control rat brain and a rat brain 60 minutes after 15 minutes ischemia. The areas are outlined on the upper right of the slices, and both images are from the same coronal plane. The scale at the bottom shows the relation between the ADC_W values and the colors used for visualization.

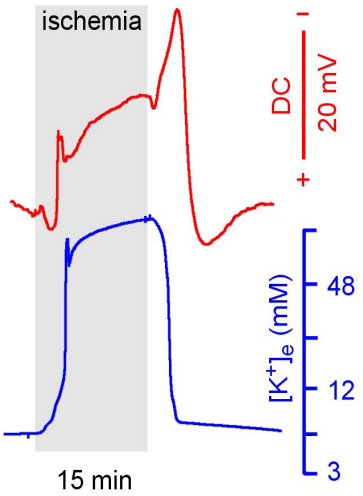

Figure 3: Time course of changes in extracellular K^+ concentration (blue) and DC-potential (red) during ischemia of 15 minutes duration. The duration of ischemia is marked by the shadowed area.

Conclusion: Our data represent the first *in vivo* measurements of the cortical extracellular diffusion parameters during recovery from transient ischemia by two different methods and their correlation with extracellular potassium concentrations and DC-potentials. The observed substantial changes in diffusion parameters could affect the diffusion of ions, neurotransmitters, metabolic substances and drugs used in the treatment of nervous system diseases. The changes in diffusion may persist for a long period after ischema and affect nonsynaptic volume transmission in the CNS.

References and acknowledgement:

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