MTU10-04

Comparison diffusion behavior of metabolites in brains of congenital portal systemic shunt and healthy mice *in vivo* at 14.1 t

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Diffusion-weighted ^{1}H MRS allows investigating the cellular compartmentalization of molecules in the living organs and may shed insight on alterations of cellular restrictions faced by metabolites in different cerebral abnormalities and diseases. The aim of this study was to determine whether diffusion behavior of metabolites in the congenital portal systemic shunt (PSS) mouse brain is different from ones of the healthy mouse *in vivo,* combining large diffusion weighting and ^{1}H MRS methods.

All experiments were performed on a 14.1T magnet using a home-built quadrature transceiver. Six adult PSS and six age-matched healthy (Ctrl) C57BL/6J mice have been prepared and anesthetized using isoflurane. ^{1}H-MRS data were acquired using localized diffusion-weighed STEAM-based spectroscopic pulse sequence (TE=16 ms and a mixing time of 113 ms), covering the b range from 0 to 45 ms/μm^2. Quantified data by LCModel were fitted using bi-exponential equation. Diffusion behavior of metabolites in the mouse brain was compared between PSS and Ctrl group.

The remarkable sensitivity and spectral resolution of localized short-echo ^{1}H MRS at 14 T allowed a precise measurement of the diffusion properties of metabolites in the brain of PSS and Ctrl mouse *in vivo* at very high diffusion weighting. The comparable diffusion properties of most investigated metabolites in the brain *in vivo* between PSS and Ctrl mice may indicate that unaltered barrier and cellular restriction dominate on the diffusion of metabolites in both group and therefore could support the hypothesis about the similarity of intracellular distribution space for these metabolites in PSS mice when compared to Ctrl mice. The slightly different diffusivity of Tau may be ascribed to possible cellular redistribution of Tau in PSS mice, however, it needs to be further explored.

MTU10-05

Intracisternal injection of [U-^{13}C]glucose for investigating brain metabolism in freely moving mice

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Purpose: To investigate brain metabolism using intracisternal delivery of [U-^{13}C]glucose, thus bypassing blood-brain barrier and avoiding effects of peripheral metabolism.

Methods: Mice (C57BL/6JRj, 8wo) were implanted a chronic cannula into cisterna magna. After recovery (24 h) an isosmolar 0.3M [U-^{13}C]glucose solution was infused using a microinjection pump. Animals were sacrificed by microwave irradiation. ^{13}C-labeling and metabolite amounts were determined using mass spectrometry and HPLC. Glycogen content was determined as glucose units after amyloglucosidase treatment.

Results: [U-^{13}C]Glucose injected at 2 μL/min (10 μL) resulted in fast label incorporation into brain lactate as well as glutamate and glutamine. Lactate labeling rapidly (within 10 min) decreased by about 50%, while enrichment in glutamate and glutamine kept increasing in the same time interval. Lactate was the only labeled compound recovered in cervical lymph nodes. [U-^{13}C]Glucose injected at 0.3 μL/min (4.5–18 μL) resulted in progressive rise of label incorporation into brain lactate, glutamate, glutamine, aspartate and GABA. Labeling of these compounds was significantly faster in awake than anesthetized animals. The absolute concentrations of glutamate and GABA were higher in the awake state whereas that of glutamine was lower (~20% changes). Brain glycogen was higher (+50%) during anesthesia and was negatively correlated with glutamate/GABA and positively correlated with glutamine.

Conclusions: Our results indicate that lactate is produced in excess of its utilization and rapidly leaves the brain, possibly through brain lymphatics. The rate of aerobic glycolysis is higher during wakefulness than anesthesia and so is the rate of transmitter synthesis, suggesting higher glutamatergic and GABAergic tone in awake animals. The correlations between brain glycogen content and glutamate/GABA and glutamine in different states indicate that glycogen synthesis/breakdown is modulated by brain activity and contributes as substrate to neurotransmitter synthesis, underlining its functional importance.

MTU10-06

Physiological roles of brain glycogen

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The role of brain glycogen has been traditionally associated with the preservation of neuronal function during energetically challenging states such as hypoxia, hypoglycaemia, ischemia, and seizures. Nevertheless, glycogenolysis also occurs in euglycaemia during an increase in neuronal activity, thus indicating that brain glycogen also supports neuronal function in non-pathological conditions. In order to address the physiological roles of glycogen in the brain, we generated a brain-specific glycogen synthase knockout mouse. These animals, that completely lack brain glycogen, show a significant deficit in learning capacity and in the activity-dependent changes in synaptic strength. Furthermore, they show greater susceptibility to hippocampal seizures and myoclonus following the administration of kainate and/or a brief train stimulation of Schaffer collaterals, which is in agreement with reports describing a relationship between brain glycogen and susceptibility to epilepsy. Within the brain, the presence of glycogen has been restricted mainly to astrocytes. Therefore, all physiologic roles of brain glycogen have been attributed exclusively to astrocytic glycogen. However our findings demonstrate the presence of an active glycogen metabolism also in neurons, which changes the current view of the role of glycogen in the brain. Taken together, our results reveal the relevant role played by glycogen in brain metabolism.