Examining Neuro-metabolic Correlations between Resting Rat Brain Activity and Cerebral Metabolite Contents/Metabolic Rates: A $^{1}H/^{31}P$ MRS Comparison Study

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Introduction

Glucose is the major substrate for the brain metabolism. The oxidative metabolism of glucose is tightly coupled to the ATP production in the mitocondria for supporting spontaneous brain activity at resting state and elevated avtivity during brain activation. It is essential to study and understand the relations beween the brain activity level and the cerebral metabolic rates of glucose utilization (CMR_{glc}) and ATP production (CMR_{ATP}) as well the steady-state concentrations of involoved metabolites including brain tissue glucose (Glc), ATP, phosphatecreine (PCr) and inorganic phosphate (Pi). These metabolic rates and metabolite concentrations can be readily measured by *in vivo* ^{1}H MRS ([Glc] and CMR_{glc}) and *in vivo* ^{31}P MRS ([ATP], [PCr], [Pi] and CMR_{ATP}) noninvasively. In this comparison study, we examined whether the cerebral metabolic rates and related metabolites measured by *in vivo* $^{1}H/^{31}P$ MRS are coupled with varied brain activity in rats? If yes, what are the correlations among them?

Methods

Animal Preparations: Male Sprague-Dawley rats were investigated under three anesthesia conditions. They were first anaesthetized by inhalation of 2% (vol-vol) isoflurane in nitrous oxide/oxygen (3:2), then switched to sodium pentobarbital with one low dose (*Low-Pen*) and another high does (*High-Pen*) for approaching an iso-electric state.

MRS Measurements: *In vivo* MRS experiments were carried out at a 9.4 T/31 cm horizontal magnet. The localized ^{1}H spectra ($4\times4\times4$ mm^3) were acquired by the point-resolved spectroscopy (PRESS) sequence with TR/TE=3000/13 ms. Glucose concentrations in the brain tissue ($[G]_i$) were quantified by the LCmodel fitting (1, 2). Blood glucose concentrations ($[G]_0$) were measured by the blood sampling. CMR_{glc} was calculated using Eq. [1] based on the standard Michaelis-Menten glucose transport model (3), where T_{max} and K_T are Michaelis-Menten glucose transport constants and are treated as a constant. Therefore, Eq. [1] can be applied to calculate relative CMR_{glc}. ATP syntheses rates *i.e.* unidirectional forward chemical exchange fluxes from P_i to ATP (F_{ATPase}=CMR_{ATP}) and from PCr to ATP (F_{CK}) were determined using the ^{31}P saturation transfer approach by means of frequency-selective saturation of γ-ATP (4).

$$\frac{CMR_{glc}}{T_{max}} = \frac{[G_0]}{([G_0] + K_T)} - \frac{[G_i]}{([G_i] + K_T)} \qquad [1]$$

EEG Measurements: The EEG signals were recorded in the rat cortex and the Shannon spectral entropy method (5) was applied to analyze EEG data and quantify the brain activity at varied brain states.

Results and Discussions

Figure 1 presents the metabolic concentrations of glucose and high energy phosphates (PCr, ATP) as well as Pi as a function of varied EEG activity under three anesthesia conditions. With the increased dose of sodium pentobarbital, the brain activity was suppressed and eventually reached iso-electric state, which was reflected by the lowest EEG entropy index. Consequently the glucose concentrations of brain tissue ($[G]_i$) and blood ($[G]_0$) decreased significantly from the isoflurane to the iso-electric condition. Meanwhile, [PCr] decreased about 8% accompanied with 42% increase of [Pi], while [ATP] was very stable. Figure 2 demonstrates the cerebral metabolic rates of relative CMR_{glc}, F_{ATPase} and F_{CK} measured at three different brain activity levels. Obviously, the cerebral metabolic rates had a better correlation with the brain activity quantified by the EEG entropy index. It is also clearly evident that the ATP metabolic rates are tightly coupled to CMR_{glc}. Therefore, this comparison study suggests that the cerebral metabolic rates related to ATP and glucose metabolisms are more sensitive to brain activity and energy changes; they are tightly coupled with basal neuronal activity. In contrast, the steady-state metabolite concentrations are more loosely correlated to the brain activity level.

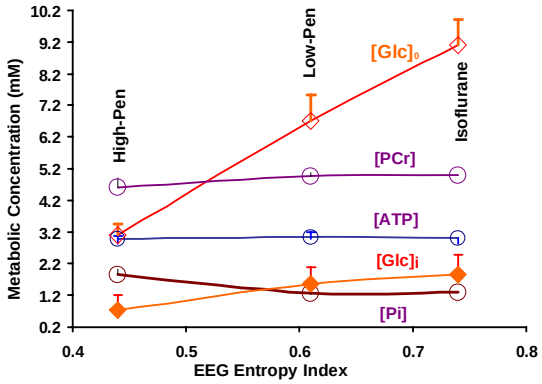

Figure 1 Metabolic concentrations measured by the $^{31}P/^{1}H$ MRS, respectively, at three different anesthesia conditions. The High-Pen anesthesia condition approached an iso-electric state.

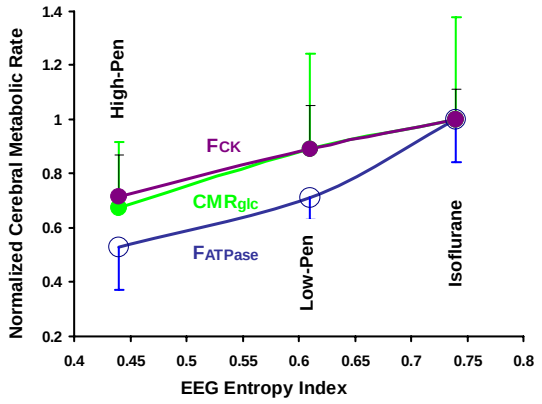

Figure 2 Correlations between EEG entropy index and normalized cerebral metabolic rates of F_{CK} and F_{ATPase} measured by the *in vivo* ^{31}P MT method, and the relative CMR_{glc} measured using *in vivo* ^{1}H MRS and glucose-blood transportation equation.

Conclusion

The ATP and glucose metabolic rates, which can be measured by *in vivo* $^{1}H/^{31}P$ MRS, are closely coupled with the varied EEG activity in the resting rat brain. Thus, the imaging of these rates should provide sensitive and quantitative measures of brain bioenergetics associated with neuronal activity and its changes during brain activation. Finally, this comparison study also provides evidence to support a tight neuro-metabolic coupling in the brain.

References

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