Journal of Magnetic Resonance 292 (2018) 155–170

Contents lists available at ScienceDirect

Journal of Magnetic Resonance

journal homepage: www.elsevier.com/locate/jmr

Quantitative imaging of brain energy metabolisms and neuroenergetics using *in vivo* X-nuclear ^{2}H, ^{17}O and ^{31}P MRS at ultra-high field

Xiao-Hong Zhu, Ming Lu, Wei Chen *

Center for Magnetic Resonance Research, Department of Radiology, University of Minnesota, School of Medicine, Minneapolis, MN 55455, USA

ARTICLE INFO

Article history:
Received 2 January 2018
Revised 27 April 2018
Accepted 8 May 2018

Keywords:
In vivo X-nuclear MRS and imaging
Brain energy metabolism
Neuroenergetics
Cerebral metabolic rate of glucose (CMR_{Glc}) and oxygen ($CMRO_2$) consumption, and ATP production (CMR_{ATP})
TCA cycle rate (V_{TCA})
NAD redox state
Ultra-high magnetic field (UHF)

ABSTRACT

Brain energy metabolism relies predominantly on glucose and oxygen utilization to generate biochemical energy in the form of adenosine triphosphate (ATP). ATP is essential for maintaining basal electrophysiological activities in a resting brain and supporting evoked neuronal activity under an activated state. Studying complex neuroenergetic processes in the brain requires sophisticated neuroimaging techniques enabling noninvasive and quantitative assessment of cerebral energy metabolisms and quantification of metabolic rates. Recent state-of-the-art *in vivo* X-nuclear MRS techniques, including ^{2}H, ^{17}O and ^{31}P MRS have shown promise, especially at ultra-high fields, in the quest for understanding neuroenergetics and brain function using preclinical models and in human subjects under healthy and diseased conditions.

1. Introduction

The brain is a high-energy consumption organ that relies on glucose as the main carbon substrate to support oxygen metabolism and it produces adenosine triphosphate (ATP) molecules *via* oxidative phosphorylation in the mitochondria. ATP is the primary source of biochemical energy essential for neurophysiology and brain function [1–3]. Approximately, one-fourth of the total brain ATP energy expenditure is devoted to "housekeeping" functions critical for biosynthesis, and maintaining cell integrity and brain tissue viability [4,5]; the rest of the ATP energy supports electrophysiological activity and neural processing at either resting or working brain state. A tight coupling between the electrophysiological activity and brain energy consumption holds for a wide range of physiological conditions. To maintain the coupling requires effective metabolic regulations between cellular ATP demand and supply through many biochemical reactions and metabolic pathways associated with energy metabolisms.

Fig. 1 is a schematic illustration of key hemodynamic and metabolic processes at the mesoscopic and sub-cellular level, including capillary blood circulation for providing nutrients, cellular glucose and oxygen metabolisms, oxidative phosphorylation of adenosine diphosphate (ADP) for producing ATP in the mitochondria, and ATP utilization to support neuronal activity and neural processing in a resting or working brain. Oxygen and glucose are supplied by cerebral blood flow (CBF) circulating through the capillary bed. Glucose is transported into the brain cells and converted into two pyruvate molecules *via* glycolysis in the cytosol. The majority of pyruvate molecules are metabolized in the mitochondria to form Acetyl-CoA, which is subsequently oxidized *via* the tricarboxylic acid (TCA) cycle to generate the reduced form of nicotinamide adenine dinucleotide (NADH); NADH serves as an electron donor in the electron transport chain reactions and is converted to oxidized NAD (NAD^+) *via* oxygen metabolism. The electron transport chain, in turn, generates an electrochemical potential gradient across the mitochondrial inner membrane *via* extrusion of H^+ ions from the mitochondria. The resulting transmembrane potential is the driving force for the conversion of ADP and inorganic phosphate (Pi) to ATP, mediated by the F_1F_0-ATP_{ase} (also known as H^+-ATP_{ase}) enzyme reaction that reversely transports the H^+ ions back into the mitochondria [1,4]. On the other hand, the ATP utilization occurs in the cytosol and cell membrane, resulting in the hydrolysis of ATP. The Na^+/K^+-ATP_{ase} activity utilizes the majority of the ATP energy released in this process to maintain the Na^+/K^+ ion gradient across the cell membrane, and is critical in supporting

* Corresponding author at: Center for Magnetic Resonance Research, Department of Radiology, University of Minnesota, 2021 6th St. SE, Minneapolis, MN 55455, USA.
E-mail address: wei@cmrr.umn.edu (W. Chen).

https://doi.org/10.1016/j.jmr.2018.05.005
1090-7807/

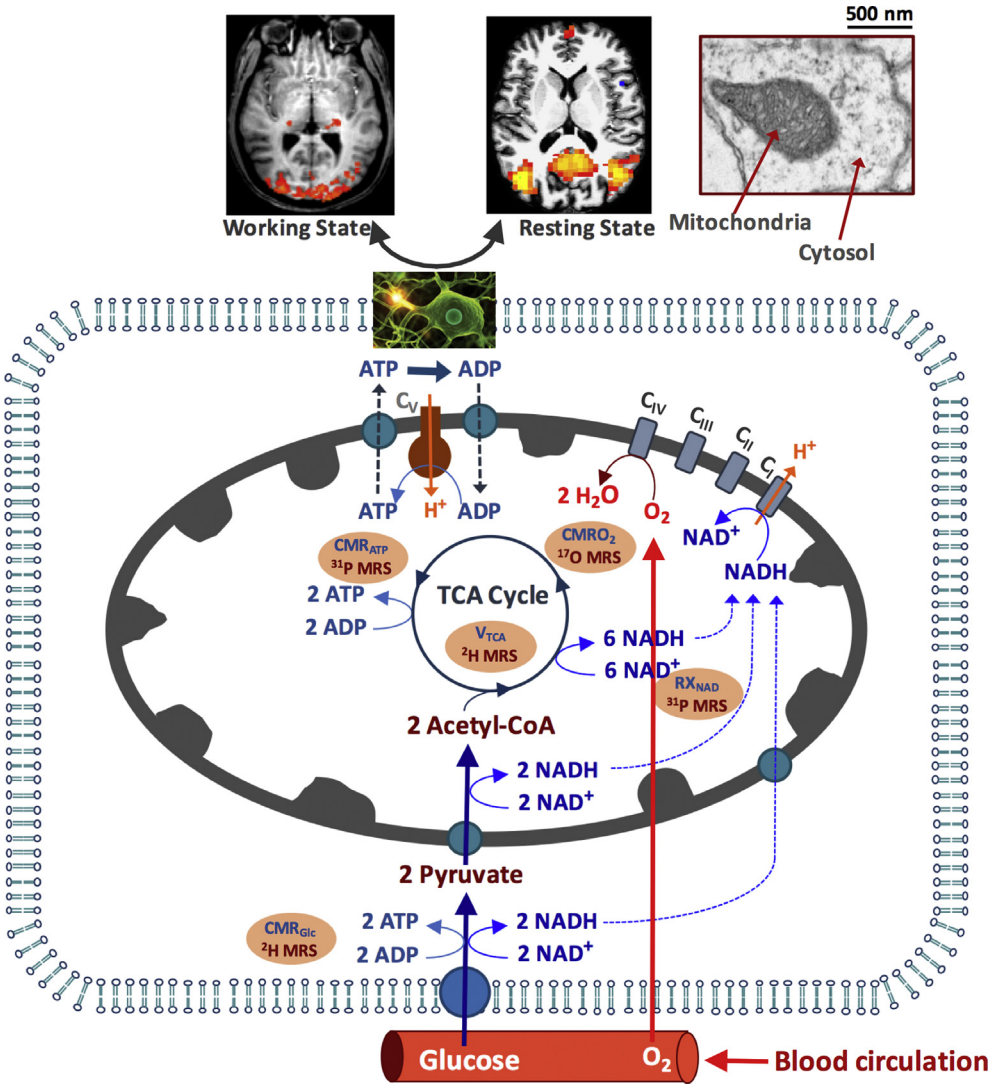

Fig. 1. Schematic diagram of major energy metabolism pathways and hemodynamics occurring in the capillary, sub-cellular compartments including mitochondria and cytosol, that are essential for brain function under a resting or working state and can be assessed using the *in vivo* X-nuclear MRS imaging methods as reviewed in this article. Oxygen and glucose supplied from feeding arteries and blood circulation in the capillary can diffuse (for oxygen) or transport (for glucose) into brain cells. Glucose is first converted to two pyruvates; most pyruvate molecules enter mitochondria and are metabolized oxidatively. The oxygen utilization is, in general, coupled with the ATP production *via* the oxidative phosphorylation of ADP in the mitochondria. The produced ATP in the mitochondria is transported to cytosol for supporting electrophysiological activities and brain functions at resting or activated brain state as demonstrated by the functional MRI (fMRI) map of visual stimulation or resting-state fMRI connectivity map in top panels. The energy metabolic pathways are tightly associated with the NAD redox reactions which are essential for regulating brain energy generation and utilization. The metabolic activities associated with different pathways can be quantitatively determined by the cerebral metabolic rates of CMR_{Glc}, $CMRO_2$, CMR_{ATP}, TCA cycle rate (V_{TAC}) and NAD redox ratio (RX_{NAD}) and noninvasively measured using the advanced *in vivo* X-nuclear MRS approaches as depicted in the shadowed texts with orange background. $\mathbf{C}_I$ - $\mathbf{C}_V$ represent five enzyme complexes involving the respiration chain reactions in the mitochondria.

neuronal signaling processes (e.g., action potential propagation, neuronal firing, neurotransmitter cycling, etc.) (see references [1,6]). The rapid ATP turnover in the brain requires efficient transportation of ATP and ADP molecules between the cytosolic and mitochondrial compartments. This is accomplished, in part, by phosphocreatine (PCr), another high-energy phosphate compound, *via* the creatine kinase (CK) reaction that catalyzes a rapid, near-equilibrium exchange between (ATP + Creatine (Cr)) and (PCr + ADP) [5,7]. Because of their role in supporting rapid ATP turnover and ATP homeostasis, the rates of CK reactions are anticipated to be much higher (~ 5 times) than the net rates of ATP synthesis and utilization in the human brain [8,9].

The human brain has an enormous energy demand despite making up only 2% of the body's total weight. A "resting-state" adult brain receives approximately 15% of the cardiac blood output and accounts for roughly 20% of the body's total oxygen and glucose consumption [2,4,10]. The steady-state ATP concentration of the brain is low (~3 mM), which means that the total ATP content in the entire human brain is only about 2 g, assuming an average adult brain weight of 1.4 kg. In contrast, the oxidative ATP synthesis rate through the F_1F_0-ATP_{ase} reaction is very high (8–9 μmole/g/min in the human brain [8,9,11]), which translates into 7–8 kg of total ATP synthesized (or utilized) by the human brain in a single day (5–6 times the weight of the average human brain). In addition, the intracellular NAD redox state plays a critical role in regulating and balancing the brain energy metabolisms between cytosolic glycolysis and mitochondrial oxidative phosphorylation for producing adequate ATP molecules [12–14]. Abnormal cerebral energy metabolism has been linked to numerous brain disorders and neurodegenerative and mental diseases including Schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's disease, mitochondrial dysfunction as well as the aging process.