World Academy of Science, Engineering and Technology
International Journal of Biomedical and Biological Engineering
Vol:14, No:10, 2020

Assessing the Blood-Brain Barrier (BBB) Permeability in PEA-15 Mutant Cat Brain using Magnetization Transfer (MT) Effect at 7T

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Abstract : Phosphoprotein enriched in astrocytes 15 kDa (PEA-15) is a multifunctional adapter protein which is associated with the regulation of apoptotic cell death. Recently it has been discovered that PEA-15 is crucial in normal neurodevelopment of domestic cats, a gyrencephalic animal model, although the exact function of PEA-15 in neurodevelopment is unknown. This study investigates how PEA-15 affects the blood-brain barrier (BBB) permeability in cat brain, which can cause abnormalities in tissue metabolite and energy supplies. Severe polymicrogyria and microcephaly have been observed in cats with a loss of function PEA-15 mutation, affecting the normal neurodevelopment of the cat. This suggests that the vital role of PEA-15 in neurodevelopment is associated with gyrification. Neurodevelopment is a highly energy demanding process. The mammalian brain depends on glucose as its main energy source. PEA-15 plays a very important role in glucose uptake and utilization by interacting with phospholipase D1 (PLD1). Mitochondria also plays a critical role in bioenergetics and essential to supply adequate energy needed for neurodevelopment. Cerebral blood flow regulates adequate metabolite supply and recent findings also showed that blood plasma contains mitochondria as well. So the BBB can play a very important role in regulating metabolite and energy supply in the brain. In this study the blood-brain permeability in cat brain was measured using MRI magnetization transfer (MT) effect on the perfusion signal. Perfusion is the tissue mass normalized supply of blood to the capillary bed. Perfusion also accommodates the supply of oxygen and other metabolites to the tissue. A fraction of the arterial blood can diffuse to the tissue, which depends on the BBB permeability. This fraction is known as water extraction fraction (EF). MT is a process of saturating the macromolecules, which has an effect on the blood that has been diffused into the tissue while having minimal effect on intravascular blood water that has not been exchanged with the tissue. Measurement of perfusion signal with and without MT enables to estimate the microvascular blood flow, EF and permeability surface area product (PS) in the brain. All the experiments were performed with Siemens 7T Magnetom with 32 channel head coil. Three control cats and three PEA-15 mutant cats were used for the study. Average EF in white and gray matter was 0.9±0.1 and 0.86±0.15 respectively, perfusion in white and gray matter was 85±15 mL/100g/min and 97±20 mL/100g/min respectively, PS in white and gray matter was 201±25 mL/100g/min and 225±35 mL/100g/min respectively for control cats. For PEA-15 mutant cats, average EF in white and gray matter was 0.81±0.15 and 0.77±0.2 respectively, perfusion in white and gray matter was 140±25 mL/100g/min and 165±18 mL/100g/min respectively, PS in white and gray matter was 240±30 mL/100g/min and 259±21 mL/100g/min respectively. This results show that BBB is compromised in PEA-15 mutant cat brain, where EF is decreased and perfusion as well as PS are increased in the mutant cats compared to the control cats. This findings might further explain the function of PEA-15 in neurodevelopment.

Keywords : BBB, cat brain, magnetization transfer, PEA-15
Conference Title : ICMIT 2020 : International Conference on Medical Imaging and Technology
Conference Location : New York, United States
Conference Dates : October 08-09, 2020