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METABOLIC PROFILE OF BRAIN AND ADIPOSE TISSUE

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ABSTRACT

Different organs have different metabolic functions and capabilities. In this article we consider how the special needs of mammalian body organs are met and how their metabolic capabilities are coordinated to meet the demands. This review explores the metabolic profile of brain and adipose tissue under fasting and well fed conditions.

KEYWORDS: Metabolic profile, brain, adipose tissue, fasting and well fed conditions.

INTRODUCTION

Organs are able to adapt to metabolic alterations in fed state and starvation. The metabolism of the brain is remarkable in several aspects. Brain has a very active respiratory metabolism the use of oxygen by the brain is fairly constant in rate and does not change significantly during active thought or sleep. Although brain represents only 2% of adult body weight it needs 10-20% cardiac output, about 750 ml of blood circulates through the brain per minute. Neurons can survive only a few minutes without blood supply.

Occlusion of blood supply to brain causes unconsciousness within 10 seconds. Glucose is preferred fuel for the brain should be in continuous supply. Glucose can freely enter the brain cells. Glucose is transported to cells via several glucose transporters reaching the brain through glucose transporter GLU T3, which is having low value of Km for glucose means i.e. it is saturated under mild conditions. Even at low concentration glucose the receptor gets saturated. Neurons are unable to store glucose as glycogen due to constitutive degradation of glycogen synthase through glycogen synthase kinase phosphorylation and ubiqitin dependent proteosomal digestion mediated by malin laforin complex.[15]

The total consumption of glucose by brain is about 120g/day i.e. about 480 Kcal. Thus approximately 60% of total carbohydrate intake by the body is metabolized by the brain. Other neuronal functions such as vesicle recycling, neurotransmitter synthesis and axoplasmic transport also contribute to synaptic energy depletion and the requirement for an elevated metabolic rate in neurons (Attwell and Laughlin, 2001, Rangaraju et al 2014, Pathak et al 2015). Energy requirement is therefore not uniform throughout the brain but instead increased in localized regions dependent on neuronal activity.

Ammonia may interfere with very high levels of ATP production required to maintain brain function. Depletion of glutamate in the glutamate synthase reaction may have additional effects on the brain. Glutamate and the compounds GABA that is derived from it are important neurotransmitters. The sensitivity of the brain to ammonia may well reflect a depletion of neurotransmitters as well as changes in cellular pH and ATP production.[16]

Brain under conditions of anoxia

In anoxia the rate of lactate production by glycolysis rises to 5 to 8 times within one minute. The Pasteur Effect is the brains protection against conditions of anoxia. This is due to the inhibition of enzyme Phosphofructokinase. Glycolysis intermediates from fructose 1, 6-diposphate onwards decrease while the other intermediates accumulate.[19]

The Pasteur Effect under aerobic conditions glycolysis is inhibited, so the brain utilizes glucose much more rapidly in the absence of oxygen.

Brain and acetoacetate

The brain is unable to utilize fatty acids as a source fuel since fatty acids complexed to albumins are unable to traverse the BBB. But brain can effectively utilize acetoacetate. The

capacity of brain to oxidize beta hydroxy butyrate via acetyl CoA becomes important during prolonged fasting or starvation. The use of beta hydroxy butyrate by the brain during extreme starvation also spares muscle proteins.[19,20,21]

Brain and starvation

During the early days of starvation the brain continues use glucose exclusively. Blood sugar is maintained by hepatic gluconeogenesis form aminoacids provided by rapid breakdown of muscle proteins. In prolonged starvation, plasma ketone bodies reach markedly elevated levels and are used as fuel by the brain this reduces the needs for protein catabolism for gluconeogenesis.[15]

Many factors contribute to age dependent brain hypo metabolism. Studies for example show that there is higher BBB permeability in seniors which may induce lower intake of nutrients to the neuron and larger accumulation of proteins such as fibrinogen, albumin, thrombin that may produce inflammation.[16]

Approximately 40% of healthy people over age of 60 experience impairment in different cognitive domains such as working memory, spatial memory, episodic memory and processing speed which is constitent with gradual decrease in energy demand as aging progresses.

ROS primarily occurs through electron leakage at ETC complex I and III during normal oxidative respiration. This causes 1-2% of oxygen into superoxide anion a precursor to hydrogen peroxide and hydroxyl free radicals. Within the brain high neuronal oxidative rate heightens the potential for ROS production and neurons are especially vulnerable to oxidative damage due to low levels of antioxidant enzymes such as glutathione (Dringen et al, 1999).

Astrocytes are glial cells play a significant role in brain energy metabolism. Astrocytes up regulate and release many neurotransmitters such as glutamate and D-serine which influence paracrine signaling between astrocytes and neurons. In physiological conditions astrocytes also express d-synuclein at very low levels. d-synuclein may contribute to synaptic vesicle biogenesis and dynamics and neurotransmission. In pathological conditions accumulation of a protein alpha synuclein aggregates in intracellular and extracellular dopaminergic neurons are one of the main hallmarks of Parkinson's disease. The brain is especially dependent on salvage pathways and this may account for the central nervous system damage that occurs in

children with Lesch-Nyhan-syndrome. This syndrome and the immunodeficiency diseases resulting from lack of adenosine deaminase are among the targets of early trials in human gene therapy.[18]

All different cells of brain astrocytes, microglia and oligodendrocytes. Each of these cells displays a unique metabolic signature and regulation of energy metabolism is ensured between astrocytes and neurons. Astrocytes breakdown glucose to pyruvate and lactate and then shuttle back to neurons for oxidation. Thus glial cells take up glutamate realeased from synapses. Astrocytes primarily metabolize glucose to lactate and release lactate the lactate in the extracellular space. Astrocytes support this glycolytic profile through the activation of several key glycolytic enzymes.[17,18]

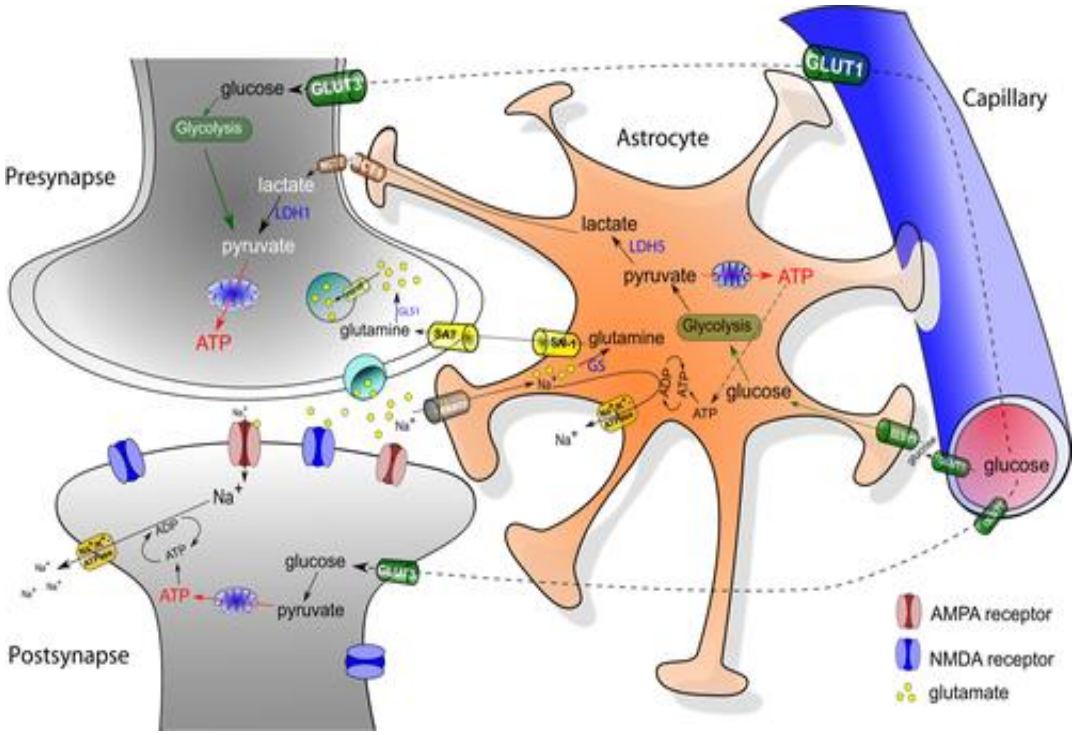

Fig. 1: Energy metabolism in brain {Melina Paula Burdone, Journal of Neurochemistry).

ADIPOSE TISSUE

Understanding of adipose tissue and adipocytes is expanding due to contribution of adipose tissue to obesity related complications. There are two types of adipose tissue white and brown adipose tissue which are visibly distinguishable based on tissue colour.[9] Brown adipose tissue found in infants and rarely found in adult humans, have number of mitochondria and cytochromes found in them, burn lipid by dissipating energy in the form of heat to maintain

euthermia, by taking up circulating fatty acids generates heat by uncoupling energy production via oxidative phosphorylation and has been considered as a new way of counteract obesity. Some individuals are fortunate to have brown adipose tissue. They eat and liberate it as heat and therefore donot become obese. A specific protein namely thermogenin has been isolated in inner membrane of mitochondria of brown adipose tissue. Fatty acids being hydrolyzed when fuel is required.[11,14]

Adipose tissue also contributes to inflammation and the innate immune response. Adipose tissue contains fibroblasts, macrophages and vascular constituents, macrophages are known to be crucial contributor to inflammation, secretion of number of inflammatory cytokines in addition to this adipocytes are involved secretion of mediators of inflammation including IL-10,IL-15, complement factor, prostaglandins. Adipose tissue IL-6 expression is positively correlated with obesity. Both expression and circulation decrease weight loss.IL-6 also decreases insulin signaling in peripheral tissues by reducing the expression of insulin receptor signaling components, it also inhibits adipogenesis and decreases adinopectin secretion.[10]

Angiotensin II is a very potent vasoconstrictor and risk for hypertension increases with BMI. Thus it has been assumed that an increased synthesis of angiotensin II by adipose tissue might contribute to obesity associated hypertension. In addition angiotensin II seems to exert different proinflammatory effects locally in adipose tissue and also stimulates the production of IL-6 and IL-8 on cultivated adipose tissue. In addition angiotensin II increases oxidative stress and activation of NAD(P)H dependent oxidase.[10]

It is store house of energy in the body. The energy stored in the concentrated form, triacylglycerol. The chylomicrons and VLDL are hydrolysed by lipoprotein lipase present on capillary walls. It is activated by insulin. They undergo daily turnover with new triglycerols molecules being synthesized and a definite fraction being breakdown. The dietary triglycerides are transported by the chylomicrons. Both chylomicrons and VLDL taken up by the adipose tissue and stored as triacylglycerols. The lipoprotein molecules are broken down by the lipoprotein lipase which is present in the capillary walls of circulatory blood cells. In well fed conditions glucose and insulin levels are increased. Insulin increases the activity of the key glycolytic enzymes. Insulin also causes inhibition of hormone sensitive lipase as so lipolysis is decreased.[12]

Glycerol is derived from dihydroxyacetone phosphate an intermediate of glycolysis therefore

for the storage of TAG both fatty acid synthesis and glycogenolysis should operate. About 25% of glucose taken by adipose tissue is metabolized by the HMP shunt pathway and rest by glycolysis. The NADPH generated by HMP shunt pathway is used for the synthesis of fatty acids. The NADH produced during glycolysis is used to reduce DHAP to glycerol-3-phosphate.[14]

Adipose tissue in fasting conditions

Adipose tissue undergoes hyperplasia to increase the number of adipocytes and hypertrophy to increase the size of each adipocyte, allowing adipose tissue to expand in times of nutrient excess, as needed during fasting and exercise.[12]

The metabolic pattern totally changes under the conditions of fasting. Under physiological conditions when metabolic fuels are low and energy demand is high such as fasing, exercise and cold exposure triacyl glycerol in the adipose tissue are hydrolysed. High glucagon, insulin ratio results in the activation of hormone sensitive lipase with subsequent increased lipolysis. Free fatty acids are transported in the blood bound to albumin and utilized by various tissues as a source of energy. The realeased free fatty acids are taken up by peripheral tissues as a fuel.[12,13]

Under well fed conditions

Under well fed conditions active lipogenesis occurs in the adipose tissues. The dietary triglycerides are transported by chylomicrons. The liver endogenously synthesizes triglycerides which are secreted as VLDL. Both chylomicrons and VLDL are taken up by adipose tissues and stored as TAG. The lipoprotein molecules are broken down by lipoprotein lipases which are present in the capillary walls of circulating blood cells.[13]

In well fed conditions glucose and insulin levels are increased. GluT4 in adipose tissue is insulin dependent. Insulin increases the activity of the key glycolytic enzymes. The stimulant effect of insulin on HMP pathway also enhances lipogenesis. Insulin also causes inhibition of hormone sensitive lipase as the lipolysis is decreased.[12,13]

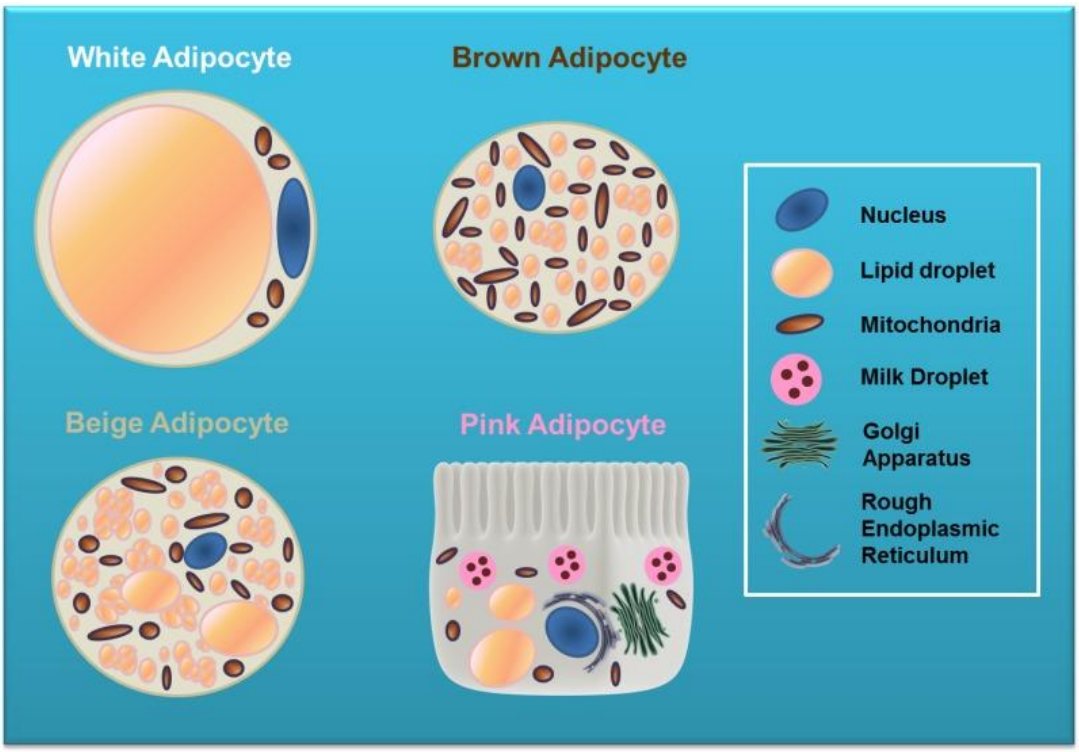

Fig. 2: Adipose tissue metabolism.

Adipocyte types are described by color hues. The primary characteristic of an adipocyte is its ability to store lipid; white, brown, beige, and pink adipocytes all share this property. However, each type of fat cell is somewhat specialized and has a distinct intracellular distribution of organelles and gene expression profile. All fat cells have Golgi and endoplasmic reticulum, but these organelles make up a more significant portion of pink adipocytes than other adipocyte types. [Allison J. Richard, et al]

Adipose tissue and Diabetes mellitus

In diabetes lipolysis is enhanced and free fatty acid levels in plasma noticed. Insulin acts through receptors on the cell surface of adipocytes. These receptors are decreased leading to insulin sensitivity in diabetes.[7,8,13]

Adipose tissue and Obesity

The fat content of the adipose tissue can increase to unlimited amounts depending on the amount of excess calories taken, this leads to Obesity.[5] A high level of plasma insulin levels is noticed but the insulin receptors are decreased and there is peripheral resistance against insulin action. When fat droplets are overloaded, TAG becomes extracellular, such triacyl glycerols cannot be metabolically reutilized and forms the dead bulk in obese individuals.[5,6,14]

Adipokines

Adipose tissue is now known to function as major endocrine system that secretes adipokines, cytokines and chemokines.[2]

Adipokines are adipose derived hormones, adipokines are important mediators of various metabolic processes such as fatty acid oxidation, gluconeogenesis, insulin signaling and energy expenditure in metabolically active tissues such as the liver, skeletal muscle and brain The important adipokines are leptin, adinonectin, resistin, IL6, tumor necrosis factor.[10] Leptin receptors are present in the specific regions of the brain. The feeding behaviour is regulated by the leptin. A defect in leptin or receptor can lead to obesity. Humans that lack either leptin or the leptin receptor are not only extremely obese but also hyperglycemic and extremely insulin resistance. Any genetic defect in leptin and its receptors will lead to extreme overeating and obesity. Treatment of such obese individuals with leptin has been shown to reverse obesity. Low levels of adinopectin will accelerate atherosclerosis.[2,3] Omentin a endocrine secreted by adipose tissue, levels are reduced in subjects with obesity and type II diabetes indicating omentin may be involved in glucose homeostasis. Invitro studies showed that amentin enhances insulin stimulation glucose uptake in human adipocytes by activating AKT signaling pathways.[3,4]

CONCLUSION

In summary, an increase in Fatty acid oxidation and Brown adipose tissue mass and activity could indeed be one of the underlying protective mechanisms against obesity-induced metabolic abnormalities. Although more research is needed, enhancing Brown adipose tissue thermogenic power through increased Fatty acid oxidation may be available in the near future as a therapy to treat obesity and its associated severe diseases.

The brain is especially dependent on salvage pathways and this may account for the central nervous system damage that occurs in children with Lesch-Nyhan-syndrome. This syndrome and the immunodeficiency diseases resulting from lack of adenosine deaminase are among the targets of early trials in human gene therapy.

Conflict of interest

None.

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