



Commentary: The Starving Brain: Overfed meets undernourished in the pathology of mild cognitive impairment (MCI) and Alzheimer's disease (AD)

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ABSTRACT

The emerging bioenergetic model for cognitive decline defines late-onset, neural impairment as symptomatic of brain starvation resulting from the physiological paradox of chronic cerebral hyperinsulinemia/hyperglycemia concurrent with episodic hypoglycemia. The catabolic injury to the brain occur linear to energy deficits and mirror the progression of peripheral, cellular insulin resistance and type II diabetes; this pathology of brain starvation is being recognized as Type III diabetes. An energetic construct of neurodegeneration centers on homeostatic energy failure, as hypothesized by Demetrius and Simon (2012)¹; the model focuses on the centralized role of astrocytes for the metabolic coupling of lactate to feed hungry neurons. Healthy fed/fasted signaling within the cells of the brain involves coordinated action of astrocytes and neurons. The astrocytes' primary mode of energy production, via brain-side, glucose transporter 1 (GLUT1), is glycolysis; glucose is metabolized anaerobically to lactate. Lactate is released by the astrocyte into the extracellular milieu and utilized as supplemental energy for neurons² (Pellerin, 2007). A recent study, "PSEN1 Mutant iPSC-Derived Model Reveals Severe Astrocyte Pathology in Alzheimer's Disease," published in Stem Cell Reports (2017)³ by a team from the University of Eastern Finland confirmed the role of astrocytes as lactate shuttles³. This study was the first to use human stem cells to demonstrate that in patients with AD astrocytes manifest pathological metabolic shifts. Conclusions of the study show astrocytes play a significant role in the early stages of the disease and contribute to metabolic changes in neurons leading to neurodegenerative pathology.

Astrocyte Lactate Shuttling

The Finland researchers discovered that diseased astrocytes produce significantly more beta-amyloid compared to healthy astrocytes; the overproduction of the toxic protein is evidence of respiratory distress and attenuating metabolic pathology³. In addition, astrocytes in AD tissue secreted more inflammatory cytokines; the cells showed alterations in energy metabolism leading to an increased production of reactive oxygen species (ROS) and a marked reduction in their production of lactate, an essential energy substrate for neurons. Most significantly, when Oksanen et al. (2017)³ co-cultured the AD astrocytes with healthy neurons, the aberrant astrocytes caused dysregulation of calcium signaling of the healthy neurons when compared to healthy astrocytes. This evidence strongly supports the energetic model concerning the centralized role of aberrant metabolic-coupling between the astrocytes and

neurons in the progression of AD³(Oksanan et al., 2017). The Finland study (2017) was the first to demonstrate that astrocytes in the AD brain manifest pathological changes in energy pathways that relate directly to the neural deficits common in degenerative pathology³.

Insulin Resistant Brain

The brain is considered an insulin-responsive yet insulin-independent organ; glucose metabolism is not regulated directly by insulin due to a low expression of GLUT4 insulin-dependent glucose transporter⁴ (Murray et al., 2014). However, hypothalamic expression of GLUT4 creates unique vulnerabilities in the brain to insulin resistance, which occurs in a similar pattern to peripheral insulin receptor resistance. The binding of insulin to the insulin receptor leads to the recruitment of GLUT4 glucose delivery. Under sustained peripheral insulin resistance, a chronic flux of insulin flows across the BBB leading to gradual impairment in hypothalamic glucose/insulin sensing with reduced recruitment and expression of GLUT4 transport; the loss of cellular sensitivity to distinguish between fed/fasted states is known to be an early biomarker in this dysregulation of glucose homeostasis⁵ (Mason, 2017).

Brain energetics involves the coordinated action of the astrocytes and neurons to maintain glucose homeostasis. Chronic hypometabolism has the potential to bankrupt cerebral energy reserves by inhibiting the synthesis of glucose into glycogen and lactate via astrocytic glycogenolysis/glycolysis; under normal conditions of low glucose availability, monocarboxylate transporters (MCTs) shuttle lactate, synthesized by astrocytes, to neurons via juxtasympaptic processes at nodes along the axon where the neuronal cells convert the lactate to pyruvate for OXPHOS in the mitochondria resulting in adenosine triphosphate (ATP)⁶ (Riske et al., 2017). Glycogen-derived lactate, produced by astrocytes, is a critical fuel source to meet the cerebral energy demands for neuron functioning and survival; the system of lactate reserve is an integral part of the negative feedback, homeostatic loop to maintain steady set points for cerebral glucose. Under energy crisis, astrocytes up-regulate GLUT1 for the production of glycogen; astrocytes contain MCT4s with low affinity, but high transport rate for lactate. In contrast, neurons under conditions of low glucose down-regulate GLUT3 and up-regulate expression of MCT2s; these transporters have a high affinity for lactate, allowing neurons to efficiently utilize lactate as fuel even in substrate-poor conditions⁶(Riske et al., 2017).

The networks in the brain with the highest energy demands serve as hubs of connectivity with other cerebral regions; early impairment in energy delivery to the hub causes the neighboring cells to be at risk for propagation

of disease. Thus, cerebral starvation of neurons gradually spreads across the landscape of the brain concurrent with impairment in the lactate shuttling by the astrocytes. Impaired cerebral circuitry correlates with measurable declines in energy metabolism; likewise, cognitive activity declines dramatically with lowered availability of cerebral ATP⁷ (Demetrius et al. 2014). Cerebral insulin resistance increases the metabolic demand for lactate; as neural demands exceed the capacity of the astrocyte shuttles, energy signaling pathways are disturbed leading to inflammation, an elevation of reactive oxygen species and brain starvation/atrophy.

Mitochondrial Congestion

Mitochondria in the AD brain are known to have reduced membrane potential, increased permeability, and produce excess ROS, which damage proteins, lipids, and nucleic acids, contributing to the pathogenesis of neurodegeneration. Poor signaling of nutrient loads between fed and fasted states appears to extend beyond macronutrients and can be observed at the level of gene and protein expression. Thus, a robust induction and/or suppression of gene transcripts occurs during the fasting-to-fed transition; signaling errors in this gene transcription process is common to many models of metabolic disease including AD and type II diabetes. Furthermore, current research implies that accelerated protein synthesis may be resultant of aberrant protein transcription and translation due to mixed signaling pathways⁸ (Muoio, 2014). Thus, the combination of increased acetyl donors and reduced deacylating capacity might underlie the elevation in mitochondrial protein acetylation observed in response to chronic nutrient overload. Cumulative evidence reveals that cerebral hypometabolism is evident in the affected brain regions of AD where mitochondrial structure is altered⁹ (Zheng et al., 2016). Likewise, the expression and activity of mitochondrial enzymes important for oxidative metabolism, including cytochrome c oxidase (COX), α -ketoglutarate dehydrogenase complex, and pyruvate dehydrogenase complex are disturbed during the co-occurrence of over-nutrition and cellular starvation⁶ (Riske et al., 2017).

Human physiology evolved to cope with dramatic fluctuations in energy supply and demand during periods of feasting and famine. Periods of feasting are typically preceded by sustained periods of energy deficit. By contrast, modern physiology is characterized by chronic over-nutrition. A large body of evidence suggests that over-nutrition initiates a state of metabolic insensitivity/inflexibility, characterized by distorted nutrient sensing, blunted substrate switching and impaired energy homeostasis, and that perpetual feeding imitates epigenetic gene modification and degenerative pathologies⁶ (Riske et al., 2017). Over-nutrition epigenetically shifts the

expression of the genome via the nutrient sensing pathways of mTOR/AMPK by up-regulating protein transcription and down-regulating key regulatory genes located on the CpG Islands of DNA. These regulator genes serve as “housekeeping” for the cells to protect polarity; the AMPK-driven, fasted state activates apoptosis/autophagy leading to organized cellular repair/death.

Frontiers Of Research

In summary, this review addresses to the longstanding question of metabolic flexibility and its role in chronic disease; in addition, it explores the modern phenomenon of neuronal energy deficits initiated by the “overfed/undernourished” paradox. Cells function optimally when they retain a capacity to switch freely between oxidative substrates in response to nutritional and physiological cues⁸ (Muio, 2014). The brain is no exception; current research supports a metabolic definition for cerebral pathology. This underscores the marked similarity of AD to peripheral insulin resistance and type II diabetes. Robust shifts in fuel sources prevent mitochondrial congestion and eliminate damaging molecular collisions. Metabolic flexibility yields strong metabolic signals that can be clearly interpreted by the cells to guide efficient nutrient partitioning and maintain energy homeostasis. Because nutrient sensing pathways are central to systemic regulation, metabolic flexibility mediates health and longevity. Exciting frontiers in research have developed treatment modalities for brain degeneration that focus on the impaired mitochondrial machinery, thereby mediating the pathology of the starving brain. Photobiomodulation¹⁰ crafts clinical grade, intranasal near infrared light to cross the blood-brain barrier; the rays of light unplug the congested mitochondrion¹⁰. Near infrared light releases the COX enzyme from the toxic grip of nitric oxide (NO); NO production dramatically increases in stressed cells and holds the potential to block the production of ATP by binding with COX. Breaking the bond between COX and NO releases oxygen to bind with NADH and activate the production of ATP to feed starving neurons¹¹.

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