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

Kelly J. Gibas

Human Bioenergetics & Applied Health Science, Bethel University, MN, USA

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ABSTRACT

Type II Diabetes affects 400 million people worldwide (IDF, 2013). The pathology is paradoxical: internal starvation activated by overfeeding. Hyperinsulinemic impairments of glucose homeostasis are treated with anti-hyperglycemics exacerbating cell starvation, inducing hypoglycemia and raising respiratory quotient. Reductions in hyperglycemia are achieved at the expense of glucose dependency and metabolic inflexibility (Gibas & Gibas, 2017). The brain is not immune from these cycles of starvation.

The bioenergetic model characterizes propagation of late-onset, sporadic Alzheimer's disease as loss of molecular fidelity and compromised energy originating in brain networks with highest metabolic demand. Impaired networks function as hubs of connectivity with other "at risk" regions causing propagation of disease to neighboring cells and compensatory up-regulation in protein synthesis, including amyloid precursor protein (Demetrius et al., 2014). Impaired brain circuits are hypo-metabolic. Cerebral energy declines after stages of quasi-stable, hyper-metabolism. Elevated insulin with low bioavailable glucose cross the BBB hyper-activating neurons to preserve brain function, thereby overloading the astrocyte-neuron lactate shuttle. Sustained deficits reprogram the neural phenotype toward lactate driven, OXPHOS. Increased OXPHOS fosters competition between normal and "metabolically charged" neurons for limited fuel. Cerebral starvation causes apoptosis of healthy neurons due to selective disadvantage.

The neuroenergetic model defines late-onset neural decline as symptomatic of "brain starvation" resulting from a physiological paradox, concurrent hyperinsulinemia and hypoglycemia, without an evolved cellular response. Catabolic degeneration occurs on a spectrum linear to energy deficit ranging from mild cognitive impairment (MCI) to Alzheimer's disease (AD); this pathology of cerebral starvation is known as Type III diabetes.

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E-mail address: Kelly-gibas@bethel.edu.

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Abbreviations

T2DM	Type 2 diabetes mellitus
ATP	Adenosine Tri-phosphate
GLUT4	Glucose transporter
PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4
PDK1	pyruvate dehydrogenase kinase 1
COX	cytochrome *c* oxidase
TCA CYCLE	Tricarboxylic acid cycle
OXPHOS	oxidative phosphorylation
MtDNA	mitochondrial DNA
AD	Alzheimer's Disease
FDG PET	fluorodeoxyglucose (FDG)-positron emission tomography (PET)
MCI	Mild cognitive impairment
BBB	blood brain barrier
mTOR	Mammalian target of rapamycin
MCTs	monocarboxylate transporters
LDH	Lactate dehydrogenase
ROS	reactive oxygen species
Aβ	amyloid-beta
NP	neuritic plaque
NFT	neurofibrillary tangle
HIF	Hypoxia-inducible factors
MCT	Monocarboxylate transporter
ANLS	Astrocyte-neuron lactate shuttle
HOMA-IR	Homeostatic model assessment of insulin resistance

1. Introduction: a starving brain

Diabetes is estimated to affect 382 million people worldwide and expected to surpass 600 million by 2035 (International Diabetes Federation, 2013). Metabolic pathologies common to metabolic syndrome, pre-diabetes and diabetes affect cerebral tissues via the blood brain barrier (BBB). FDG PET modalities confirm that impairments in peripheral glucose homeostasis, with sustained hyperinsulinemia, are known to occur upstream to dementia and neural decline by decades; resting state metabolic reductions in the brain, confirmed via PET, can be a proxy for neuronal activity and characterize a spectrum of neural decline starting with early mild cognitive impairment (MCI) and progression to Alzheimer's disease (AD) (Gibas and Gibas, 2017). Similar to diabetes, energy deficits in the brain initiated by peripheral insulin resistance usually occur in the presence of ample nutrition. Cerebral hypometabolism is known to resemble the “overfed/undernourished” paradox common to insulin resistant peripheral tissue. Simultaneous fed/fasted signaling is a physiological paradox created by sustained elevations in insulin, which in evolutionary terms, is rarely encountered by cells in vivo; a proper cellular response program does not exist. Current bioenergetic research believes the enduring cycles of hyper/hypoglycemia concurrent with chronic hyperinsulinemia, common to peripheral and cerebral metabolic impairment, sit at the epicenter of late-onset brain degeneration seen with Alzheimer's and Parkinson's disease; pathologies of brain degeneration are increasing with the pandemic spread of obesity and diabetes. Neural atrophy and disease may be maladaptive responses to persistent starvation. Energetic models characterize the cascade into late-onset neurodegeneration as “Type III Diabetes” (De la Monte and Wands, 2008).

2. Overfed meets undernourished

Hypometabolism in peripheral tissues is characterized by inefficient mitochondrial ATP production; research suggests deficits in oxidative ATP may be resultant of cellular insulin resistance and impaired GLUT4 translocation causing impairments in glucose sensing and utilization. Chronic deficits in oxidative energy, common to insulin resistant states, initiate maladaptive signaling cascades aimed at modulating diminishing ATP: impairments in energy signaling triggers chronic mTOR-HIF-1 activation, up-regulation of glycolytic enzymes (PFKFB3/PDK1), down regulation of mitochondrial enzymes of oxidative respiration (cytochrome *c* oxidase (COX), α-ketoglutarate dehydrogenase complex, and pyruvate dehydrogenase complex), disturbed GLUT1 expression and metabolic shifts toward glucose dependency. The sustained hyperactivation of PFKFB3 (master regulator of glycolysis) and PDK1 (primary inhibitor of pyruvate utilization in the TCA cycle) initiate the reprogramming of hypo-metabolic cells toward emergency survival, a dependency on anaerobic glycolysis for energy, and a high tolerance for acidic extracellular environments due to excess lactate production. In addition, a shortage of oxygen, due to slowing mitochondrial oxidative phosphorylation (OXPHOS) is also known to increase lactate production. Consequently, to minimize cell acidification, both lactate and protons are forced to exit the cells compounding intra/extracellular instability (Proia et al., 2016).

This metabolic reversion to the primitive fermentation of glucose in the cytoplasm of the cell, as a mechanism of survival, is known as the *Warburg Effect*. It has been suggested that reprogrammed “renegade” cells become immune to homeostatic regulation; Warburg identified cancer cells as having this renegade phenotype (Seyfried, 2012). Reprogrammed renegades are an upstream, metabolic shift occurring many years before pathology can be detected. Starving cells revert to glycolysis and lactate production for emergency fuel substrate; however, anaerobic fermentation produces only 52,000 cal/mole of glucose compared to 686,000 cal/mole synthesized in oxidative respiration (Demetrius et al., 2014). Thus, renegade cells are said to acquire a molecular “sweet tooth” using 20 times more glucose via non-oxidative energy metabolism via the up-regulation of glycolytic enzymes and inhibition of oxidative metabolic pathways (Demetrius et al., 2014).

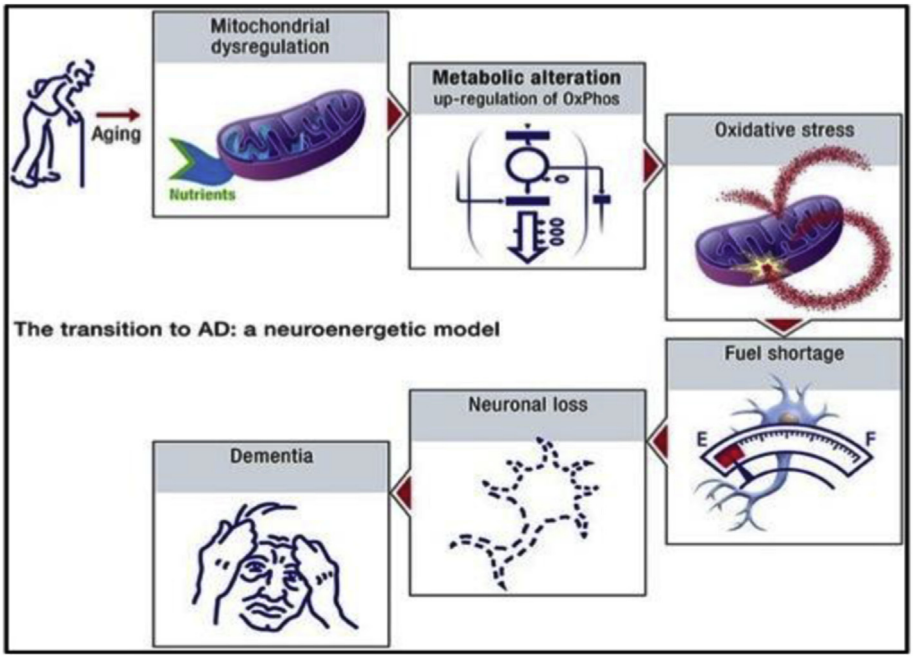


Fig. 1. According to research by Demetrius et al. (2014), 81% of people with late-onset, cognitive decline have prediabetes or diabetes supporting to a neuroenergetic model of gradual cognitive decline which occurs on a spectrum linear to cerebral metabolic alterations (Demetrius et al., 2014).

Furthermore, the inefficient use of mitochondrial respiration, characteristic of insulin resistant tissue, is known to cause swelling, collapse, and deterioration of the inner mitochondrial bilayers leading to defects in mtDNA. As emphasized by Demetrius et al. (2014), any disturbance in ATP availability will compromise cell viability and eventually leads to mtDNA damage; this damage occurs in both the peripheral and cerebral system (Demetrius et al., 2014). The brain is not immune to cycles of starvation. (Fig. 1).

3. Brain energetics: adaptation to starvation

The brain composes only two percent of total body mass, yet 50 percent of the glucose utilized in the body supplies the brain. Brain cells are metabolic systems; they maintain viability by converting free energy from nutrients in the external environment into chemical and electrical energy used to sustain life. Alzheimer's disease (AD) is the most common form of dementia and affects millions worldwide; however, brain degeneration of AD is known to occur decades before deficits in cognition are measurable. FDG PET methods can confirm deficient energy metabolism in the brain regions most affected by degeneration. Murray et al. (2014) postulate that clinical symptomatology of AD will not occur without correlative reductions in the rate of cerebral glucose metabolism; likewise, the severity of cerebral impairment is linear to the glucose deficit (Murray et al., 2014). Furthermore, research shows that impairment in cerebral glucose metabolism, in

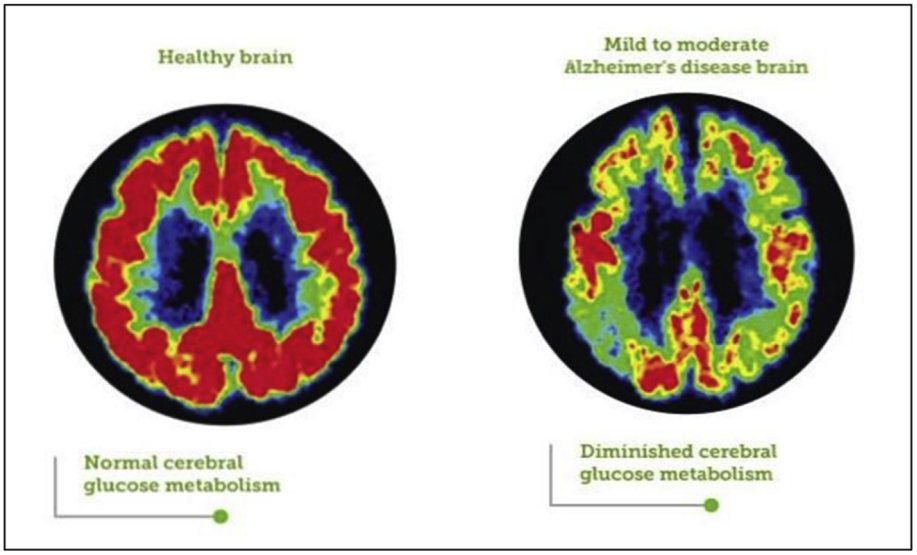


Fig. 2. The healthy brain on the left shows strong glucose availability and metabolism, while the impaired brain on the right reflects the characteristic hypometabolic state induced by insulin resistance initiated in the peripheral tissues leading to excess insulin and declining glucose transport across the BBB. Research shows hypometabolism reflects a spectrum starting decades before the clinical diagnosis of cognitve decline (Murray et al., 2014).

vulnerable brain regions, precedes the onset of dementia by decades and can accurately predict decline from normal cognition to mild cognitive impairment (MCI) and AD with over 80% accuracy (Mosconi et al., 2008). Thus, resting state metabolic reductions in the brain, confirmed via PET, are a proxy for neuronal activity (Figs. 2 and 3).

The neuroenergetic model, as hypothesized by Demetrius and Simon (2012), introduces a contrasting metabolic perspective to the traditional nuclear-genomic theory of brain degeneration; the model boldly defines the progression of pathological, age-related cognitive decline, neural atrophy and amyloid/tau accumulation as symptomatic of "brain starvation," (Demetrius et al., 2014). Energetic studies demonstrate the propagation of age-induced sporadic AD, characterized by profound loss in molecular fidelity and compromised energy production, originates in neural networks with high metabolic demands (hippocampus). The networks with highest energy demands serve as hubs of connectivity with other "at risk" cerebral regions; impairment in energy to the hub causes propagation of disease to neighboring cells. The starvation spreads across the landscape of the brain. Impaired cerebral circuitry shows measurable declines in energy metabolism; likewise, cognitive activity declines dramatically with lowered availability of cerebral ATP (Demetrius et al., 2014).

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 transport (Murray et al., 2014). This phenomenon is brain protective and often referred to as the "selfish brain" hypothesis. The blood-brain barrier (BBB) and its transport properties sharply contrast with peripheral tissues; the brain has extremely tight junctions between the vascular endothelial cells. Murray et al. (2014) note that FDG PET identified specific compartments in the brain involved in glucose uptake: the glucose-blood-tissue transfer by GLUT1 on astrocytes located in the blood brain barrier and neuronal GLUT3 glucose transporters, which are insensitive to insulin and hypothalamic dependent (Murray et al., 2014). Brain energetics involves coordinated action of both astrocytes and neurons. The astrocytes' primary mode of energy production, via brain-side, GLUT1 transport, is glycolysis; glucose is metabolized anaerobically to lactate. Lactate is released into the extracellular milieu and used as supplemental

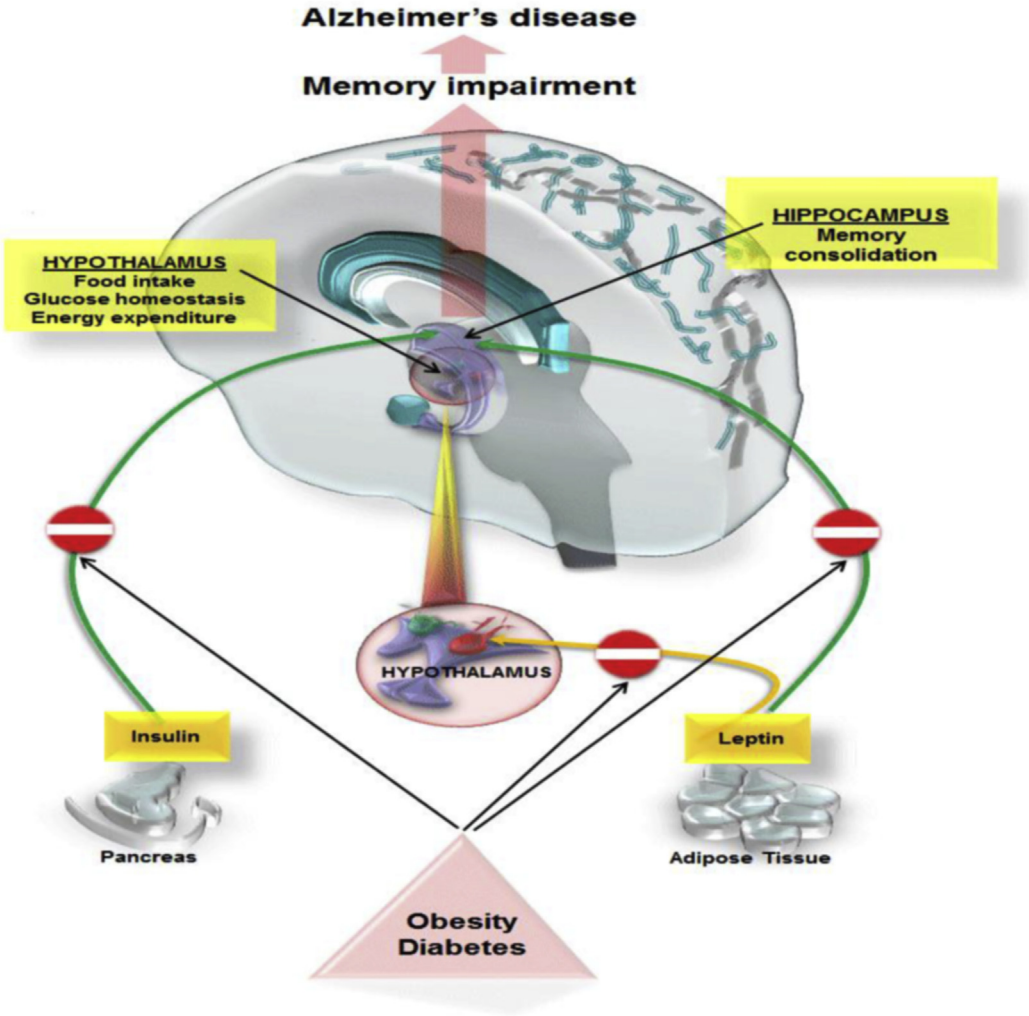


Fig. 3. The hypothalamus is positioned as control center for both peripheral and cerebral glucose metabolism via a negative feedback loop; as shown by the red circles, peripheral insulin resistance impairs proper "fed" signaling between the cell-hypothalamus-pancreas resulting in the chronic over-release of insulin to attenuate hyperglycemia; excess leptin is also secreted from the adipose tissues resulting in leptin-resistance. The signaling errors lead to a down-regulation of insulin and leptin receptors giving the brain mixed messages of simultaneous "feasting/fasting." The homeostatic impairment results in feed-forward loops in both the body and brain driven by lactate; the body exhibits hypersinulinemia with hyperglycemia, while the brain hyperinsulinemia with hypoglycemia causing a chronic down-regulation in body-facing GLUT1 with up-regulation of brain-facing GLUT1 (Folch et al., 2015). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

energy for neurons, similar to the intracellular utilization of anaerobic glycolysis (Cori Cycle) by peripheral tissue (Pellerin et al., 2007). Glucose uptake by astrocytes is disproportionately high compared to their energy requirements (15% of brain energy), which verifies current research showing that astrocytic glycolysis supports the energy requirements of neurons as part of the normal, negative feedback loop for maintenance of cerebral glucose homeostasis via lactate shuttling (Mason et al., 2017).

Research confirms that brain insulin resistance occurs primarily in the hypothalamus at the BBB causing perturbed energy sensing and the sustained, preferential utilization of lactate by anaerobic glycolysis and astrocytic shuttling as neuroprotection from starvation (Mason et al., 2017). Neurons are not insulin-dependent; however, they are insulin-responsive (Mason et al., 2017). Although insulin-mediated glucose transport is not required by glucosensing neurons, neuronal GLUT3 glucose transport is highly dependent on the ability of the hypothalamus to sense and signal cerebral energy supply. In a fed state, insulin crosses the BBB, signaling the hypothalamus to cue for expression of neuronal GLUT3 glucose uptake; this negative feedback system of hypothalamic signal-response mediates glucose homeostasis in the brain. While there is evidence that insulin is produced *de novo* in different brain regions, the majority of the insulin is shown to cross from the periphery through the BBB (Mason et al., 2017). Insulin is concentrated to levels 50 × higher than in circulating plasma independently of peripheral hormone status (Derakhshan and Toth, 2013; Blã¡zquez et al., 2014; Havrankova et al., 1981). Peripherally produced insulin crosses the BBB via a saturable transport system; the pancreas serves as the feedback effector for glucose homeostasis in both the body and brain. However, the acute difference between the two systems lies in the unique relationship of insulin to GLUT expression. In the body, insulin sensitive GLUT4 transporters mediate glucose utilization at the cell level by a coordinated effort of intra-cellular insulin receptors; peripheral tissue is primarily insulin-sensitive. Insulin connects with the insulin receptor on the cell surface initiating second messengers to translocate GLUT4 transporter tubules to the cell surface for the utilization of serum glucose; as glucose and insulin levels in the blood drop, the homeostatic system makes a critical shift from the fed to the fasted state. This shift, known as metabolic flexibility, sits at the epicenter of insulin resistance pathologies (Gibas and Gibas, 2017).

In the brain, immediate glucose is needed for survival; neurons require approximately 85% of all brain ATP, while astrocytes use roughly 15%. To safeguard the brain's energy homeostasis, the hypothalamus regulates glucose sensing and neuronal glucose utilization. Studies show that hypothalamic cells exhibit a stronger expression of GLUT4 *insulin-dependent* transporters due to their role in glucose-sensing via intracellular insulin receptors (Mason et al., 2017). Neurons utilize glucose thorough the expression of GLUT3 transportation. GLUT3 neuronal transporters are not sensitive to insulin signals, but are insulin-responsive; therefore, neurons do not read the energy status of the extracellular environment. Instead, neurons depend on nutrient sensing by the hypothalamus and astrocytes. The hypothalamus, as the master control center of cerebral homeostasis, stimulates the expression of the GLUT3 neuron transporters to the cell surface in response to “fed” signals cued by insulin (Mullins et al., 2017). The hypothalamus is sensitive to insulin signals crossing the BBB and translates the energy status to the neurons, the primary utilizers of glucose. In the fed state, the flux of peripheral insulin is elevated, signaling the hypothalamus (via second messengers) to express GLUT3s for glucose utilization; likewise, during the “fasted” state when insulin/glucose is low, astrocytic GLUT1 are activated and begin the process of glycogenolysis, the catabolic breakdown of glycogen stores to synthesize lactate. Lactate is shuttled from astrocytes to neurons via MCT transportation; neurons convert extracellular lactate to pyruvate for OXPHOS. The centralized, regulation of glucose homeostasis by the hypothalamus is designed to protect the brain against starvation; however, when insulin crossing the BBB is elevated and glucose transport is low, a centralized, insulin-specific defect in crosstalk significantly impairs the energy status in the brain (Mason et al., 2017).

4. The neuroenergetic model

The energetic model suggests the same biochemical survival pathways triggered with insulin resistant, peripheral starvation characterizes the pathology in AD. Deficits in cerebral ATP initiate similar energetic brain adaptations with profound metabolic alterations. Research demonstrates that brain starvation stems from insulin resistance in the hypothalamus, a region of centralized, cerebral control with a greater expression of GLUT4 insulin-sensitive, glucose transportation. Excess insulin crossing the BBB causes signaling errors leading to sustained deficits in both sensing/uptake of glucose by hypothalamic GLUT4 transporters. This aberrant signaling epigenetically reprograms starving neurons into the renegade phenotype with a trajectory of apoptosis (Demetrius et al., 2014). Neuronal energy deficits caused by insulin resistance and mitochondrial impairment occur in the presence of sufficient oxygen and ample nutrition, a situation that resembles the “overfed/undernourished” paradox of insulin resistant peripheral tissue. Cells in vivo rarely encounter this physiological paradox of simultaneous fed/fasted signaling; thus, the selection pressure needed to evolve a proper response program does not exist (Zheng et al., 2016).

Current research suggests that aberrant energy signals, occurring in response to both peripheral and cerebral insulin resistance, set off cascades of survival signals activated by chronic anabolism in the mTOR pathway. Due to differentiated substrate utilization in brain tissue, termed “selfish brain,” cerebral mTOR activation inadvertently up-regulates mitochondrial protein synthesis at the expense of cerebral ATP; protein synthesis is a major energy-consuming process. This process leads to toxic accumulation of beta-amyloid concurrent with the catabolic degeneration of neurons (Zheng et al., 2016). In this bioenergetic hypothesis, the unregulated, overproduction of beta-amyloid resembles the unfettered, anabolic proliferation of cancerous tissue; research suggests that both pathologies (cancer/neurodegeneration) are initiated by aberrant fed/fasted nutrient signaling, hyperinsulinemia and chronic activation of the mTOR pathway, which stimulates pathological growth/inflammation concurrent with starvation, cachexia and apoptosis of healthy cells. As Zheng et al. (2016) imply, a lack of selection pressure prevents the evolution of a proper cellular response system to attenuate the physiological paradox inherent to simultaneous fed/fasted nutrient signaling common to insulin resistant states (Zheng et al., 2016). Research confirms pathological links between metabolic disease (diabetes/insulin resistance) characterized by impaired glucose sensing/utilization and mitochondrial dysfunction, aberrant mTOR signaling, cancerous proliferation and neurodegeneration (Demetrius et al., 2014).

5. Glycogen-lactate energy transport

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 juxtasynaptic 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) (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 glucose transport 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 conditions (Riske et al., 2017).

Unlike peripheral cells, neurons lack the necessary glycolytic enzymes for the intracellular production of lactate; neurons preferably catalyze pyruvate from lactate for oxidative respiration due to the presence of LDH1, while astrocytes utilize LDH5 for non-oxidative synthesis of lactate from pyruvate (Riske et al., 2017). Hence, the cerebral, cell-to-cell metabolic coupling of lactate-derived energy mirrors the intracellular Cori Cycle activated in peripheral tissue during acute energy deficits (Gibas and Gibas, 2017). Research suggests that this vital glycogen-derived, lactate shuttle of reserve energy between astrocyte and neuron is deranged during cerebral insulin resistance; prior studies have shown that severe hypoglycemia, induced by hyperinsulinemic states, elicits depletion of brain glycogen and reduces cerebral ATP resulting in neuron death in the hippocampus (Matsui et al., 2017). An insulin resistant, hypo-metabolic state inhibits cerebral glucose availability/uptake by chronic up-regulation of cerebral GLUT1 expression in astrocytes resulting in pathological reductions in brain glucose with severe deficits in glycogen-lactate-pyruvate synthesis (Riske et al., 2017). Furthermore, insulin resistance in the brain results in sustained inhibition of the key enzymes of glycogenolysis, glycogen phosphorylase and phosphofructokinase; the inhibiting serves to “protect and spare” the limited supply of glucose from storage as glycogen (Proia et al., 2016).

6. Mitochondrial regulatory pathways

A role for dysfunctional mitochondria in AD pathogenesis has been postulated; mitochondria play a critical role in cell viability and death as they regulate energy, oxygen metabolism and cell death pathways. Studies suggest that mitochondrial impairment and oxidative stress are attributive, inextricable perpetrators in the reduction of neuronal energy in neurodegeneration (Zheng et al., 2016). Oxidative stress, an imbalanced biochemical state, causes the cells to produce more reactive oxygen species (ROS) than the antioxidant activity can withstand; oxidative stress is common with cellular energy deficits (Mullins et al., 2017). Cumulative evidence reveals that cerebral hypometabolism is evident in the affected brain regions of AD where mitochondrial structure is altered (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 significantly reduced as a form of “glucose sparing” during starvation (Riske et al., 2017). Similar to insulin resistant peripheral cells, mitochondria in the AD brain are known to have reduced membrane potential, increased permeability, and produce excess reactive oxygen species (ROS), which damage proteins, lipids, and nucleic acids, contributing to the pathogenesis of neurodegeneration. Furthermore, current research implies that accelerated protein synthesis, initiated by chronic mTOR complex 1 signaling, leads to accumulated plaque/tangles, depletes electrical energy and produces damaging ROS in the impaired mitochondrial machinery (Zheng et al., 2016).

For decades, amyloid-beta (Aβ), neuritic plaque (NP) and neurofibrillary tangle (NFT) aggregation hypotheses dominated studies on brain pathogenesis. However, population-based autopsies of the brains of aged people who were not diagnosed with a neurological disease consistently report the presence of amyloid plaques, neurofibrillary tangles, Lewy bodies, inclusions, synaptic dystrophy, the loss of neurons and the loss of brain volume; these findings suggest that other processes and pathologies may be important contributors to late onset neurodegeneration The presence of age-related protein abnormalities and inclusion bodies in the ageing brain point to defects in protein homeostasis (proteostasis); this idea is supported by mounting evidence from studies with animal models (Zheng et al., 2016). The mTOR complexes modulate nutrient availability with cell growth and proliferation, promoting protein synthesis and inhibiting autophagy (Zheng et al., 2016). Protein homeostasis is distorted in numerous neurodegenerative diseases, like Parkinson's and Alzheimer's disease, making mTOR a therapeutic target.

With ageing and degeneration, the brain shows increased levels of many lysosomal proteins and enzymes; neurons and astrocytes show abnormal endosomes, lysosomes and autophagosomes. A current study by Zheng et al. (2016) supports the 2010 research by Spilman et al. showing the aberrant energy demands of excess protein synthesis, caused by elevated mTOR activity, shunts the limited supply of ATP causing a further reduction of cerebral energy availability and worsening hypo-metabolism (Zheng et al., 2016; Spilman et al., 2010). Research suggests a significant outcome of inhibiting mTORC1 via rapamycin (mTOR inhibitor) was a dramatic decrease in protein synthesis. Zheng et al. (2016) showed that decreases in protein synthesis (−55%) in neurons, via rapamycin, had linear ATP-saving effects (+26%). The Zheng et al. (2016) results imply that increased protein synthesis is initiated by enhanced mTORC1 signaling and may be a common feature of neuronal mitochondrial dysfunction resultant of starvation signaling. A reduction of protein synthesis restores proteostasis and may be vital to the preservation of ATP in neurons with mitochondrial impairment (Zheng et al., 2016).

One of the enduring mysteries in AD is the different distribution of NFTs and NPs in the disease. The various lines of evidence reviewed above and the novel analysis presented enable us to formulate a bold new hypothesis that considers brain insulin resistance as an important link between Aβ and Tau pathologies in AD and a primary determinant of their regional distribution (Mullins et al., 2017). Baseline differences in the reliance on glycolysis to generate energy, the expression of GLUT1 and insulin signaling genes may determine the vulnerability of different brain regions to Tau and/or Aβ pathology (Mullins et al., 2017). Extensive temporo-parietal areas of the AD brain show significant metabolic reliance on glycolysis and generation of lactate as evidenced by the increased expression of GLUT1 transporters (Small et al., 2009; Kadir et al., 2010; Vlassenko, 2016). Furthermore, elevated lactate is associated with high interstitial Aβ, which assembles into Aβ oligomers (Proia et al., 2016). Mullins et al. (2017) suggest that the distribution of regional glucose metabolism via glycolysis in healthy young adults correlates spatially with Aβ deposition in individuals with AD. This implies a pathogenic link between chronic glycolysis in early life and the eventual development of Aβ pathology (Mullins et al., 2017).

7. Cerebral insulin resistance

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; a loss of cellular sensitivity to distinguish between fed/fasted states is known to be an early biomarker in this dysregulation of glucose homeostasis (Mason et al., 2017). Chronic elevation of insulin crossing to the brain perturbs the negative feedback loop mediating glucose regulation between neurons (GLUT3) and astrocytes (GLUT1) via maladaptive "fed/fasted" signals common with prolonged hyperinsulinemia (Gibas and Gibas, 2017). In systemic and organ-specific insulin resistant states, the ability of insulin to stimulate glucose uptake via GLUT transporters is impaired. The impairment in insulin signaling requires higher than normal concentrations of extracellular insulin to maintain normal glucose uptake to satisfy energy demands (Mullins et al., 2017). This co-occurrence of hyperinsulinemia with hyperglycemia in peripheral tissue initiates a positive, pancreatic feed-forward loop via the role of the hypothalamus as homeostatic control center of systemic glucose regulation. Thus, peripheral insulin resistance will inhibit hypothalamic recruitment of neuronal GLUT3 glucose transporters; this reduces GLUT3 expression resulting in mixed signals of overfed (elevated insulin) and undernourished (impaired GLUT3 expression) (Gibas and Gibas, 2017). Research suggests, the confusion in homeostatic cross-talk leads to deficits in both peripheral and cerebral energy; the negative feedback between glucose driven GLUT3 and lactate driven GLUT1 expression deviates into a maladaptive feed forward loop driven primarily by synthesis of glucose-sparing lactate (Mason et al., 2017).

Persistent energy deficits actuate a prolonged activation of the HIF-1/mTOR survival path, maladaptive energy reprogramming, morphological changes to neuronal phenotype, astrocyte inflammation and neuron apoptosis (Demetrius et al., 2014; Mason et al., 2017). Specific characteristics of astrocytes position the cells to sense and respond dynamically to changes in neuron activity; the astrocytes are especially adept to sense cues of starvation, resulting from insulin resistance and impairments in GLUT3 expression. Similar to the peripheral system, as the hypothalamus loses sensitivity to insulin and nutrient sensing, there is known to be a corresponding up-regulation of lactate as a "glucose sparing" substrate. Moreover, a 2011 study by Bero et al. discovered that a chronic up-regulation in regional lactate production is closely linked to interstitial Aβ levels; this linear association established an additional link between glycolytic energy metabolism and a key pathogenic protein in AD (Bero et al., 2011). There appears to be a putative interchange, initiated impaired cerebral glucose homeostasis, between increased dependency on glycolysis, increased production of lactate and resultant increases in extracellular Aβ (Mullins et al., 2017).

8. The genesis of starvation: miscued signaling

The BBB is a dynamic structure that regulates the rates of homeostatic uptake and release for a variety of hormones, chemicals, and proteins (Daneman, 2012). Thus, fluctuations in plasma levels of glucose and insulin affect energy uptake across the BBB via the crosstalk between the hypothalamus, GLUT-1 and GLUT-3 transporters embedded within the BBB endothelium (Liang, 2010). This vital crosstalk ensures the ability of the brain to respond accurately to variable energy demands and controls cerebral glucose homeostasis (Liang, 2010; Leybaert et al., 2007). Circulating insulin and glucose concentrations regulate the endothelial GLUT1 protein concentrations. A study by Cornford and Hyman (2005) demonstrated that glucose transport across the BBB *increases* with higher expression of blood-facing, luminal GLUT-1, which is normative for healthy, insulin sensitive patients (Leybaert et al., 2007). However, higher expression of brain-facing GLUT-1 transport was accompanied by *decreased* glucose transport to the brain; decreases in blood side GLUT1 transport caused low glucose delivery across the BBB due to peripheral insulin resistance (Mullins et al., 2017). Research suggests cerebral energy deficits occurred due to down-regulation of blood-facing GLUT1 transporters with a compensatory up-regulation of astrocyte brain-facing GLUT1 expression to mediate energy deficits via augmented synthesis of lactate. This brain-facing up-regulation of GLUT1 is normative in acute glucose deprivation, but turns pathological during sustained cerebral hypo-metabolism common with insulin resistant states (Mullins et al., 2017). Insulin receptor expression is also reduced in the BBB under prolonged peripheral hyperinsulemia; increased insulin and decreased glucose cross the BBB resulting in ensuing insulin resistance in hypothalamic GLUT4 transporters. Under prolonged hypothalamic insulin resistance, the fed/fasted signaling of the negative feedback loop for cerebral glucose homeostasis is significantly disturbed leading to brain starvation.

Under normal conditions, insulin is known to cross the BBB in concentrated form, up to 50 times higher than in circulating plasma; with sustained hyperinsulinemia, cerebral insulin receptors down-regulate losing sensitivity to the action of insulin, which further decreases glucose availability leading to intensified miscuing of the fed/fasted state within the brain (Mullins et al., 2017). Ultimately, during the progression of brain insulin resistance, the rate of cerebral insulin/glucose transport is decelerated by peripheral insulin resistance. Interesting to bioenergetics research and consistent with the current suggestions of brain hyperinsulinemia (Demetrius et al., 2014; Mason et al., 2017; Blā¡zquez et al., 2014), deficits in cerebral energy and dysregulation of luminal/abluminal GLUT1 transport are shown to improve with benign dietary ketosis (beta-oxidation) and caloric restriction. This supports the centralized role of impaired glucose/insulin regulation in the starving brain; dietary ketosis and intermittent fasting are known to increase insulin sensitivity thereby enhancing glucose availability (Demetrius et al., 2014; Mason et al., 2017; Cornford and Hyman, 2005) (Fig. 4).

9. The Inverse Warburg Effect: renegade neurons

Ironically, insulin resistance and metabolic inflexibility in the brain and peripheral tissue lead to differing physiological responses; cerebral starvation up-regulates oxidative respiration of lactate with increased protein synthesis via the up-regulated expression of GLUT1 glucose/lactate uptake and delivery by the astrocytes; this phenomenon is referred to as the *Inverse Warburg Effect* (Urayama et al., 2016). Unlike peripheral cells, neurons lack the necessary glycolytic enzymes for aerobic glycolysis (*Warburg Effect*) during times of starvation. Instead, under glucose deprivation, neurons rely on the up-regulation of OXPHOS through the MCT extracellular transport of astocytic lactate as the primary metabolite for conversion to pyruvate in the TCA cycle (Mason et al., 2017). Neurons, unlike peripheral cells, are unable to up-regulate intracellular, non-oxidative respiration and instead rely on metabolic coupling or lactate shuttling (Demetrius and Simon, 2012). The master regulatory enzyme of non-oxidative glycolysis, PFKFB3, has strong expression in astrocytes; however, in neurons, the enzyme is weakly activated and easily degraded. Under conditions of reduced energy supply in the brain, astrocytes provide energy for neurons via metabolic coupling of lactate; this temporary "shuttling" keeps a steady supply of ATP for brain metabolism during acute glucose deficits via the increased expression of GLUT1

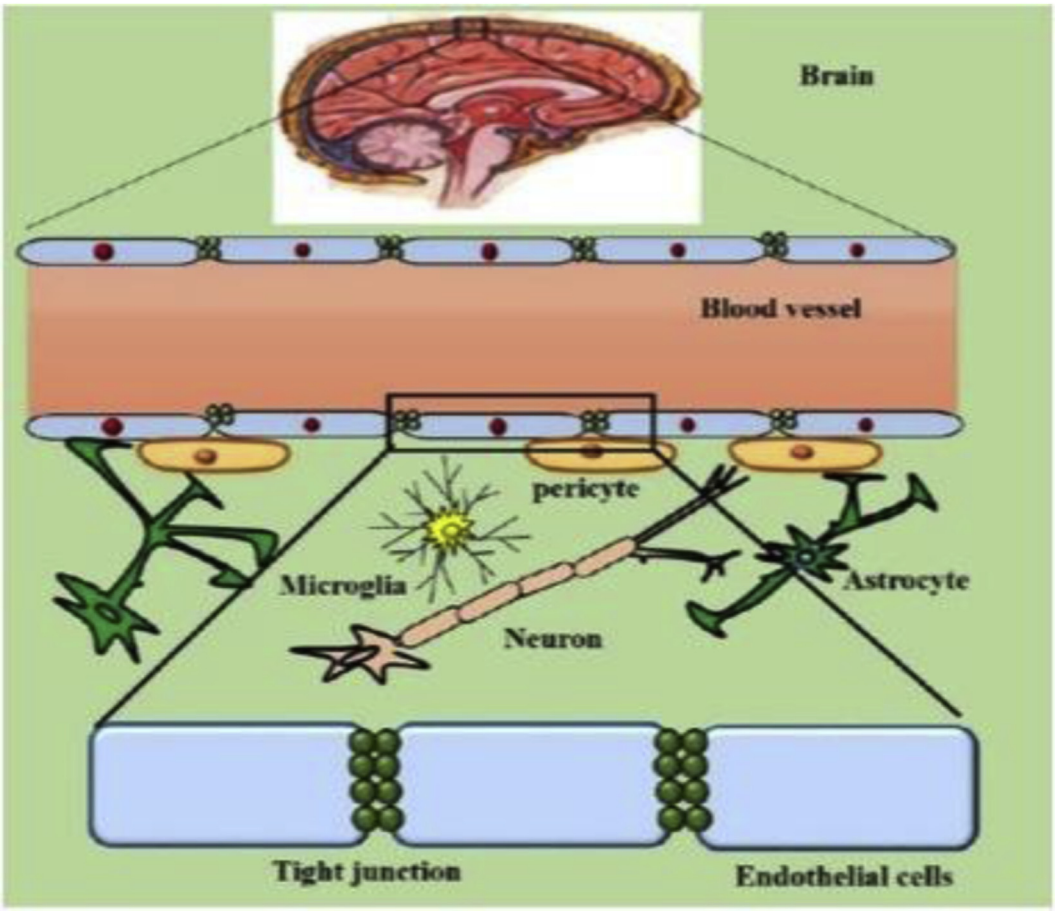


Fig. 4. Research shows an early indicator of cerebral hypometabolism is the chronic up-regulation of brain-side (abluminal) GLUT1 transporters with corresponding down-regulation of blood-side (luminal); increased insulin and decreased glucose cross the BBB resulting in ensuing insulin resistance of hypothalamic GLUT4 transporters. With hypothalamic insulin resistance, the fed/fasted signaling of the negative feedback loop for cerebral glucose homeostasis is disturbed leading to brain starvation (Khalaj-Kondori et al., 2015).

(Mason et al., 2017). Lactate, synthesized by glycogen stored in astrocytes, provides supplementary fuel for "hungry" neurons via the astrocyte-neuron lactate shuttle (ANLS); thus, it has been postulated that astrocytes serve a dynamic nursing/chaperoning role to mediate short-term energy deficits by rearranging fuel substrates (Bouzier-Sore et al., 2003) (Fig. 5).

Under chronic mTOR-HIF-1 activation, as noted in both peripheral and cerebral insulin resistance, the overdependence on lactate can lead to brain degeneration via a pathogenic feed-forward loop (Mullins et al., 2017). Survival mechanisms inherent to mTOR-HIF-1 activation are adaptive in short-term hypoxia/starvation; HIF-1 mediates acute energy deficits through up-regulation of lactate and hyper-phosphorylation of protein. In the short term, anaerobic lactate production is neuro-protective (Mason et al., 2017). Neuro-protection has been defined as interventions that prevent the death of vulnerable neurons and slow disease progression (Mason et al., 2017). The pro-survival, neuro-protective role of lactate was experimentally demonstrated in numerous studies; lactate's adaptive features are activated during normative fed/fasted cycling and during short bouts of exercise-induced hypoxia (Matsui et al., 2017).

However, the neuro-protective chaperoning/shuttling of fuel by astrocytes, when extended beyond acute glycogen reserves, results in hypometabolic shifts, or reprogramming, in neurons up-regulating protein phosphorylation in response to activation of the HIF-1/mTOR pathway. The increased production of protein is energy consuming requiring a significant demand for ATP, resulting in a catastrophic energy declines. It has been postulated that sustained impairments in cerebral energy will overwork the ANLS exposing neurons to elevated risk for degeneration and apoptosis. Impairments in fuel distribution have been shown to initiate metabolic reprogramming in "starving" neurons via a compensatory up-regulation of oxidative phosphorylation (OXPHOS) to attenuate a diminishing supply of energy; this reprogramming hypothesis supports current research showing that brain regions with the highest energy demand temporarily shift into a lactate driven hypermetabolic state that proceeds clinical pathology (Demetrius et al., 2014; Matsui et al., 2017). Hypometabolic/hypermetabolic shifts cause the emergence of a pathological, renegade pattern within the neuronal phenotype; this starvation pattern resembles the up-regulation of aerobic glycolysis evidenced in peripheral cells exposed to chronic energy-deficits. Accelerated OXPHOS in reprogrammed neurons, referred to as the Inverse Warburg Effect, nurtures a deadly competition between the healthy and unhealthy "renegade" neurons vying for a diminishing fuel supply (Demetrius et al., 2014). Sustained energy shortages foster catabolic degeneration of healthy neurons due to their selective disadvantage (Demetrius et al., 2014) (Fig. 6).

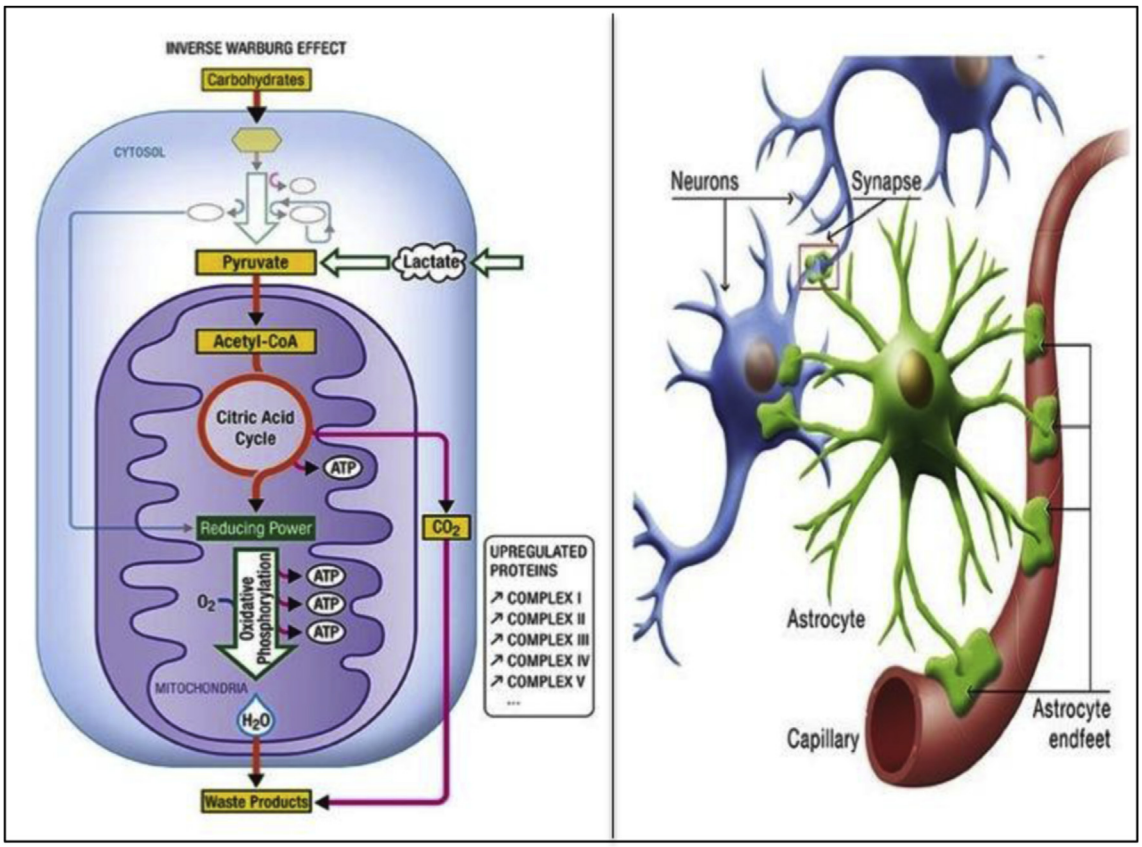


Fig. 5. Shown on the left, during sustained glucose shortages, neurons lack the glycolytic enzymes to rely on an intra-cellular lacate production similar to the peripheral Cori Cycle, thus they depend on lactate shuttling by astrocytes. The starving neurons up-regulate the oxidation of lactate with increased protein synthesis, due to the HIF-1/mTOR pathway, to mediate the glucose deprivation. This phenomenon is referred to as the Inverse Warburg Effect (Demetrius et al., 2014).
Depicted on the right, lactate, synthesized by glycogen stored in astrocytes, provides supplementary fuel for "hungry" neurons via the astrocyte-neuron lactate shuttle (ANLS); thus, it has been postulated that astrocytes serve a dynamic nursing/chaperoning role to mediate short-term energy deficits by rearranging fuel substrates (Demetrius et al., 2014).

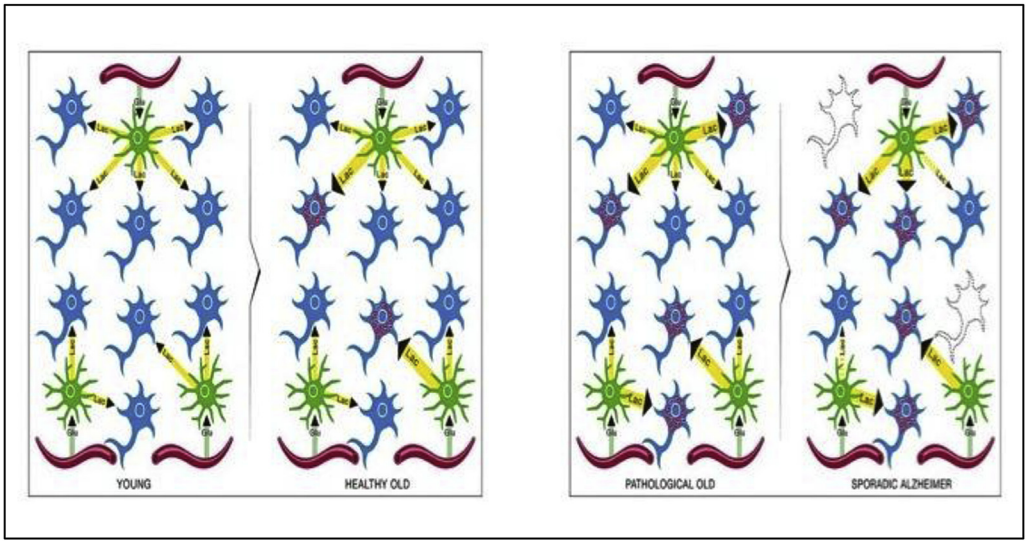


Fig. 6. The aging brain naturally increases its production of lactate; however, in the chronic hypometabolic brain, lactate shuttling by astrocytes increases due to sustained deficits in glucose delivery across the BBB with co-occurring insulin resistance in hypothalamic GLUT4 transporters. This results in competition for limited lactate supplies between healthy and unhealthy dysregulated (renegades) neurons noted in red; the process of degeneration is gradual and occurs on a spectrum decades before cognitive decline is diagnosed via significant neuronal apoptosis (noted by black/white outlines) (Demetrius et al., 2014). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

10. Mediating starvation: fat for fuel

Research confirms that cerebral glucose metabolism is decreased in MCI and AD with a characteristic regional pattern over the medial/lateral parietotemporal and frontal cortices that can be detected decades before the onset of neurodegeneration (Mullins et al., 2017). Intriguingly, the same pattern of relative hypometabolism was shown to correlate with the clinical biomarker of HOMA-IR (homeostatic model assessment of insulin resistance) in post-menopausal women (Mullins et al., 2017), adults with prediabetes/T2D (Thomas and Baker, 2013), and those at higher risk for AD due to parental history (Willette et al., 2015). The HOMA-IR provides an estimate of systemic insulin resistance and β cell function by combining fasting insulin and glucose levels into a single metric. These results suggest an early vulnerability in glucose metabolism that may culminate in clinical AD. A study of patients with MCI and AD showed that HOMA-IR is negatively associated with glucose metabolism in brain areas most vulnerable to AD pathology, but not in areas typically unaffected by AD (Willette et al., 2015). Interestingly, HOMA-IR has a paradoxical, positive association with hippocampal glucose metabolism in MCI patients prior to conversion to clinical dementia; this supports conclusions regarding the compensatory up-regulation of glycolysis/lactate synthesis in regions of the brain with the greatest energy requirements to attenuate starvation (Murray et al., 2014; Willette et al., 2015).

Beta-oxidation of fatty acids, benign dietary ketosis and intermittent fasting (caloric restriction) have been shown to be insulin sensitizing for both the body and the brain; fatty acid metabolism is exclusively activated during “fasted” states of caloric restriction or “pseudo” fasted states induced by fatty acid oxidation concurrent with the restriction of dietary carbohydrates (Gibas and Gibas, 2017). Free fatty acids supply cellular energy via recruitment and expression of long-chain fatty acid transporters allowing for a physiological “rest” for intracellular insulin receptors and GLUT transporters. It has been suggested that insulin sensitization,

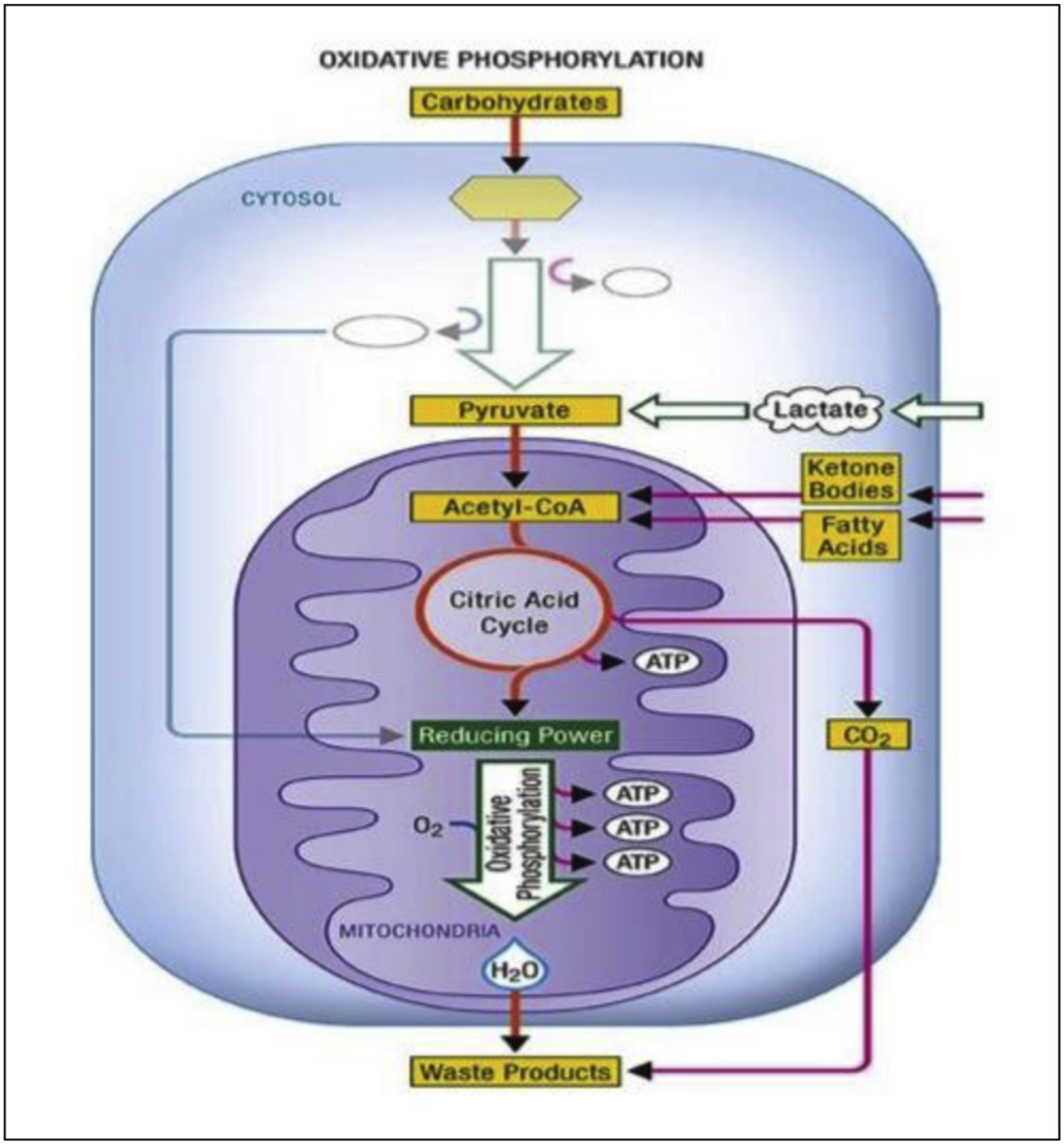


Fig. 7. As noted in the above figure, fatty acids can be metabolized in the liver into ketone bodies, which are carried in the blood in the form of β-hydroxybutyrate; ketones metabolize intra-mitochondrial into two molecules of acetyl coenzyme A, which enter the TCA cycle directly. Beta-oxidation, facilitated by the pancreatic release of glucagon, satisfies energy demands in the absence of glycolysis and insulin signaling, making fat oxidation, ketogenesis, and calorie restriction via intermittent fasting, potent metabolic regulators of cerebral glucose availability through the normalization of homeostatic, negative feedback signaling (Demetrius et al., 2014).

inherent to beta-oxidation, is activated by reductions in fasting/post-prandial insulin levels with a corresponding reset in homeostatic signaling between insulin and glucagon (Gibas and Gibas, 2017). Likewise, fatty acids can be metabolized in the liver into ketone bodies, which are carried in the blood in the form of β-hydroxybutyrate; ketones metabolize intra-mitochondrial into two molecules of acetyl coenzyme A, which enter the TCA cycle directly. Beta-oxidation, facilitated by the pancreatic release of glucagon, satisfies energy demands in the absence of insulin signaling, making fat oxidation, ketogenesis, and calorie restriction via intermittent fasting, potent metabolic regulators of cerebral glucose availability through the normalization of homeostatic, negative feedback signaling (Gibas and Gibas, 2017) (Fig. 7).

Dietary Ketosis is known to regulate signaling impairments and normalize the recruitment and expression of GLUT transport by restoring metabolic flexibility (Gibas and Gibas, 2017). Likewise, β-Hydroxybutyrate oxidized into acetoacetate generates one molecule of NADH; this resembles lactate oxidation into pyruvate except lactate oxidation occurs in the cytosol and competes with oxidative glycolysis. In contrast, ketones metabolize directly into the mitochondrial pathway; glucose must be converted in the cytosol to pyruvate by glycolysis before conversion to acetyl-CoA in the TCA cycle. Oxidative glycolysis is a complicated, biochemical process, especially under conditions of cerebral hypometabolism, which is known to impair glycolytic enzymes and inhibit oxidative respiration (Mullins et al., 2017). Beta-oxidation, effectuated during the restriction of carbohydrates, benign dietary ketosis and caloric restriction via intermittent fasting, is a burgeoning, yet largely unexplored, pathway of energy offering a viable, alternative fuel for the starving brain (Blã¡zquez et al., 2014; Gibas and Gibas, 2017).

11. Clinical application

Early stages of memory loss and the comorbidity of Metabolic Syndrome are symptomatic of cerebral hypo-metabolism induced by chronic insulin resistance. Consequential to systemic hyperinsulinimia, aberrant crosstalk between the mitochondria and nuclear genome results in a primary dysregulation of the modulatory kinases mediating metabolic state and intracellular/extracellular nutrient sensing: mTOR and AMPK. The suppression of AMPK signals with chronic over expression of the IGF1/PI3K/AKT/mTOR pathway will adapt rRNA synthesis away from nutrient availability and toward ATP consuming processes: the biosynthesis of cholesterol, triglycerides, glycogen with inhibition of fatty acid oxidation, histone acetylation causing a down-regulation of NAD+ and SAHH cofactors leading to global DNA hypo-methylation with local hypermethylation and the inhibition of SIRT (sirtuin) expression (Liang, 2010; Leybaert et al., 2007). These epigenetic shifts mediate metabolic inflexibility in the genome by channeling fuel substrates toward cytosolic glycolysis, substrate level phosphorylation (SLP) and away from mitochondrial fatty acid oxidation mediated by the suppression of the pyruvate dehydrogenase complex, the major regulatory gateway of metabolism between glycolysis and citric acid cycle/OXPHOS (Demetrius et al., 2014).

As shown in clinical research (Table 1), the activation of the AMPK pathway via induced and controlled dietary ketosis inhibits mTOR signaling, reduces the biosynthesis of proteins, cholesterol and triglycerides, increases cerebral blood flow/ketone substrate and activates metabolic flexibility via SIRT1 expression, thereby enhancing the catabolic breakdown of energy (Gibas and Gibas, 2017). It is known that ketogenesis is associated with down regulated mTOR activity and up regulation of AMPK due to the cellular shift in the AMP/ATP ratio. The AMPK activation of SIRT1, an NAD + dependent deacetylase, regulates energy metabolism (metabolic flexibility) and attenuates insulin resistance and diabetes due to its primary role as a NAD + sensor. Research anticipates the convergence of these nutrient sensing pathways with microRNA transcriptional factors binding to target genes to regulate global metabolism, disease state/progression as well as the modification of DNA replication, apoptosis and cellular senescence. Clinical experience supports the metabolome as the physiological epicenter for future research on brain starvation and neurological degeneration. The expression and/or silencing of microRNAs such as let-7 on the genome is highly regulated by global DNA methylation and histone modification determined largely by nutrient status and chaperone protein transcription modulated by the mTOR/AMPK energy sensing pathways. Nutritional status epigenetically modifies the human genome by regulating the key nutrient sensing pathways leading to common diseases of civilization characterized by aberrant lipid synthesis, pathological LP-IR scores (particle concentration and size), elevated HgA1c/fasting insulin/HOMA-IR and global DNA hypo-methylation with local

Table 1
Ongoing clinical trials.

ClinicalTrials.gov Identifier	Title of study	Sponsor(s)	Purpose of study	Date received	Date last verified
NCT02501876	Type 2 Diabetes Mellitus as Catalyst for Alzheimer's Disease (DIACEA)	Hospital Universitari Vall d'Hebron Research Institute	Evaluation of whether the presence of diabetes and or its related genes favors the conversion of MCI to AD	June, 2015	April, 2017
NCT03024944	TAU PET Imaging in Northern Manhattan Study of Metabolism and Mind (TAUPET)	National Institute on Aging (NIA)	Evaluation of whether diabetes status (T2DM) and pre-diabetes, compared with normal glucose tolerance, is associated with increased tau accumulation in the brain.	January, 2017	April, 2017
NCT02460783	Intermittent Calorie Restriction, Insulin Resistance, and Biomarkers of Brain Function	National Institute on Aging (NIA)	Compare two forms of diet and their effects on insulin resistance and the brain, weight and brain chemicals associated with AD	May, 2015	February, 2017
NCT02409238	Insulin Resistance and Mild Cognitive Impairment (IRMCI) Study (IRMCI)	SingHealth Polyclinics	Evaluating the cognitive effects of reducing insulin resistance using Intensive Lifestyle Modification (exercise and weight loss) with Metformin in pre-diabetic and diabetic individuals with mild cognitive impairment. (MCI)	March, 2015	March, 2016
NCT03140865	Wake Forest Alzheimer's Disease Clinical Core (ADCC)	Wake Forest University Health Sciences	Evaluation of whether glucose and insulin regulation reduces amyloid burden and toxicity while directly enhancing synaptic health, brain metabolism, tau regulation and neurovascular function	December, 2014	May, 2017
NCT02463084	Macronutrient Effects on Alzheimer's Disease (MEAL-2) (MEAL-2)	Wake Forest University Health Sciences	Study compares the effect of a diet high in saturated fat (SF) on memory and other cognitive functions, MRI measures of brain structure, function, and perfusion as well as insulin, lipids, cortisol, and glucose in middle aged adults with normal cognition or mild cognitive impairment	December, 2014	April, 2017

hyper-methylation. Future research on dietary ketosis and neurological degeneration should focus on the metabolome: activation of the AMPK pathway, SIRT1 expression, amplification of the role of microRNAs to reduce the biosynthesis of mis-folded amyloid protein, reactivation of the insulin degrading enzyme and improvement in global methylation (Blã¡zquez et al., 2014; Mullins et al., 2017; Gibas and Gibas, 2017).

Ethics committee approval and informed consent

Human subjects were not involved in the review; therefore, ethics committee approval and informed consent were not necessary.

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All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept. There is only one author for this review: Dr. Kelly J. Gibas.

Declaration of conflicting interests

The Author declares that there is no conflict of interest.

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The author exclusively prepared this review.

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