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Review Article

The Starving Brain: Overfed Meets Undernourished in the Pathology of Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD)

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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.

Keywords: Alzheimer's disease; Type 2 diabetes; Insulin resistance; Inverse warburg effect

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

Introduction

A starving brain

Diabetes is estimated to affect 382 million people worldwide and expected to surpass 600 million by 2035 [1]. 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) [2]. 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

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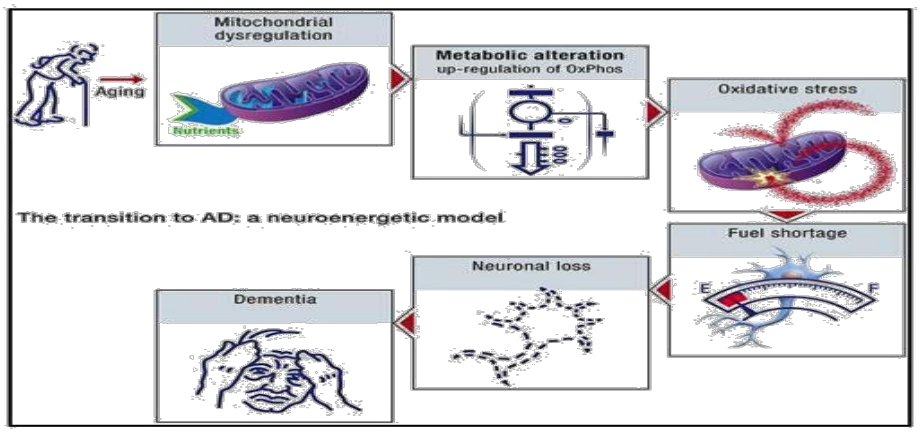

Figure 1: According to research by Demetrius, et al. [2015], 81% of people with late-onset, cognitive decline have prediabetes or diabetes supporting to a neuroenergetic model of gradual cognitive decline which occurs on a spectrum linear to cerebral metabolic alterations [6].

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" [3].

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 hyper-activation 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 [4].

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 [5]. 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 [6]. 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 [6]. 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 [6]. The brain is not immune to cycles of starvation (Figure 1).

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 [7]. Furthermore, research shows that impairment in cerebral glucose metabolism, in 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 [8]. Thus, resting state metabolic reductions in the brain, confirmed *via*

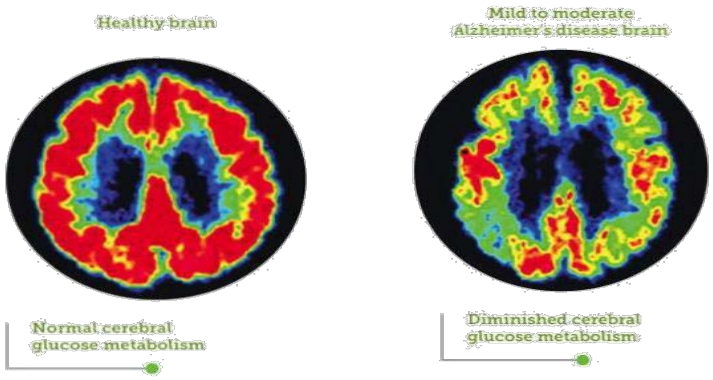

Figure 2: The healthy brain on the left shows strong glucose availability and metabolism, while the impaired brain on the right reflects the characteristic hypometabolic state induced by insulin resistance initiated in the peripheral tissues leading to excess insulin and declining glucose transport across the BBB. Research shows hypometabolism reflects a spectrum starting decades before the clinical diagnosis of cognitve decline [7].

PET, are a proxy for neuronal activity (Figure 2).

The neuroenergetic model, as hypothesized by Demetrius & 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" [6]. 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).

Cross talk between hypothalamus and gluts

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 [7]. 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 [7]. 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 energy for neurons, similar to the intracellular utilization of anaerobic glycolysis (Cori Cycle) by peripheral tissue [9]. 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 [10].

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 [10]. Neurons are not insulin-dependent; however, they are insulin-responsive [10]. 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 [11]. Insulin is concentrated to levels 50 × higher than in circulating plasma independently of peripheral hormone status [12-14]. 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 [2].

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

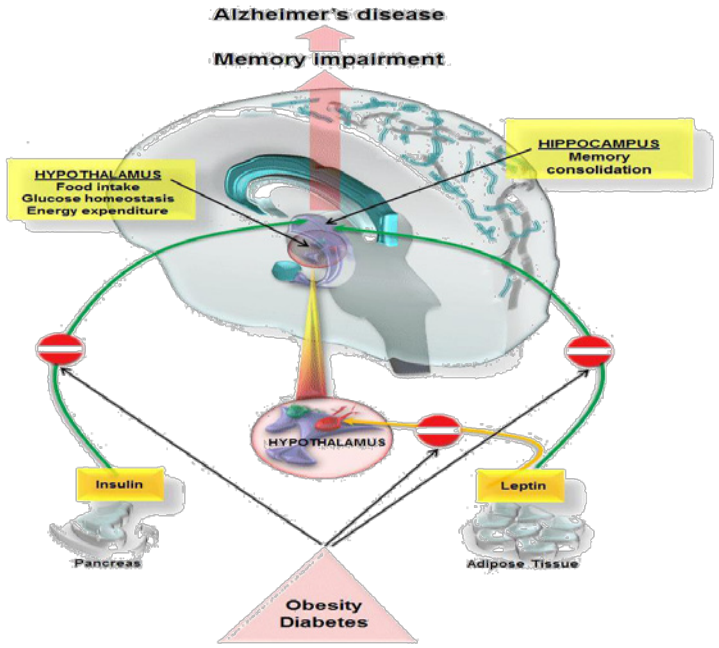

Figure 3: The hypothalamus is positioned as control center for both peripheral and cerebral glucose metabolism *via* a negative feedback loop; as shown by the red circles, peripheral insulin resistance impairs proper "fed" signaling between the cell- hypothalamus-pancreas resulting in the chronic over-release 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 [17].

in glucose-sensing *via* intracellular insulin receptors [10]. 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 [15]. 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 [10].

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 [6]. 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 [16] (Figure 3).

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 [16]. 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 [16]. 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 [6].

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) [18]. 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 [18].

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 [18]. 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 [2]. 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 [19]. 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 [18]. 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 [4].

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 [16]. 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 [15]. Cumulative evidence reveals that cerebral hypometabolism is evident in the affected brain regions of AD where mitochondrial structure is altered [16]. 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 [18, 19]. 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 [16].

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 [16]. The mTOR complexes modulate nutrient availability with cell growth and proliferation, promoting protein synthesis and inhibiting autophagy [16]. 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 [16,20]. 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 [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 [16].

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 [15]. 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 [15]. 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 [21-23]. Furthermore, elevated lactate is associated with high interstitial Aβ, which assembles into Aβ oligomers [4]. Mullins, et al. [2017] suggests 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 [15].

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 [10]. 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 [2]. 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 [15]. 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) [2]. 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 [10].

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 [6,10]. 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 [24]. 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 [15].

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 [25]. 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 [26]. This vital crosstalk ensures the ability of the brain to respond accurately to variable energy demands and controls cerebral glucose homeostasis [26,27]. Circulating insulin and glucose concentrations regulate the endothelial GLUT1 protein concentrations. A study by Cornford & 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 [27]. 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 [15]. 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 [15]. 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 [15]. 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 [6,10,13], deficits in cerebral

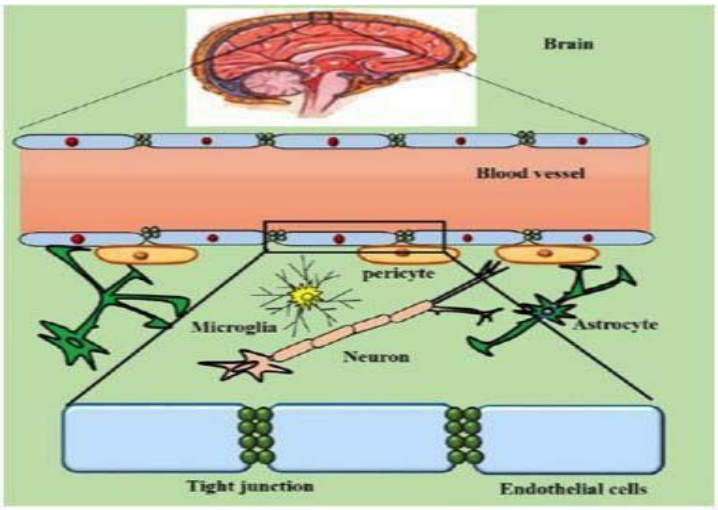

Figure 4: Research shows an early indicator of cerebral hypometabolism is the chronic up-regulation of brain-side (abluminal) GLUT1 transporters with corresponding down-regulation of blood-side (luminal); increased insulin and decreased glucose cross the BBB resulting in ensuing insulin resistance of 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 [29].

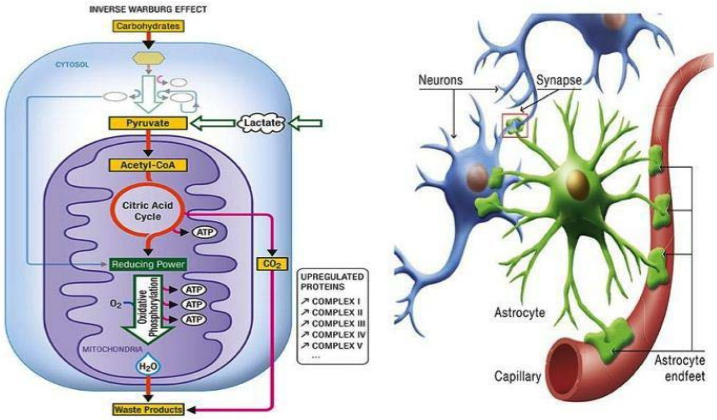

Figure 5: Shown on the left, during sustained glucose shortages, neurons lack the glycolytic enzymes to rely on an intra-cellular lacate production similar to the peripheral Cori Cycle, thus they depend on lactate shuttling by astrocytes. The starving neurons up-regulate the oxidation of lactate with 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 [6].

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 [6,10,28] (Figure 4).

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 [30]. 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 [10]. Neurons, unlike peripheral cells, are unable to up-regulate intracellular, non-oxidative respiration and instead rely on metabolic coupling or lactate shuttling [31]. 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 [10]. 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 [32] (Figure 5).

Depicted on the right, lactate, synthesized by glycogen stored

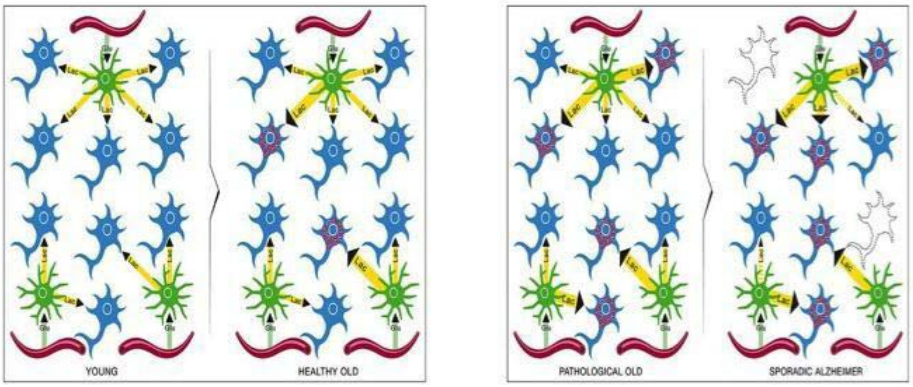

Figure 6: The aging brain naturally increases its production of lactate; however, in the chronic hypometabolic brain, lactate shuttling by astrocytes increases due to sustained deficits in glucose delivery across the BBB with co-occurring insulin resistance in hypothalamic GLUT4 transporters. This results 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) [6].

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 [6].

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 [15]. 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 [10]. Neuro-protection has been defined as interventions that prevent the death of vulnerable neurons and slow disease progression [10]. 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 [19].

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 [6,19]. 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 [6]. Sustained energy shortages foster catabolic degeneration of healthy neurons due to their selective disadvantage [6] (Figure 6).

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 [15]. 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 [15], adults with pre-diabetes/T2D [33], and those at higher risk for AD due to parental history [34]. 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 [34]. 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 [7,34].

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 [2]. 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, inherent to beta-oxidation, is activated by reductions in fasting/post-prandial insulin levels with

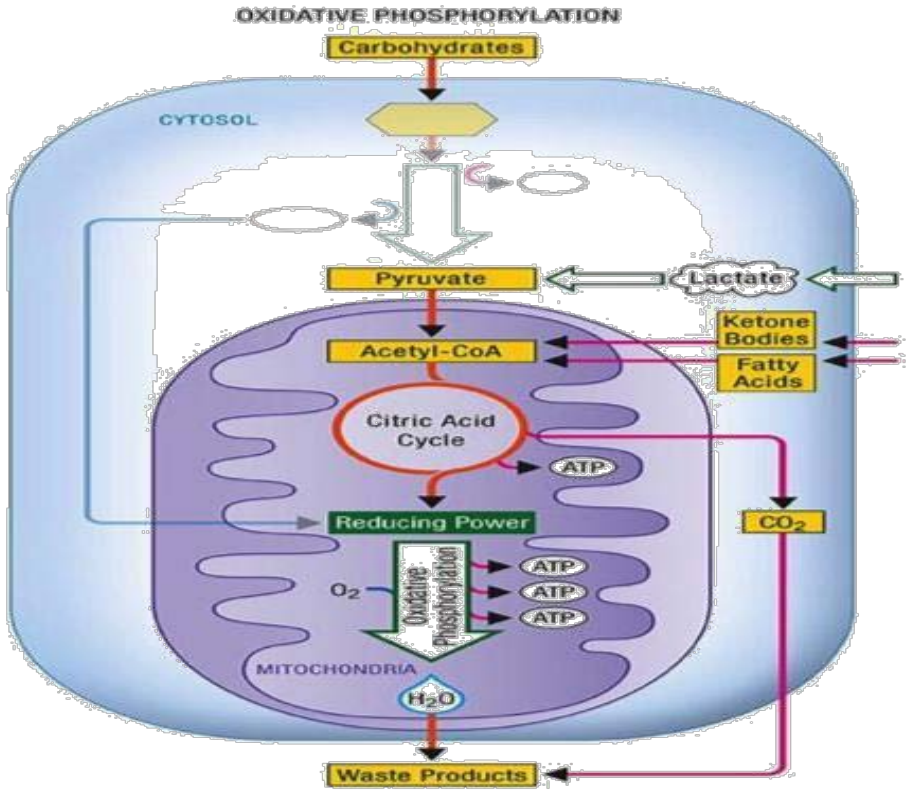

Figure 7: As noted in the above figure, fatty acids can be metabolized in the liver into ketone bodies, which are carried in the blood in the form of β-hydroxybutyrate; ketones metabolize intra-mitochondrial into two molecules of acetyl coenzyme A, which enter the TCA cycle directly. Beta-oxidation, 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 [6].

a corresponding reset in homeostatic signaling between insulin and glucagon [2]. 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 [2] (Figure 7).

Dietary Ketosis is known to regulate signaling impairments and normalize the recruitment and expression of GLUT transport by restoring metabolic flexibility [2]. 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 [15]. 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 [13,2].

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Authorship Statement

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.

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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