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BRAIN METABOLISM AND ALZHEIMER'S DISEASE: THE PROSPECT OF A METABOLITE-BASED THERAPY

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Abstract: The brain is one of the most energy-demanding organs in the body. It has evolved intricate metabolic networks to fulfill this need and utilizes a variety of substrates to generate ATP, the universal energy currency. Any disruption in the supply of energy results in various abnormalities including Alzheimer's disease (AD), a condition with markedly diminished cognitive ability. Astrocytes are an important participant in maintaining the cerebral ATP budget. However, under oxidative stress induced by numerous factors including aluminum toxicity, the ability of astroctyes to generate ATP is impaired due to dysfunctional mitochondria. This leads to globular, glycolytic, lipogenic and ATP-deficient astrocytes, cerebral characteristics common in AD patients. The reversal of these perturbations by such natural metabolites as pyruvate, α-ketoglutarate, acetoacetate and L-carnitine provides valuable therapeutic cues against AD.

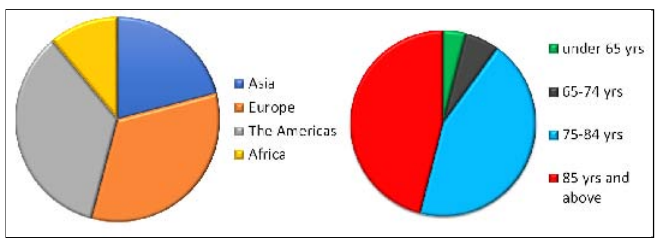
Key words: Alzheimer's disease, metabolism, mitochondria, energy, ketoacid therapy.

Introduction

Alzheimer's disease (AD) is the most common type of dementia and is characterized by disruptions in the functioning of the brain. In individuals over the age of 60, the incidence of this disease is higher than that of stroke, musculoskeletal disorders, cardiovascular complications and cancer (1). Nearly 20-30 million people worldwide, suffer from this disorder and it seems to affect individuals irrespective of geographical location, social status, and years of schooling (2). Diagnosis of AD involves biomarkers using brain imaging techniques and protein analysis in the cerebrospinal fluid (2). AD is characterized by perturbations in cerebral functions resulting from a number of interrelated biochemical events within the brain. These cerebral dysfunctions culminate in difficulties processing new information, completing familiar tasks, confusion, withdrawal from social activities, memory loss and changes in personality (3). Although no unique causative factor of AD has yet been identified, several hallmark events have been found to be highly correlated with the occurrence of this disorder such as ApoE, β amyloid oligomers accumulation, and defective tau proteins (4).

Genetic factors modulating the encoding of apolipoprotein E (APOE) have been shown to play a role in the pathogenesis of sporadic AD as this protein that is produced by astrocytes, is pivotal in the shuttling of cholesterol in the neurons (5). Variants of the gene responsible for the insulin-degrading enzyme (IDE) that plays a role in the degradation of β amyloid, may also predispose individuals to the disease. Accumulation of β amyloid oligomers has been linked to alteration in glutamate receptors, mitochondrial dysfunction and disturbance in signaling pathways related to synaptic plasticity which may accelerate the cognitive decline (6). Mutations in presenilin genes are also associated with the early onset of AD. Presenilin-2 is important in the processing of amyloid precursor protein (APP), which in turn is essential for neural development. Thus, mutations in presenilin genes lead to a pronounced deficiency in neurogenesis (7).

Figure 1
AD distribution according to countries and age groups.
(Adapted from (2))



Metabolomic studies on cerebrospinal fluid of patients with AD have revealed elevated levels of methionine (MET), 5-hydroxyindoleacetic acid (5-HIAAA), vanillylmandelic acid and xanthosine (8). Additionally, alterations in tryptophan, MET and purine metabolic pathways have been observed in patients with AD (9). These metabolomic changes were subsequently shown to be linked to abnormal tau metabolism, a known hallmark of AD (10). Tau proteins are crucial for the stabilization of microtubules and are abundant in the neurons (11). Indeed, studies examining central metabolism in relation to AD have uncovered disturbances in glycolytic glucose breakdown, pyruvate oxidation as well as excessive protein degradation in the brain which are hypothesized to ensue from abnormality in intracellular glucose homeostasis mediated by a deficiency at the insulin/insulin receptor level in neurons (12,13). Calcium is an important intracellular messenger within the brain, essential for neuronal development, synaptic transmission, plasticity as well as regulation of metabolic pathways. Homeostasis of this moiety has been shown to be

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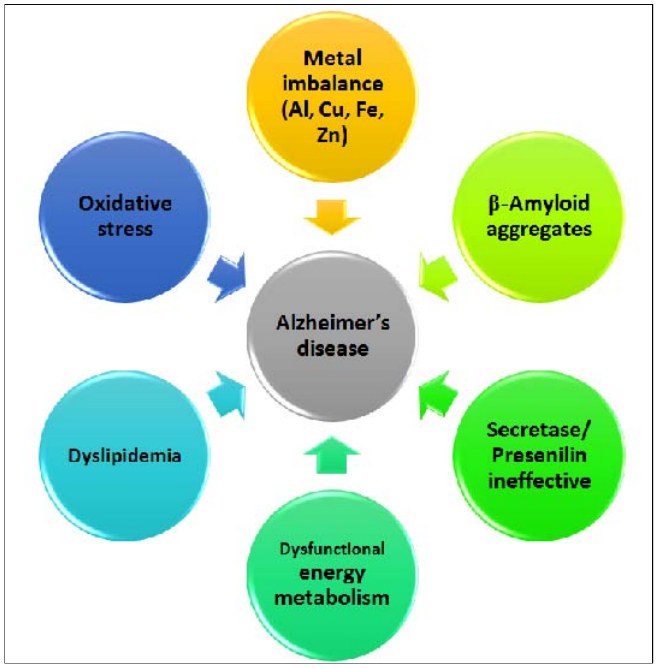
perturbed during AD pathogenesis (14). The associations between Ca homeostasis disruption and other molecular indicators of AD such as neurofibrillary tangles and β amyloid deregulation have been reported. (15). This perturbation in Ca affects organellar communication and results in decreased energy production and consequently deficits in brain function (16). The levels of both acetylcholine and the corresponding receptors are diminished in patients with AD. Oxidative stress triggered by a variety of conditions including metal toxicity, abnormal superoxide dismutase (SOD), a superoxide scavenging enzyme and a leaking mitochondrion, the cellular-energy machine, is also known to contribute to AD (17) (Figure 2).

Figure 2

Biochemical dysfunctions known to be associated with AD

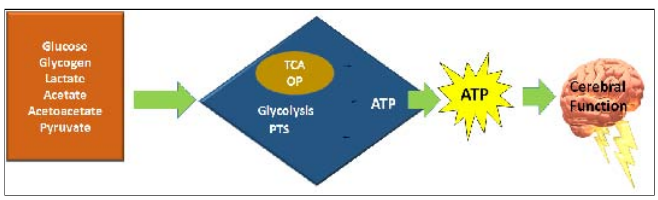


Fulfilling cerebral energy demand: role of key players

Although the brain accounts for only 2% of the body's mass, it consumes about 20% of its energy reserves and up to 50% of the available arterial blood depending on activity and need (18). Indeed, a major portion of the energy consumption fuels the processes of neurotransmitter production/recycling, vesicular trafficking, maintenance of ion gradients for the propagation of action potentials and memory (19). The neurons as well as neuroglia, in particular astrocytes, are the key users of this energy. Astrocytes play a very important role in providing structural and nutritional support to neurons via the neuron-astrocyte nutrient shuttle. Astrocytes which outnumber neurons by a factor of 10:1 form the bricks of the brain by interacting with the vascular endothelia and neurons (20). Additionally, astrocytes are key modulators of the blood brain barrier. As individuals age, the primary source of energy shifts from solely glucose to a wide variety of metabolites including lactate, acetate and ketone bodies which support neurons in their cellular functions (21). Glucose, stored as glycogen, is broken down to pyruvate which is metabolized to lactate using lactate dehydrogenase (LDH) and nicotinamide adenine dinucleotide (NAD). This lactate may be funneled to the neurons using the astrocyte neuron lactate shuttle (ANLS) (22). It can then be converted into pyruvate and NADH, a process mediated by NAD and LDH. We have recently reported the presence of a mitochondrial LDH in astrocytes that can play a key role in ATP production and antioxidant defense (22) (Figure 3). The majority of the energy of the brain (~ 90%) is generated in the mitochondria via oxidative phosphorylation. The production of adenosine triphosphate (ATP), the universal energy currency, necessitates the formation of reactive oxygen species (ROS) that are nullified with the aid of a plethora of antioxidative tools such as superoxide dismutase (23, 24). Dysfunctional mitochondrial activity can also be a cause of AD (25). Although both the neurons and astrocytes participate in energy-requiring tasks in the brain, the neurons are by far the major consumer of ATP. In fact, 80% of the brain's energy budget is attributed to these specialized cells (26).

Figure 3

The process of ATP production by astrocytes (TCA: Tricarboxylic acid cycle, PTS: Phospho -transfer system, OP: Oxidative phosphorylation)



A down regulation of energy metabolism has been observed both in early as well as progressive stages of AD due to oxidative damage to the mitochondria. Nutritional studies on patients with AD have revealed greater promise of meeting the energy consumption deficit by providing patients with energy dense foods (27). Studies of glucose metabolism in neurons and glial cells have shown very early metabolic changes in patients with AD, although the exact mechanisms of such impairments have yet to be determined (28). Thus, the importance of astrocytic function and energy homeostasis cannot be ignored in the proper functioning of neurons and consequently the brain.

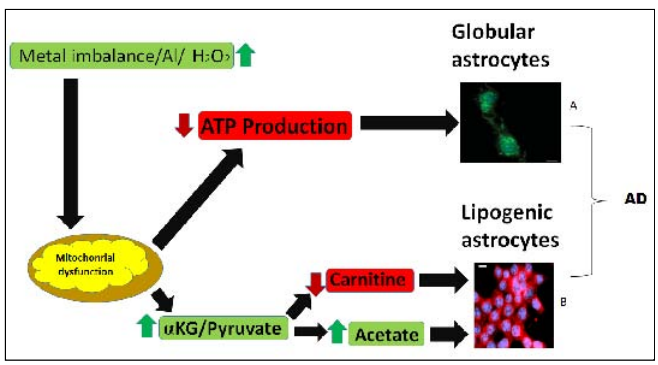
Aluminum toxicity, oxidative mitochondrial dysfunction and AD

In trace amounts, numerous metals are known to be essential for most biological systems; however, in elevated amounts all

metals are toxic. The toxicity of metals is usually mediated by their ability to generate an oxidative environment, bind to essential biomolecules and interfere with metalloproteins (29). While Copper (Cu), Iron (Fe) and Zinc (Zn) are essential, their elevated concentrations result in an intracellular oxidative environment that is not conducive to mitochondrial energy production (30). Aluminum (Al), on the other hand, has no known biological function and has been shown to be increased in the brains of patients with AD. Its enhanced bioavailability triggered by industrialization and its widespread occurrence in our daily products, has become a cause of concern due to its negative influence on all life forms (32). Although the role of Al in the pathogenesis of AD has not been fully elucidated, the ability of this metal to interfere with Fe-containing proteins is a key feature that endows Al its toxic attribute. Indeed, in the presence of Al., the intracellular levels of free Fe increase with the concomitant production of ROS. In fact, abnormal levels of free Fe have been found in patients with a number of neurodegenerative disorders including AD and have been attributed to Al. These ROS are responsible for numerous aberrant biological reactions that culminate in disease conditions (33, 34).

Figure 4

Oxidative stress and biochemical processes involved in the pathogenesis of AD. Red= decrease in levels, green= increase in levels. Inset: A) Astrocytes stained with Hoestch (nucleus= blue) and FITC-Phalloidin (actin= green). B) Astrocytes stained with Hoestch (nucleus= blue) and Oil red-O (lipids= red). Microscopy was performed at 60X ocular objective. Scale bar= 10μm. Figure adapted from (30)



Astrocytes are important constituents of the brain and outnumber the neurons by numerous folds. They participate in a variety of key functions that enable a complex organ like the brain to perform its task effectively. They provide structural support, help the neurons in their energy needs, clear neurotransmitters like glutamate and contribute to the production of lipids, a major component of the brain (35). Hence, any perturbation in astrocytic function has major implications in cerebral performance. Indeed, as a consequence of Al and oxidative stress, the astrocyte undergoes marked biochemical alterations that affect the brain's ability to execute various tasks. These eventually lead to neurological disorders. The morphology of astrocytes are severely affected by Al. Astrocytes rely heavily on their philopodia for their functioning in term of brain scaffolding as well as nutrient exchange (35). The decreased production of ATP due to the down regulation of energy metabolism results in the loss of cellular morphology. Indeed, cellular as well as mitochondrial morphology is known to be abnormal in patients with AD (36, 37). In this instance, the cells are globular instead of normal star-like shaped. It is unable to form filamentous cytoskeletons. Prolifin-2, which is a vital component mediating the polymerization of actin, is also low under Al stress. The decreased ATP production coupled with diminished activity of prolifin-2 acts in tandem to render astrocytes ineffective when exposed to Al and oxidative stress (32).

The morphological changes triggered by ROS are compounded by a shift in mitochondrial metabolism geared towards the production of the antioxidants NADPH and ketoacids. An elevated amount of both pyruvate and α-ketoglutarate has been reported in astrocytes subjected to hydrogen peroxide (H_2O_2) and Al respectively (24, 30). A switch to ICDH-NADP dependent metabolism affords NADPH and αKG. The latter detoxifies ROS with the concomitant formation of succinate (38). This dicarboxylic acid signals the activation of metabolic processes reflective of anaerobiosis via the stabilization of hypoxia inducible factor 1-α (HIF1α) (39). The presence of mitochondrial LDH in astrocytes is a potent tool to produce pyruvate. This ketoacid can readily fuel the TCA cycle and helps in the synthesis of ATP when O_2 supply is adequate. However, under ROS stress, pyruvate can nullify these toxic moieties, a reaction that liberates acetate. The latter may subsequently be channeled towards lipid synthesis. Indeed, ROS-exposed astrocytes are highly lipogenic and ineffective in performing β oxidation, a metabolic network dedicated to the catabolism of lipids (40). The channeling of αKG to quell oxidative stress is known to further arrest lipid degradation (41).

L-carnitine, which is essential for shuttling lipids into the mitochondria, is synthesized with the aid of αKG. This is a multi-step enzymatic pathway which relies heavily on αKG as a cofactor. Specifically, the enzyme butyrobetaine dioxygenase (BBDOX), which depends directly on αKG, is down regulated under Al and ROS stress. This decreased activity of BBDOX is accompanied by lowered L-carnitine levels and disrupts lipid homeostasis. The net effect of this metabolic adjustment is decreased lipid oxidation resulting in diminished ATP synthesis and increased lipogenesis (i.e. fat accumulation) (42,43). Irregular lipid accretion is a common occurrence in the pathogenesis of AD. Studies on animals have revealed that disruptions causing chronic energy imbalance like in diabetic situations are conducive to accelerated cognitive aging and AD. Under duress of Al accumulation and toxicity as well as the ensuing oxidative stress, the homeostasis between lipid

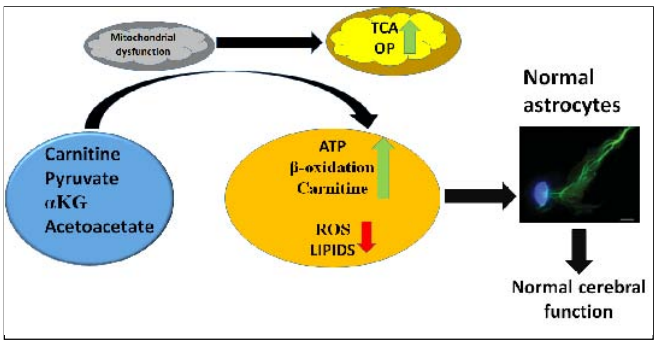
production and degradation are markedly perturbed (44,45). The metabolic shift triggered by the Al-induced oxidative environment results in the enhanced production of NADPH and lipids with the concomitant reduction in mitochondrial ATP production. The channeling of ketoacids in combating ROS leads to a diminution of L-carnitine, a crucial ingredient in the conversion of lipids into ATP. These molecular disruptions caused by Al and ROS provide therapeutical cues against AD and inform efforts how to manipulate metabolism in order to remedy this disease (Figure 4).

A metabolite-based therapy for AD

Current therapies for treating AD are aimed at gene therapy in an effort to prevent the accumulation of β amyloid oligomers, as well as tau protein. Supplementation of acetylcholine-esterase inhibitors like donepezil helps diminish the elevated levels of glutamate in AD patients (46,47,48,49). Additionally, high energy nutritional medication aimed at improving the energy deficits commonly observed in AD is also employed. Intake of α-lipoic acid to combat the oxidative stress and promote neuronal energy production is also recommended (50,51). As ketoacids and L-carnitine have been shown to reverse the mitochondrial dysfunction evoked by these toxins, these metabolites are potentially excellent candidates to remedy AD (52). As the dyslipidemia observed in astrocytes due to Al toxicity has been shown to be arrested by ketoacids, supplementation with pyruvate, acetoacetate and αKG may aid in the alleviation of the symptoms associated with AD (53,54,55). These natural metabolites are relatively inexpensive and may be devoid of any side-effects associated with pharmaceutical products. Their antioxidant attributes coupled with the ability to fuel the mitochondria will have a net positive effect on this energy-making machine. The diminution of oxidative tension and the generation of ATP will allow the brain to improve its performance since the astrocytes will be able to assist the neurons in their cognitive function (56,57). Furthermore, αKG will promote the synthesis of L-carnitine, a natural amino acid pivotal for the effective metabolism of fatty acids into ATP. These three-pronged benefits inherent in ketoacids that involve the reduction of ROS, production of L-carnitine and charging of the mitochondria with appropriate fuels will increase ATP production, a factor at the root cause of AD (40). Ketoacids have been utilized in remedying renal dysfunction, muscle fatigue, heart defects and burns (58,59,60). In a more recent example, L-arginine's positive effects on supplementation of energy expenditure regardless of age, previous incidence of diseases or activity shows promise as a metabolite therapy (61). The ketoacids like αKG and ornithine alpha-ketoglutarate, a precursor of amino acids such as glutamine, arginine and proline have shown to be effective modulators of muscle protein metabolism. They have also been reported to maintain muscle mass during aging. (62). Hence, following clinical trials, the approval of this metabolite-based therapy for AD may be relatively quick.

Figure 5

A suggestion for the metabolite-based therapy for AD. Inset: Fluorescence microscopy showing normal astrocytes- Hoestch (nucleus= blue) and FITC-Phalloidin (actin= green). Scale bar= 10μm. Figure adapted from 31



Conclusion

Alzheimer's disease, a neurodegenerative condition of the brain is a major health issue. It is expected to exacerbate due to an aging population in numerous countries. Although the exact causes and the underlying pathogenesis have yet to be unraveled, the incidence of this disease in humans, coupled with studies in model organisms and cellular systems have linked this disorder to the breakdown of mitochondrial functions. This disruption has been correlated with the generation of elevated levels of ROS as well as oxidized lipids, proteins and nucleic acids. These negative consequences that can be triggered by a variety of factors including metal toxicity result in metabolic shutdown of the main energy pathways such as the tricarboxylic acid cycle and the electron transport chain (ETC) as evidenced by the down regulation of key enzymes such as aconitase, αKGDH, Complex I, Complex II and Complex IV. Additionally, a pooling of pyruvate and αKG that has been observed, serves as antioxidants to combat oxidative stress. Production of L-carnitine is diminished due to the reduced availability of αKG for normal functioning as it is utilized in combating ROS. Owing to the lowered L-carnitine production, lipid catabolism is halted and as a result, high accumulation of lipids in the extracellular space has been observed, another hallmark of AD. Supplementing these cells with ketoacids, has been shown to result in reduced levels of ROS, as well as higher levels of L-carnitine, lower lipid levels and increased mitochondrial ATP production. A metabolite-based therapy aimed at reviving the mitochondria and ATP synthesis may prove to be a potent therapy against AD. Their natural occurrence, ready accessibility and limited side effects make them ideal therapeutic tools to combat AD. Hence, pyruvate, αKG, acetoacetate and L-carnitine may serve as prospective treatments against this neurodegenerative disorder.

Ethical Standards: All research presented complies with the current laws of the country.

Conflict of interest: The authors declare that there is no conflict of interests regarding the publication of this paper.

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