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Review

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Re-energising the brain: glucose metabolism, Tau protein and memory in ageing and dementia

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Abstract

Memory naturally declines as we age, but the rapid loss of memory can be distressing for people living with Alzheimer's disease (AD). How memories are formed and retrieved in the brain is not fully understood; it is thought to require plasticity to the synapses connecting neurons in a network of engram cells. Plasticity may occur either through changes to the volume and location of molecules and organelles within the synapse, or gross structural changes of synapses. Memory naturally declines as we age, as do many of the mechanisms required for learning and memory, such as changes in concentrations of the cytoskeletal structural protein Microtubule-Associated Protein Tau, reduced brain glucose metabolism, and sensitivities to insulin. The biggest risk factor for developing AD is ageing, yet only few studies try to reconcile the natural decline in functions we see with ageing with the dramatic impairment of these pathways in AD, such as Tau protein and energy homeostasis by neurons. This review will therefore explain the changes to metabolism, Tau protein, and memory impairment during ageing, and explore the latest research that links these processes to neurodegeneration seen in AD, and other Tauopathies. Understanding how ageing and dementia diverge may offer an important and underutilised avenue for therapeutic interventions to target metabolism in both "healthy" ageing and disease.

Keywords: Alzheimer's disease, Tau, ageing, metabolism, memory, glucose, lifestyle

INTRODUCTION

Ageing is the strongest risk factor for dementia[1,2]. Episodic memory and many cognitive functions are

known to decline progressively with ageing. Alzheimer's disease (AD)-related cognitive decline occurs more rapidly from a critical age than in healthy ageing, whereas vascular dementia, primarily associated with major stroke, causes a rapid then steady decline[3]. Numerous processes are known to be affected by ageing, including glucose metabolism, insulin resistance[4], inflammation (termed "Inflammageing")[5], protein translation[6,7], and protein concentrations such as that of AD-associated microtubule-associated protein Tau (Tau)[8,9].

As commonly quoted, despite accounting for 2% of body mass, the brain requires ~20% of the energy generated through oxidative metabolism[10]. Most of this energy is accounted for in regions of highly active neurons through synaptic function and restoration of neuronal membrane potentials[11]. Memory and problem-solving are therefore energetically expensive brain functions as they require temporally and spatially specific patterns of neuronal activity.

To understand how metabolism links to cognitive functions, it is important to know the pathways that neurons can use for energy. Neurons can perform the metabolism of glucose through mitochondrial oxidative phosphorylation (OXPHOS) or cytosolic aerobic glycolysis (nonoxidative metabolism of glucose despite the presence of abundant oxygen). OXPHOS is the most efficient pathway for producing energy in the form of 36 ATP, as compared to 2 ATP in aerobic glycolysis. A disadvantage of OXPHOS is associated with the free radical hypothesis, which suggests that reactive oxygen species from OXPHOS damage biomolecules and cause ageing[12,13]. Aerobic glycolysis has been shown to occur in neuronal somata to provide the energy required for neurons to function at rest or during neuronal activity, despite oxygen being available for OXPHOS[14,15]. Glycolysis is known to be required during high energy expenditure, such as long-term memory formation[16,17]. Traditionally, aerobic glycolysis was seen to compensate for the limited ATP production by rapid glucose metabolism. However, more recently, it is thought to produce metabolites for the building blocks of biosynthesis required for differentiation, and growth such as synaptic plasticity[18-20]. Neurovascular coupling allows neurons to control the vasodilation of blood vessels to maintain oxygen and glucose requirements. However, the limit of blood supply to the brain means that glucose stored as glycogen can also be metabolised for energy. Due to the storage of glycogen in astrocytes, the astrocyte-neuron lactate shuttle has been hypothesised. In response to glucose sensing, astrocytes can upregulate glycolysis into lactate, which can be shuttled from astrocytes to neurons. The use of this lactate is unknown, but it has been suggested to be metabolised through OXPHOS[21]. However, astrocytes also perform aerobic glycolysis, which is stimulated by glucose and glutamate uptake into astrocytes; this mechanism directly couples neuronal activity to aerobic glycolysis[22,23]. In addition, when blood glucose level is low, such as during intense exercise, fasting, or diabetes, ketone bodies can be metabolised for energy. Although controversial, "ketogenic diets" have been suggested for multiple neurological disorders and epilepsy, in particular to mimic fasting and reduce neuronal activity and lactate concentrations[24-26].

One hypothesis is that mitochondrial impairment may shift energy consumption from oxidative phosphorylation towards glycolysis or ketolysis[27]. Mitochondrial impairment, through numerous mechanisms, has been linked to many neurodegenerative conditions (for Review[28]). However, the shift towards aerobic glycolysis can be a cell proliferation process, or can occur in cancer in the presence of healthy mitochondria[29,30]. It therefore raises the question of how might alterations in energy metabolism influence memory impairment and pathology seen in neurodegeneration. This review will address two main aspects. First, it will delve into how metabolism may alter the function and homeostasis of Tau, a protein required for cytoskeletal structure[31], which has more recently been shown to bind with synaptic vesicles, mitochondria, and ribosomes[32]. In Taopathies such as AD and frontotemporal dementia, Tau forms pathological aggregates. Thus, understanding the links between metabolism and the physiological or

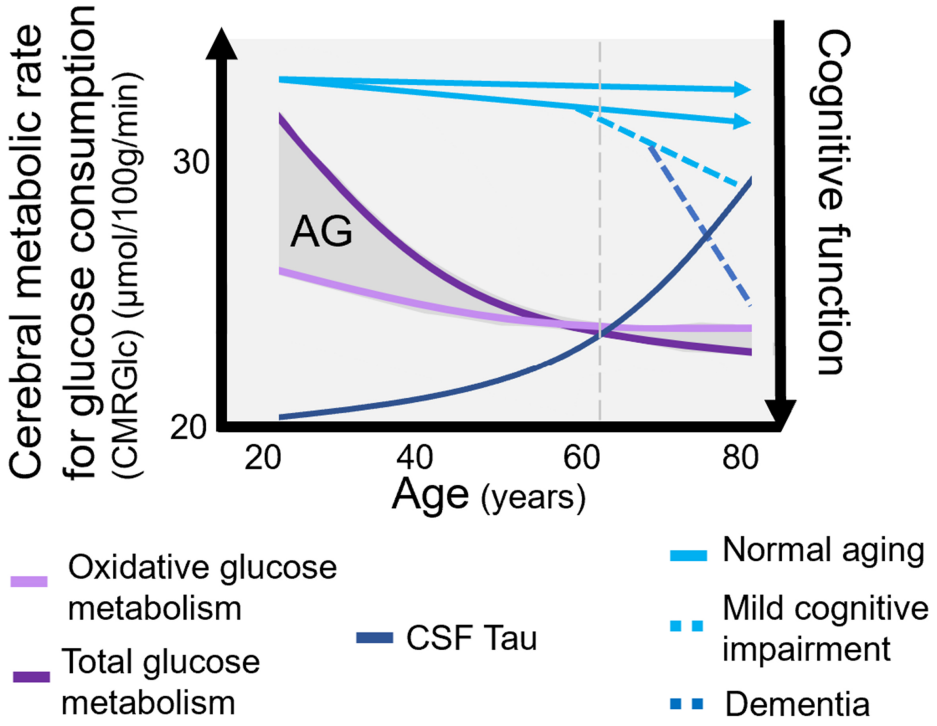

Figure 1. Glucose hypometabolism (purple; left axis) in the hippocampus has been shown to correlate with cognitive impairment (blue line; right axis) and can predict mild cognitive impairment and late-onset AD from age-related cognitive decline. Tau CSF concentration in AD is superimposed (dark blue) and has anatomical similarities to glucose hypometabolism, both of which can predict cognitive decline[3,33,39,40]. AG: Aerobic glycolysis; AD: Alzheimer's disease; CSF: cerebrospinal fluid.

pathological roles of Tau holds important therapeutic potential. Secondly, it will explore how metabolism and its influence on Tau protein can feed back to memory impairment. This review will therefore focus on how links established in the first aspect between metabolism and Tau could trigger the memory impairments observed in Tauopathies.

METABOLIC DEFICITS AND TAU PATHOLOGY

It has been debated whether Tau pathology causes metabolic deficits or metabolism can directly influence Tau pathology. During ageing, there is a progressive hypometabolism of glucose in the brain. Even greater glucose hypometabolism in the hippocampus can predict the progression to late-onset AD and mild cognitive impairment (MCI) compared with age-related cognitive impairment[33,34]. AD is characterised by decreased cortical[35] and hippocampal[33] glucose metabolism that is thought to reflect reduced synaptic activity[36]. Reduced cerebral glucose metabolism is also seen in young cognitively normal carriers of the late-onset genetic risk factor for AD, Apolipoprotein E4 (ApoE4). ApoE4 also exacerbates Tau-mediated pathology[37,38]. Figure 1 shows the relationship between glucose consumption and cognitive function with age; Tau Cerebrospinal fluid (CSF) concentration is superimposed[3,33,39,40]. In several studies, glucose hypometabolism follows a similar anatomical progression to the Braak stages of AD, and Tau pathology seen in Progressive Supranuclear Palsy and Corticobasal Degeneration[41-43]. However, it is noted that variations in the age of disease onset may have caused discrepancies between studies[44-47]. Furthermore, Tau pathology and glucose hypometabolism were shown to correlate with cognitive decline[48]. No correlation exists between amyloid-β pathology and cognitive impairments[49].

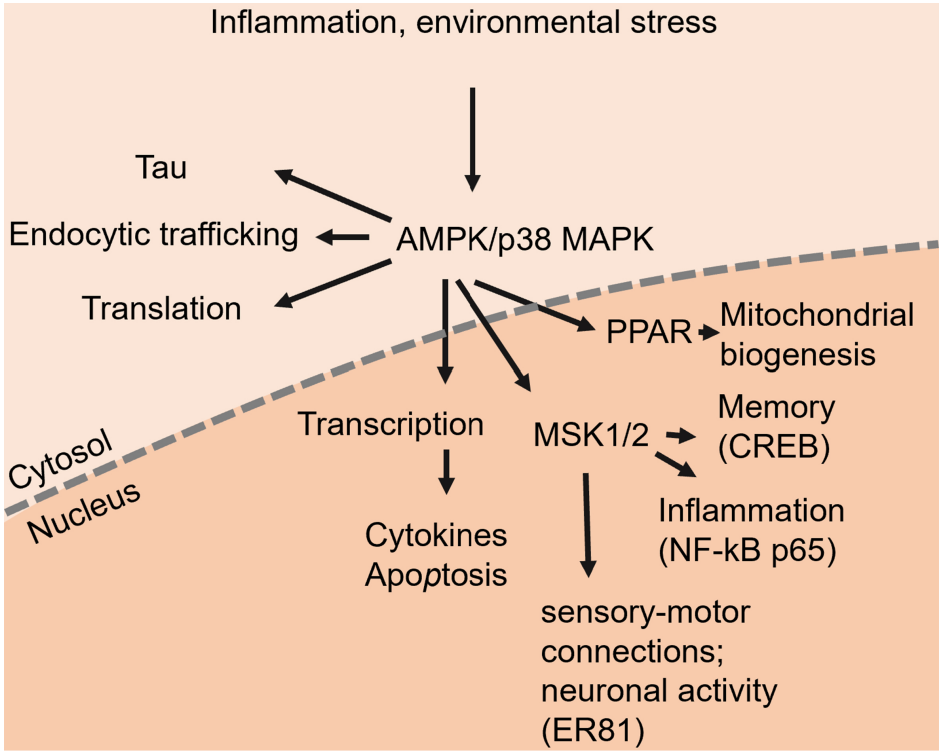

Figure 2. A direct link between environmental stress, such as low glucose availability, and Tau is known to occur through the AMPK/p38MAPK pathway[50,53]. This pathway has been targeted for therapeutics for use in AD[54]. AMPK: AMP-activated protein kinase; p38MAPK: P38 mitogen-activated protein kinase; PPAR: p38MAPK, Proliferator-activated receptor; MSK1/2: mitogen- and stress-activated protein kinase; CREB: cAMP response element-binding protein; ER81: Ets transcription factor; AD: Alzheimer's disease.

There is a direct link between glucose hypometabolism, or ischemia, and Tau pathology [Figure 2]. Glucose deprivation activates the environmental stress and inflammation sensing protein P38 mitogen-activated protein kinase (p38 MAPK), which phosphorylates Tau protein and can lead to hyperphosphorylation, loss of synaptic integrity, and ultimately cell apoptosis[50-53]. Agonists targeting a protein downstream of p38MAPK, Proliferator-activated receptor (PPAR)-δ/γ , are being investigated, but the efficacy cannot be determined as the recent phase 2 clinical trial was underpowered[54]. Reduced PPARδ and increased p-p38 MAPK were shown in rats with obesity, metabolic syndrome, and tissue hypertrophy, whereas increased PPAR activation can stimulate mitochondrial biogenesis and respiration[55,56].

METABOLIC DEFICITS: OXPHOS OR AEROBIC GLYCOLYSIS?

Different models of metabolic deficiency exist to explain protein pathology and memory impairment in AD. Models often refer to damaged mitochondria, or an imbalance between metabolism pathways due to limited oxygen supply. Models related to OXPHOS and aerobic glycolysis will be discussed.

Tau and OXPHOS

Numerous physical links between Tau and mitochondria have been made. Mutant Tau has been shown to impair mitochondrial axonal transport in AD mouse models and human induced pluripotent stem cells (iPSCs)[57,58]; human Tau (hTau) expression impairs mitochondrion fusion and fission in *Drosophila* and mouse neurons, and hTau mice[59,60]; hTau or mutant Tau reduces mitochondrial quality control through mitophagy in N2a cells and *C. elegans* neurons[61]; and mutant Tau directly reduces the mitochondrial membrane potential required for ATP-synthesis in triple transgenic mice[62], or iPSC-derived neurons from

people with Tau mutation causing frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17)[63].

The "inverse-Warburg effect" refers to a model based on the upregulation of glycolysis in the presence of oxygen (aerobic glycolysis) that occurs in cancer cells, known as the Warburg effect[29,64]. It is in part based on a negative correlation between the prevalence of cancer and AD[65,66]. However, the model suggests that upregulation of OXPHOS in neurons with impaired mitochondria to maintain adequate ATP levels leads to increased reactive oxygen species (ROS) and pathological ageing[64]. Mitochondrial impairment could occur from numerous factors including pathological proteins such as Tau, toxins, calorie surplus[67], or lipid metabolites[68]. In support of the model, although controversial, multiple studies suggest antioxidants, which reduce ROS, can have beneficial effects on Tau pathology and cognitive behavioural symptoms[69,70]. Antioxidant treatment increases lifespan and reduces hyperphosphorylated Tau, mitochondrial dysfunction, and oxidative stress induced in superoxide dismutase 2 knockout (SOD-/-) mice[71]. Conversely, OXPHOS downregulation has also been shown to occur in AD, with differences between OXPHOS gene regulation in MCI and AD, suggesting there may be changes to mitochondrial function as AD progresses[72-74].

ApoE4, required for forming complexes with lipids including cholesterol, is the strongest risk factor for late onset AD. ApoE4 reduces OXPHOS and increases aerobic glycolysis in astrocytes. ApoE4 causes lysosomal autophagic dysfunction, leading to damaged and high-ROS mitochondria accumulating in neurons[75].

It is therefore possible that any changes to OXPHOS regulation are not due to impaired mitochondria but instead to compensate for impaired aerobic glycolysis.

Tau and aerobic glycolysis

Whether aerobic glycolysis may be advantageous or detrimental to AD and Tau pathology is unclear. Lactate, a product of aerobic glycolysis, is known to be required for long-term memory and can potentiate NMDA receptor-mediated currents and induce transcription of synaptic plasticity-associated genes[16,76]. Lactate was also shown to be beneficial for memory function during normal ageing. However, increased lactate in APP/PS1 mice may indicate that impaired lactate processing pathways may contribute to cognitive decline in AD[77].

A shift from OXPHOS to aerobic glycolysis can be neuroprotective, leading to increased dendrite and axon growth in AD models[78], whereas reduced aerobic glycolysis has been linked to increased Tau deposition in preclinical AD[79]. In particular, glucagon-like peptide 1 (GLP-1), which shifts metabolism from OXPHOS to aerobic glycolysis, has been shown to increase cell viability during ischemia and hypoxia[80].

Increased aerobic glycolysis and impaired oxygen consumption occur in the brains of ApoE4 carriers[81-83]. This "Warburg like" endophenotype was shown to occur in young female ApoE4 carriers decades before AD symptom onset. Additionally, young female ApoE4 carriers showed decreases in resting energy expenditure and oxygen consumption, which was exaggerated following a dietary glucose challenge[81].

Aerobic glycolysis, which is associated with growth and development, gradually decreases with age, whereas mitochondrial OXPHOS remains relatively constant [Figure 1]. It is therefore possible that aged and impaired mitochondria in ApoE4 astrocytes could cause dramatic dysfunction later in life when the transition of metabolism in the brain shifts from aerobic glycolysis to OXPHOS.

METABOLISM AND TAU: THERAPEUTIC AVENUES AND LIFESTYLE INTERVENTIONS

Current therapeutics for AD do not target metabolism as a primary pathway, even though many lifestyle factors known to reduce the risk of AD inherently alter metabolism, such as diet and exercise.

Exercise

Exercise has been stated to reduce the risk, and improve symptoms of AD through improved blood flow, lactate production, and Brain-derived neurotrophic factor (BDNF) secretion[84]. In one study, "moderate" physical activity, but not "light" or "vigorous" physical activity, was shown to upregulate cerebral glucose metabolism in adults at risk for AD[85]. However, other studies have found the benefits of high-intensity interval training in ameliorating AD-like pathology through the regulation of astrocytes[86]. Another study linked low-volume intense interval exercise to AMPK and p38 MAPK signalling, and increased expression of PPARγ activator protein[87,88]. Whether aerobic or anaerobic/high-intensity interval training offers overlapping of different protective effects against AD remains unclear. However, although clear links between exercise and reduced cognitive decline have been shown, the connection between exercise and protein pathology in humans is less clear[89]. In rodent AD models, exercise has also been shown to ameliorate Tau hyperphosphorylation, oxidative damage, and cognition[90,91]. Tau phosphorylation also occurs due to obesity. For instance, a 20-week high-fat diet in wild-type rats caused abnormal Tau phosphorylation in the cortex and hippocampus. However, this aberration was mitigated and memory performance concurrently improved after 8 weeks of exercise[92]. Some studies suggest that longer and/or higher-intensity exercise is more efficient in reducing Tau levels[93,94].

Ketone body metabolism

Diet is another lifestyle factor that has been linked to AD. Intermittent fasting and caloric restriction, ketogenic diets, and Mediterranean diets (MedDiets) have been studied with varying results. Fasting and ketogenic diets cause ketone bodies to be metabolised in place of glucose. Although ketone body metabolism has been shown to improve memory in MCI and promote brain health[95-97], studies have suggested that this is dependent on ApoE genotype. Ketogenic agents were shown to improve cognition in ApoE3 but not ApoE4 carriers[98,99]. In a AD mouse model, a ketone ester diet was shown to alleviate psychiatric and cognitive symptoms, as well as reduce hyperphosphorylated Tau[100], or restore exploratory behaviour[101]. It has been suggested that ketone body metabolism can compensate for dysfunctional glucose metabolism, but ketone metabolism requires functional mitochondria and may be impacted as mitochondrial damage progresses[25].

Mediterranean diet

The MedDiet has been suggested to reduce cognitive decline and risk of AD[102,103]. Numerous factors within this diet contribute to these benefits, such as antioxidants and cereals[104]. A recent study has shown the benefits of the MedDiet, specifically noting that green leafy vegetables were linked to a reduction in AD pathology, whereas higher consumption of fried and fast foods was associated with increased Tau pathology[105]. The importance of the MedDiet is underscored by its ability to decrease the risk of dementia, independent of genetic predisposition[103]. Although MedDiets are associated with lower postmortem AD pathology, this effect primarily pertains to β-amyloid load[105].

Lactate and pyruvate

Furthermore, the question arises as to whether lactate or pyruvate could be used as a therapeutic intervention. The "lactate shuttle" hypothesis has changed our perception of lactate as a waste molecule to a signalling molecule. Although thus far, ROS produced from OXPHOS have been associated with free radicals causing ageing, another hypothesis suggests that lactate causes ROS bursts that are important for signalling survival pathways and ER chaperones[106]. Lactate has therefore been discussed as a potential

therapeutic avenue, and as the molecule responsible for the neuroprotective effects of exercise[107]. Some studies showed decreased CSF lactate in AD[108,109], whereas other studies suggest increased CSF lactate[110-112] or no change[113]. Liguori *et al.* (2015) found a negative correlation between CSF lactate and CSF Tau, with higher CSF lactate levels in mild compared to moderate-severe AD. They proposed a model in which Tau induces mitochondrial dysfunction, followed by impaired glycolytic metabolism. As Tau pathology advances in more severe AD cases, the increase in CSF lactate becomes less pronounced due to the greater impact on metabolism[112]. Similarly, Bonomi *et al.* (2021) identified a negative correlation between CSF lactate and Tau in AD, and suggested that low CSF lactate was "the advent" of Tau pathology[108]. Furthermore, elevated CSF lactate and cerebral Tau have been shown to co-occur following aneurysmal subarachnoid haemorrhage and are predictors of metabolic distress and poor long-term cognitive outcomes[114].

Pyruvate upregulation has also been suggested as a therapeutic avenue for dementia[115]. However, research outcomes regarding pyruvate levels in individuals with AD have been mixed, with some studies reporting increases[110,116] while others indicating decreases[117,118] in CSF. Systemic administration of pyruvate, but not lactate, has been demonstrated to mitigate ROS-induced pathology and improve spatial memory in a rat model of AD[119]. Conversely, in an AD mouse model, systemic pyruvate administration was found to increase glycogen stores and enhance spatial memory, yet it resulted in impaired performance in a passive avoidance task associated with fear memory. These paradoxical effects were attributed to pyruvate-induced heightened explorative behaviour[120]. Notably, pyruvate treatment has not exhibited reductions in Tau pathology, although there are limited studies investigating this relationship in AD[121] and investigating the differences observed in CSF lactate and pyruvate concentrations between several different studies.

CONCLUSION

This review has highlighted the importance of metabolism, and the changes to metabolism that occur inherently with ageing, and how these may exacerbate cognitive decline seen in dementia. Brain activity, particularly the activity-dependent functions required for learning and memory, functions at the limits of energy available to the brain both in terms of oxygen and glucose. Therefore, any perturbations, including damage to oxygen supply, genetics that decrease metabolic rate, or mitochondrial damage, can easily tip the balance into an energy deficit. Alongside the factors discussed in this review, gender is an important consideration in the onset of dementia. AD is known to be more prevalent in females; the reasons for this are unknown but may be due to hormones, or as has been suggested, women live longer but tend to be less physically active than men[122]. In addition, stress has been shown to cause divergent pathologies in the brains of male and female mice; furthermore, stress exerts a direct effect on metabolism, potentially to the extent that it can precipitate "stress-induced diabetes"[123,124].

This review has discussed how balances between OXPHOS and anaerobic glycolysis may impair normal brain function, but it provides limited discussion on ischemia. Ischemia is an important consideration as oxygen supply will determine the metabolic resources available during intensive neuronal activity. Tau protein is also known to be altered during ischemia events, such as stroke or cardiac arrest[125,126].

Metabolism and Tau pathology mutually influence the function of each other through the p38 MAPK pathway[50] and through the ability of Tau to alter mitochondria directly[57,61,62]. As such clear links are present between metabolism, cognitive dysfunction, and Tau pathology, OXPHOS and aerobic glycolysis are currently undervalued therapeutic avenues that could offer impactful treatment options for targeting Tau and amyloid-beta pathology alone. Metabolomics of dementia patients has been shown to reveal differences in disease-linked metabolites but has yet to be fully leveraged for diagnostic or treatment purposes[127-129].

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Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

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Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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