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Astrocyte glycolysis in Alzheimer's disease: when the stars burn out

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Alzheimer's disease (AD) is the most common form of dementia characterized pathologically by the deposition of amyloid plaques and hyperphosphorylated tau containing neurofibrillary tangles. The disease presents clinically with progressive memory loss and disruption of cognitive function. Currently, there is no cure for AD; recent advances in the therapeutics aimed at clearing the amyloid protein from the brain have led to potential disease stabilization, however, this does not prevent eventual disease progression (Cummings et al., 2024). The mechanisms that cause AD are complex and not fully understood. The main theories for disease development focus on the lack of clearance of amyloid or an increased accumulation of this protein. Changes to brain metabolism, genetic predispositions, inflammation, and the process of aging, all have roles in the establishment of the main sporadic form of the disease.

Astrocytes have a key role in maintaining the cellular homeostasis of the brain. They provide neurons with metabolic substrates, remove cell waste products, and have altered morphology and function in the presence of AD amyloid plaques. Their name comes from the original histological description of astrocytes as "star-shaped" cells. They are known to aid in the digestion of the amyloid protein and promote the removal of amyloid from the brain. Blood-based biomarker studies have also suggested that activation of astrocytes into an inflammatory phenotype is needed before people develop the cognitive deficits of AD (Bellaver et al., 2023). These cognitive deficits are closely aligned with the formation and spread of neurofibrillary tangles throughout the brain. The integral nature of the role of astrocytes in maintaining brain physiology, clearance of the amyloid protein, mediation of inflammation, and the obvious structural changes in the presence of amyloid, suggests they have a key role in the development of AD.

Almost all the functional roles an astrocyte performs, which may contribute to the development of AD, are processes that require the expenditure of energy and hence are metabolism-dependent. Astrocyte metabolic function needs to be maintained for the astrocyte to continue to provide brain homeostasis. If this "star-shaped" cell starts to burn through its energy resources in an abnormal or inefficient way, then this is likely to have consequences for the brain's overall function. We have recently shown that astrocytes derived from people living with sporadic and familial forms of AD have deficits in metabolic pathways including both mitochondrial function and glycolysis (Bell et al., 2024). These abnormalities were corrected by overexpression of one of the rate-limiting enzymes of glycolysis, hexokinase 1 (Bell et al., 2024). Additionally, the astrocyte metabolic deficits correlate with neuropsychological changes seen early in AD, suggesting that the metabolism of this cell type is important in determining the overall cognitive performance of the brain.

Therefore, astrocyte metabolism may have a key role in maintaining cognitive function through allowing the astrocyte to maintain brain physiology. Astrocyte metabolism, through its actions on brain homeostasis, may also be key in preventing the propagation of AD pathology throughout the brain. What are the consequences when our brain stars start burning out in AD? Can this be directly linked to cognitive function and potential disease progression?

We are not the first group to suggest the relationship between astrocyte metabolic function and cognitive performance. A recent study published in *Nature* outlined the importance of astrocytic adenosine A2B receptors in recognition memory in mouse models (wild-type and Adora2b$^{flox/flox}$) (Theparambil et al., 2024). Astrocyte adenosine A2B receptors are activated by neuronal adenosine release, which through the actions of the protein kinase A signaling pathway, activates astrocytic glycolysis. Blocking this receptor on the astrocytes impairs glucose upregulation, astrocyte lactate release, and memory tasks performed by the mouse. This paper links astrocyte glycolytic function directly with memory acquisition. Work in a separate mouse model has shown that neurotransmitters released by astrocytes [d-serine (a product of astrocyte glycolysis) and glutamate] are essential for the initial phase of memory acquisition and the development of long-term depression in certain brain areas (Koh et al., 2022). Glutamatergic release by astrocytes can modulate neuronal activity leading to long-term depression, but only certain types of astrocytes can release glutamate (Koh et al., 2022). These astrocytes are found in several places within the brain, including in the hippocampus. This has important implications for AD, considering that the hippocampus and medial temporal lobe are some of the first parts of the cortex to develop amyloid deposition. Other studies have suggested that the end metabolite of astrocyte glycolysis, lactate, may have a role in the development of long-term potentiation and memory storage. Suzuki et al. (2011) showed that although the glucose molecule itself is not important in the process of long-term potentiation formation, lactate is, and the blocking of lactate transporters on astrocytes in animal models prevents learning and memory. In summary, the above papers suggest that astrocyte glycolysis and its metabolites are important factors in the formation of memories in animal models. These animal model studies correlate with the findings of our work and that of others in human-derived astrocytes (Ryu et al., 2021). Therefore a clear hypothesis that dysfunctional astrocyte glycolysis could lead to cognitive impairment can be proposed.

As previously mentioned, amyloid deposition in the brain affects the function and structure of astrocytes and has been shown to reduce astrocyte metabolism. Astrocyte glycolysis increases after exposure to amyloid, but this increase is not sustained (Zyśk et al., 2023). Amyloid deposition alters astrocyte mitochondrial oxidative phosphorylation which an initial switch to glycolysis compensates for. Fatty acid oxidation is then relied upon in astrocytes as a compensatory metabolic pathway due to the amyloidogenic disruption to oxidative phosphorylation (Zyśk et al., 2023). Work in an animal model of AD (5×FAD mouse) further supports the idea that supplementing astrocyte glycolysis prevents the cognitive deficits that develop through the deposition of amyloid (Zheng et al., 2021). This again highlights the importance of astrocyte glycolysis in AD, and how correcting deficits in glycolytic pathway enzymes could ameliorate the effect of amyloid deposition on cognitive function.

Reactive astrocytes are seen in increased numbers in the AD brain, especially around amyloid plaques. This is thought to be part of the reason for the increased inflammatory environment within the brain as AD progresses. Potentially, reactive astrocytes upregulate glycolysis to allow their change shape (Xiong et al., 2022). Upregulation of glycolysis in reactive astrocytes may have both positive and negative effects on the AD brain, with further work needed to understand the complexity of this relationship (Xiong et al., 2022). It has been shown that to establish the inflammatory response in astrocytes, an intact glycolytic pathway is needed. The astrocyte inflammatory response is mediated in part by nuclear factor-kappa B (NF-κB), and without an intact glycolytic pathway in astrocytes, this response is muted (Robb et al., 2020). Interestingly, the activation of the NF-κB pathway in astrocytes has both positive and negative effects as well. Activation of the NF-κB signaling pathway in astrocytes promotes a mechanism in microglia that leads to amyloid clearance from the brain, with complete loss of astrocyte NF-κB signaling associated with the accumulation of both tau and amyloid (Jong Huat et al., 2024). Chronic activation of the NF-κB pathway however promotes a detrimental inflammatory response that can lead to neuronal senescence (Jong Huat et al., 2024). This suggests that if optimal regulation of astrocyte glycolysis and metabolism is not achieved, the inflammatory component of AD could be propagated through unregulated NF-κB pathway function. In human studies, reactive astrocytes are postulated to be key in the development of the cognitive decline seen after the deposition of tau starts. In a blood-based biomarker study of cognitively normal individuals with a positive amyloid signature, tau deposition only occurred when reactive astrocyte phenotypes were seen, which was identified by increased levels of glial fibrillary acidic protein within the blood (Bellaver et al., 2023).

Combined, the above studies highlight how dysfunctional astrocyte metabolism may both contribute to the development of the pathology characteristically seen in the AD brain, but also propagate this pathology once established. We have also highlighted the importance of astrocyte metabolism in memory maintenance in the non-AD brain. A large body of work investigating astrocyte metabolism and structural changes in AD focuses on either animal models or models derived from carriers of signal gene mutations. This has clearly developed our understanding of the metabolic component to astrocyte dysfunction in AD, but cannot inform us on how the presence of underlying metabolic deficits may contribute to disease progression. The use of patient tissue and various cellular reprogramming methods highlights complementary model systems which can help address this problem, and help to further our understanding of the sporadic form of AD. As age is a major contributing risk factor for the development of AD, semi-direct or direct reprogramming methods afford some potential advantages as many aging features are retained from the parental cells. These models allow for the identification or validation of therapeutic targets in patient-derived cells; the identification of the hexokinase 1 is an example of this. Amyloid and tau may be central to the pathology of AD, but the environment and conditions that allow the accumulation of these proteins, in sporadic AD at least, may be determined by metabolic resilience of the brain.

If metabolic failure is a key factor in the development of AD, the question remains as to why protein deposition changes are seen before metabolic failure occurs. This is evidenced in both human imaging studies and several animal

models. Potentially this question is answered by the fact that deficits in metabolic enzyme function or pathway expression are seen in AD but not completely lost (Ryu et al., 2021; Bell et al., 2024). The complex, interlinking mechanisms that allow glycolysis, oxidative phosphorylation, and other cellular metabolic pathways to compensate for deficits in a particular metabolic system, may also explain why these changes are seen later in the disease course. As described above, the disruption caused to mitochondrial oxidative phosphorylation by amyloid deposition is compensated for by glycolysis and fatty acid metabolism in animal models (Zyśk et al., 2023). This compensatory effect may hide already present metabolic pathway deficits until amyloid accumulation has exceeded a certain level. The progression of aging further accelerates dysfunctional metabolism which in turn leads to poorer clearance of amyloid protein. The accumulation of amyloid then leads to worsening metabolic failure which initiates a vicious cycle of brain damage (**Figure 1**). This manifests itself as changes in brain imaging markers of metabolism and eventually poorer cognitive performance. Development of metabolic failure in this way may be less important in familial forms of AD, which are thought to be driven primarily by protein accumulation. This may also in part explain why sporadic AD develops much later in life as aging, poorer metabolic function, and failure of amyloid clearance mechanisms are needed to allow protein deposition.

Future work needs to focus on understanding how hexokinase 1 deficits in astrocytes contribute to the development of amyloid deposition in AD, or how this deficit may propagate reactive astrogliosis. Potentially, glycolysis-related molecules could become a new therapeutic avenue for AD, although the complex interaction between metabolic systems within the brain would need to be considered during drug development. Delivery of such therapeutic agents would also need considerable thought, with enzymatic induction or replacement both being options.

Sporadic AD is complex, with multiple initiating disease processes leading to the pathological features of AD along with other factors which affect progression once the disease has begun. Our understanding of the role of amyloid accumulation has led to developments of protein treatment approaches which have provided hope to thousands of people with AD. Now, work must focus on understanding other pathogenic pathways which interact with amyloid, and investigating adjunct therapeutic targets to maximize the patient population benefiting from these advances.

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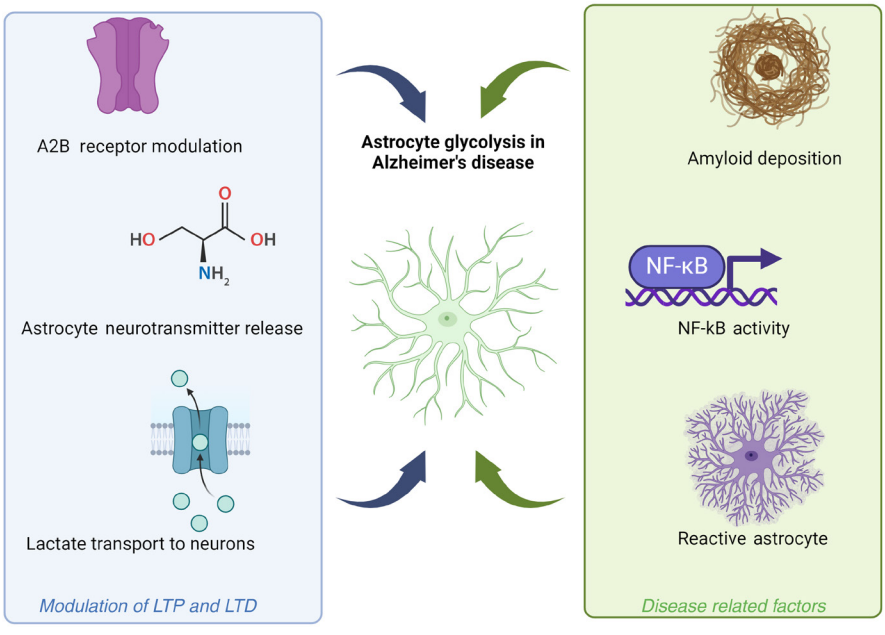

Figure 1 | **Astrocyte glycolysis in Alzheimer's disease.**
The main astrocyte-related factors are linked to both astrocyte glycolysis and memory formation (blue box) and factors that are more specific to Alzheimer's disease but contribute to the efficiency of glycolysis when Alzheimer's disease is established (green box). Created with BioRender.com. LTD: Long-term depression; LTP: long-term potentiation; NF-κB: nuclear factor-kappa B.

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