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Vulnerable Powerhouses: A Staged Model of Astrocytic Mitochondrial Failure and Energetic Buffering Collapse in Alzheimer's Disease

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Abstract

Alzheimer’s disease (AD) is defined biologically by amyloid-β and tau pathology, yet its earliest phases are marked by profound functional fragility, vascular dysfunction, and astrocytic mitochondrial stress. We propose that early AD can be interpreted as a progressive failure of astrocytic energetic buffering, determined primarily by a narrowing mitochondrial stability margin. Within this framework, astrocytes act as dynamic stabilizers of neural microdomains. They couple localized synaptic activity to glutamate clearance, potassium spatial buffering, and neurovascular signaling—processes that depend on specialized, compartmentalized mitochondrial ATP regeneration and calcium handling. We outline a four-stage model in which subclinical mitochondrial fragility precedes compensatory glycolytic overuse, lipid- and inflammation-linked reactive states, secondary amyloid/tau amplification, and eventual network decompensation. In this model, mitochondria are not merely collateral victims of AD pathology but are the central orchestrators of tissue recoverability.

Keywords: astrocytes; mitochondria; glycogen; lipid droplets; neurovascular coupling; mitochondrial transfer; Alzheimer’s disease; allostasis; recoverability

1. Introduction: Alzheimer’s disease as loss of energetic recoverability

Alzheimer’s disease (AD) pathology is conventionally organised around amyloid-β (Aβ) plaques and tau neurofibrillary tangles. These hallmarks remain central to biological diagnosis, biomarker classification and therapeutic development [1-4]. Yet amyloid pathology alone does not fully describe how early functional fragility within the AD brain arises, why some individuals tolerate substantial amyloid burden for long periods of time [3], or how metabolic and vascular changes interact with proteinopathy before overt dementia [5]. A complementary perspective is therefore needed: one that treats AD not only as a disease of protein accumulation, but also as a progressive loss of the physiological systems that normally keep neural activity recoverable.

Neuronal cells operate under fluctuating demand. Synaptic transmission, action potentials, glutamate recycling, ion restoration, calcium handling and local biosynthesis are all energetically costly, and their

costs vary rapidly across space and time [6,7]. Vascular delivery of oxygen and glucose is dynamically coupled to neural activity, but neurovascular coupling is mediated through multicellular signalling and hemodynamic responses that unfold on coarser spatial and temporal scales than the synaptic events they support [8,9]. The result is not a failure of vascular supply in healthy tissue, but a scale-matching problem: local demand can fluctuate faster and more locally than blood-derived substrate delivery can be adjusted. Crucially, imaging in awake mice models demonstrates that while initial hyperemic responses are driven by rapid direct neuronal signaling, astrocytes are required to dynamically amplify neurovascular coupling during sustained cortical activation, matching prolonged circuit demand to vascular supply [10].

This scale-matching issue must be accounted for to maintain cerebral homeostasis, a problem which the distinctive metabolic architecture of astrocytes is well positioned to solve. Namely, astrocytes store glycogen which can be mobilised during metabolic demand, and participate in glucose- and lipid-mediated astrocyte-neuron metabolic cooperation [11-15]. Glycogen is central to the present model as it provides a local reserve that can be rapidly mobilised when vascular supply is inefficiently fast, or when repeated activity imposes transient demand peaks. Astrocytes also contact synapses through fine perisynaptic astrocytic processes (PAPs) and blood vessels through endfeet, allowing them to participate in neurovascular coupling to provide longer-lasting metabolic support [8,16].

These metabolic processes occur throughout astrocyte morphology, in PAPs, end-feet and, in some contexts, gap-junction-coupled astrocytic networks. Effective buffering, therefore, requires the appropriate spatiotemporal delivery of metabolic support as well as adequate total energy production [17]. This point is strengthened by in silico multiscale modeling which indicates that astrocyte morphology constrains metabolic enzyme localisation, ATP delivery, and lactate export to neurons [18]. This also means AD-like morphological remodelling can impair the efficiency of local metabolic support, rather than merely reduce cell volume.

Astrocyte homeostatic roles, themselves, are energetically costly. Firstly, astrocytes are major mediators of extracellular glutamate clearance through transporters such as EAAT2/GLT-1 [19], a mechanism which synchronises local neural activity to astrocytic metabolic output given that glutamate uptake is coupled to Na^+/K^+-ATPase activity. Once internalised, glutamate can be oxidatively metabolised in the Tricarboxcyclic acid cycle (TCA cycle), effectively offsetting its own transport costs over longer operational timelines [20,21]. Secondly, astrocytes contribute to extracellular potassium homeostasis. As activity-dependent K^+ elevations alter neuronal excitability, this uptake and spatial redistribution of K^+ functions to stabilize local network activity [22].

In childhood extending into early adult life the metabolic demand of the brain is met with higher rates of aerobic glycolysis, but as the brain ages, and synaptic turnover and myelination dynamics change, the brain loses some of this capacity [23,24]. This reduction is particularly relevant in AD, where glucose hypometabolism often precedes overt clinical decline [25]. As astrocytes perform a substantial proportion of cerebral aerobic glycolysis [11,14], reduced glycolytic reserve likely compromises their ability to bridge the mismatch between local demand and vascular supply.

Astrocytic buffering therefore has two inseparable dimensions: matching metabolic support to fluctuating circuit demand, and absorbing the ionic and neurotransmitter consequences of that activity. We therefore propose that astrocytes can be viewed as energetic stabilisers of neural microdomains. Their role is not simply to provide fuel, but to preserve recoverability: the capacity of active circuits to absorb demand peaks, restore homeostatic balance, and return to a stable operating regime.

This Perspective develops a staged model in which early AD involves progressive failure of astrocytic energetic buffering which astrocyte mitochondrial oxidative function is a key orchestrator of. The model is deliberately complementary to amyloid and tau accounts. It does not deny the pathogenic importance of Aβ and tau; rather, it asks whether an earlier narrowing of the energetic margin between homeostatic failure

and success may make neural tissue more vulnerable to proteinopathy, and whether proteinopathy subsequently amplifies an already unstable astrocyte-neuron-vascular system.

To synthesize these dynamics, we begin by outlining our four-stage progression model, which moves from subclinical energetic fragility and allostatic compensation to secondary pathological amplification and self-sustaining network decompensation (summarized immediately below in Section 2 and Table 1), before unpacking the molecular and architectural constraints that drive these transitions.

2. A staged model of progressive astrocytic buffering failure

Within this framework, AD can be interpreted as the progressive breakdown of a system that initially remains functional because astrocytic buffering compensates for local energetic mismatch. We propose four stages.

Stage 1: Subclinical energetic fragility

The earliest stage is characterised by mild but persistent narrowing of the energetic margin which develops over long periods of time. On a systems level factors that are likely to affect astrocyte energetic buffering include aging, cardiovascular physiological changes (such as high blood pressure, high cholesterol, diabetes) and predisposed body-wide metabolic enzyme inefficiencies that lead to differing reserve capacities of enzyme systems. These system level factors are actuated on a cellular level through subtle mitochondrial inefficiencies, impaired mitochondrial localisation in PAPs or endfeet, weak glycogen replenishment, mild Ca^{2+} dysregulation, altered lipid handling or intracellular transport defects. At this stage, astrocytic buffering remains largely effective, and overt symptoms may be absent. The key feature is not failure, but reduced robustness: the system can still recover from peaks of demand, but with less reserve.

Stage 2: Compensatory buffering and hidden overuse

As fragility persists, astrocytes compensate more intensely to preserve local function. This may involve increased glycogen mobilisation, glycolysis, lactate production or exchange, sustained glutamate and K^+ buffering, and adaptive changes in mitochondrial pyruvate handling, and mitochondrial quality control. This stage would include the apparently paradoxical possibility that early, pre-symptomatic restriction of astrocytic mitochondrial pyruvate entry is protective if it strengthens glycolytic/lactate support and reduces amyloid/tau accumulation [26]. It may also include protective mitochondrial transfer from astrocytes to neurons [27]. The shift from buffering to chronic compensation in stage 2 could be described as allostatic drift rather than as immediate failure: function can remain apparently preserved because astrocytes perform more work to maintain the same output.

This interpretation is consistent with recent literature on astrocyte metabolic reprogramming. Reactive astrocytes can upregulate glycolysis, fatty-acid oxidation and other metabolic pathways to meet increased energy demands; such changes may be adaptive in acute settings but maladaptive when sustained [28-30]. In AD-focused work, astrocytes have been described as metabolic sensors whose reprogramming may contribute to energy-driven brain vulnerability, including altered glycolysis, mitochondrial function and lactate-related support [31-33]. Crucially, metabolic profiling of patient-derived cell models from individuals living with sporadic AD reveals that these specific glycolytic and mitochondrial functional deficits are cell-autonomous and innate, directly corroborating the existence of a restricted stability margin [32,33]. In early AD models, enhanced astrocytic glycolysis and increased lactate production have been reported in ways that can influence Aβ burden, synaptic plasticity and cognition, illustrating that metabolic support may become harmful when excessive, mistimed or chronically engaged [34]. This compensatory increase in astrocytic glycolysis may preserve local metabolic support in early disease, but could also alter glial reactivity [35-37] and the extracellular metabolic signalling environment. Specifically, increased L-lactate

has been linked to increasing Aβ aggregation and plaque load in mice [34] and reduced microglial phagocytosis [38]. Thus, early allostatic drift in the form of glycolytic compensation may protect astrocyte-neuron support while simultaneously predisposing the glial network to poor Aβ handling. Conversely, a competing paradigm suggests that early stages are instead marked by a deficit in the astrocyte-neuron lactate shuttle (ANLS) [39], indicating that the direction, volume, and benefit of lactate mobilization remain highly stage- and context-dependent. Astrocytes also possess glycolytic and mitochondrial reserve capacity for ATP regeneration, implying that repeated stress can be tolerated only while these reserves remain available and appropriately localised [32,40].

Stage 2 is therefore not simply "more glycolysis", "more lactate support", or "more Oxidative Phosphorylation". It is coordinated metabolic allostasis. Compensation masks fragility, but at the cost of reduced reserve capacity and increased dependence on correct spatial organisation. Morphological atrophy, loss of fine branches or altered enzyme localisation would be expected to weaken the altruistic support mode [18]. Interestingly, this proposed bioenergetic fragility is not strictly restricted to the central nervous system; peripheral cell models derived from individuals living with dementia—including patient fibroblasts and platelets—exhibit pervasive structural and functional mitochondrial deficits, as well as altered peripheral glycolytic kinetics [41-44]. As there are limited systemic clinical manifestations of Alzheimer's disease, this organism-wide mitochondrial fragility may only become a pathological reality in organs such as the brain where cell replication and turnover are remarkably low, rendering post-mitotic neural circuits uniquely vulnerable to chronic, uncompensated mitochondrial deficits.

Stage 3: Secondary pathological amplification

The transition from compensated allostasis (Stage 2) to irreversible pathological amplification (Stage 3) hinges on specific intracellular logistical bottlenecks. Within this framework, mitochondria act as the primary limiting variables because buffering often occurs in spatially restricted microdomains. ATP-consuming work is generated at sites of glutamate uptake, K^+ clearance, Ca^{2+} signalling, membrane remodelling and local metabolite exchange [45,46]. In a highly ramified astrocyte, failure may therefore arise not only from insufficient global ATP production, but from a mismatch between where energy is produced and where it is consumed.

This distinction is particularly important for PAPs. Mitochondria located in the soma or thicker processes may support global cell maintenance and longer-timescale regeneration via glycogen breakdown [47], whereas mitochondria positioned near fine perisynaptic processes or endfeet are better placed to support local ionic work, calcium handling and metabolic exchange [45,47]. Astrocyte buffering capacity, therefore, may also depend on the maintenance of this heterogeneous population of functionally specialised mitochondria. In AD, Aβ-associated DRP1-mediated mitochondrial fission [48] likely results in a loss of this heterogeneity and a more homogenised–potentially "PAP-like"–phenotype, narrowing the metabolic flexibility required to perform specialised tasks.

Multiscale modelling reinforces this architectural point: astrocyte morphology and intracellular enzyme placement can strongly influence ATP availability and lactate export, so AD-related atrophy or branching remodelling may reduce local support even before catastrophic cell-wide bioenergetic failure [18].

Persistent energetic stress and chronic compensation eventually alter the molecular environment. Mitochondrial stress can increase oxidative burden, reduce ATP regeneration and impair calcium handling. Altered glucose utilisation can also amplify this oxidative environment through the accumulation of the glycolytic byproduct methylglyoxal (MG), a potent mediator of glycation stress [49]. Compensatory increases in glycolytic flux (which start in stage 2) may therefore come at the cost of increased MG accumulation, promoting RAGE-mediated ROS production [50]. Crucially, the relationship between MG and oxidative stress is bidirectional [51], meaning that MG represents an additional node through which the

pathological environment in AD could self-amplify. Even in later stages of glucose hypometabolism, reduced diversion of glucose into non-glycolytic pathways may further favour MG accumulation [12,52,53], suggesting that dicarbonyl stress likely remains a pathological driver throughout the AD continuum.

If astrocytic mitochondrial oxidative phosphorylation becomes insufficient for fatty-acid degradation, lipid droplets may accumulate and trigger reactive pathways linked to STAT3 activation, neuronal oxidative stress, microglial activation and demyelination [15]. Additionally, altered fatty-acid and cholesterol handling may impair Aβ clearance pathways, including autophagy-lysosomal degradation and amyloid-degrading enzyme activity [54-56], which could form a self-amplifying loop if resulting Aβ deposition exacerbates mitochondrial dysfunction further. Under chronic Aβ exposure, mitochondrial transfer between, astrocytes and neurons, may also shift from protective donation of healthy mitochondria to release of damaged, ROS-generating mitochondria [27], which may provide an additional self-amplifying mechanism, as ROS can both promote Aβ production whilst impairing Aβ clearance pathways [55,57,58].

At this stage, Aβ and tau emerge both as consequences and causes of destabilisation. Impaired recovery and altered extracellular homeostasis may promote amyloidogenic processing or reduce Aβ clearance. Recent evidence in an AD mouse model indicates that aerobic exercise improves astrocyte mitochondrial quality and promotes astrocyte-to-neuron mitochondrial transfer through CD38-related mechanisms, reducing neuronal oxidative stress, plaque burden and cognitive dysfunction [27]. This suggests that astrocytes may buffer not only by exporting metabolites, but also by donating bioenergetic machinery. Under chronic Aβ exposure, this transcellular logistical pathway likely becomes corrupted; astrocytes therefore release damaged or aged mitochondria into the extracellular space that generate excess reactive oxygen species and contribute to neurite atrophy [27].

Mitochondrial stress, oxidative burden and Ca^{2+} dysregulation caused by export of damaged mitochondria from astrocytes, may promote tau phosphorylation in neurons, which eventually will lead to hyperphosphorylated tau aggregates disrupting microtubule-based molecular motors. This corrupts intracellular logistical networks further, halting the transport and proper positioning of healthy mitochondria to active synapses while also potentially impairing mitochondrial quality control through defective mitophagy, as has been demonstrated in neurons [59], promoting the accumulation of damaged mitochondria and ultimately culminating in localized synaptic energy deprivation [60,61]. The relationship is therefore bidirectional: energetic buffering failure may facilitate proteinopathy, and proteinopathy may further impair buffering.

Stage 4: self-amplifying decompensation

Once Aβ, tau, mitochondrial dysfunction, lipid dysregulation, inflammatory reactivity, transport defects and Ca^{2+} disruption interact strongly, the system may enter self-amplifying decompensation. Buffering no longer merely operates inefficiently; it becomes unable to restore local stability. Mitochondria may generate less usable ATP, fail to reach sites of demand, release excessive ROS, fail to degrade fatty acids, or be transferred in damaged form to neurons. Astrocytic glycogen and glycolytic compensation may become insufficient or mistimed, and neurovascular responses may no longer match demand.

At this stage, failure is expected to emerge first at the level of individual microdomains, then progressively across larger circuit territories. Interestingly, brain PET and functional brain imaging studies show this exact relationship with amyloid deposition and glycolytic failure occurring first in brain regions that form connectivity networks, such as the default mode network, before spreading to other brain networks. The result is not simply reduced performance, but increasing instability under demand, poorer recovery and spread of dysfunction across networks. The system has shifted from compensated fragility to self-sustaining instability.

This stage of disease is often where clinical intervention or clinical features of disease become most manifest. The self-amplifying decompensated nature of this stage may explain why targeting using one area of Alzheimer pathology, such as amyloid accumulation has limited effectiveness [62,63].

Figure 1. Proposed stages of astrocytic energetic buffering failure

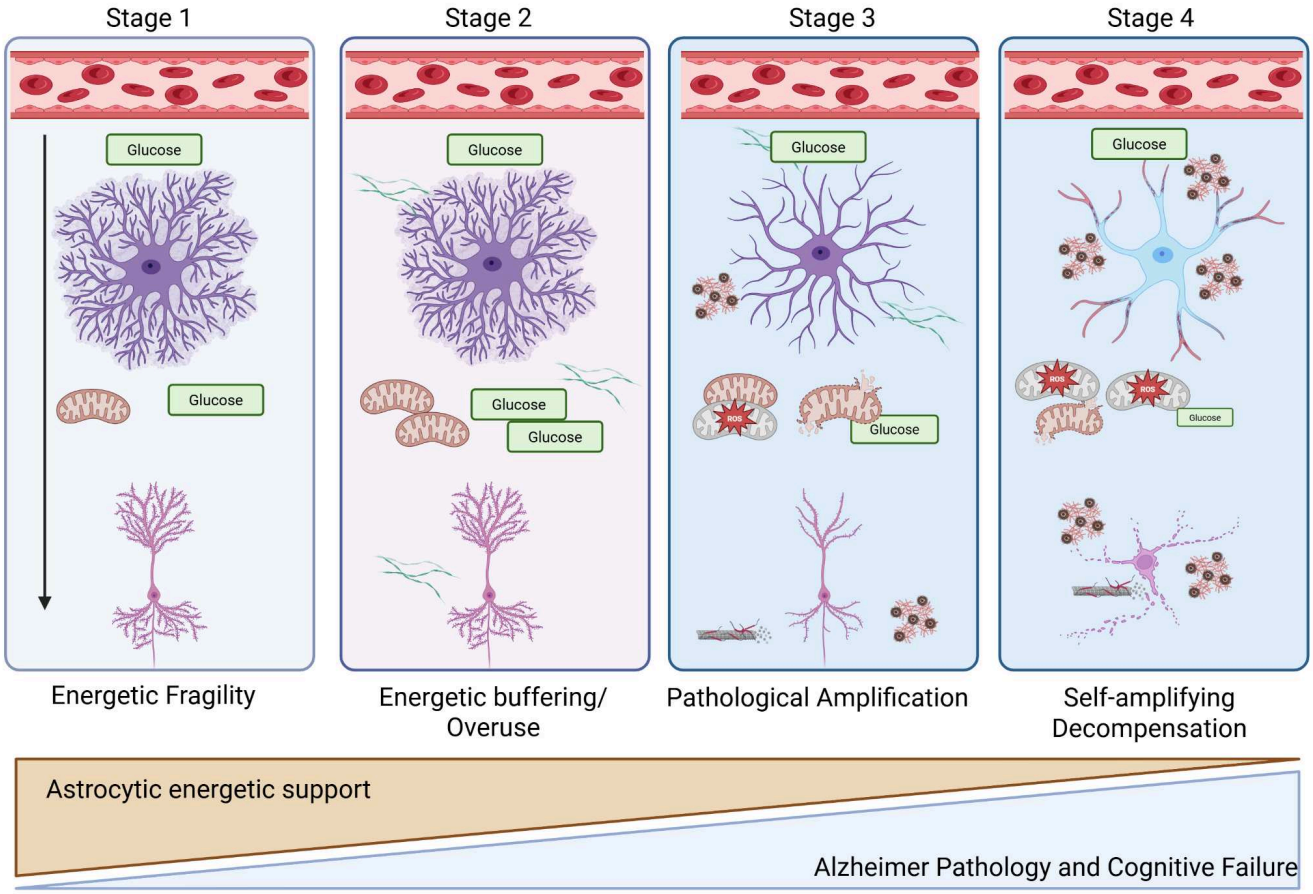

Figure 1. Proposed stages of astrocytic energetic buffering failure: Schematical description of the four-staged progression of AD introduced in the paper. During Stage 1, an early energetic fragility appears in the system, inducing an astrocytic compensation; the system essentially remains in equilibrium, but further metabolic resources are needed to achieve this. Stage 2 is characterised by an overuse of this compensatory mechanism, mitochondrial and glycolytic capacity has to be increased further to maintain energetic buffering but glycolytic and mitochondrial capacity limits start to be reached. Stage 3 is where the switch from compensation to amplification occurs, astrocyte morphology changes, amyloid and tau accumulation starts to impede astrocyte metabolism further leading to poorer neuronal support and pathological support, such as the transfer of dysfunctional mitochondria and reduced metabolism products. Stage 4 is essentially system collapse with amplification of pathology occurring independent of astrocytic buffering.

Table 1. Proposed staged signatures of astrocytic energetic buffering failure

Stage	System state	Astrocytic / metabolic features	Predicted measurable signatures	Clinical / functional phenotype
1. Subclinical energetic fragility	Reduced energetic margin; buffering still sufficient.	Subtle mitochondrial inefficiency/mislocalisation ; mild coupling or vascular fragility; preserved glycogen reserve; early lipid strain.	Repeated-load variability; delayed recovery; subtle task metabolic abnormalities; baseline markers may remain normal.	Preserved baseline function; cognitive fatigue or reduced resilience under sustained demand.
2. Compensatory buffering / hidden overuse	Function preserved through increased allostatic effort.	Increased glycogen mobilisation, glycolysis/lactate handling and ionic buffering; protective MPC-like shift; beneficial mitochondrial quality control/transfer.	Load-dependent EEG/MEG instability; altered fatigue slopes; dynamic hypermetabolism; GFAP or astrocytic stress markers.	Near-preserved average performance with disproportionate fatigue, fluctuation or slower recovery.
3. Secondary pathological amplification	Persistent mismatch recruits self-reinforcing pathology.	Mitochondrial stress; impaired fatty-acid degradation; lipid droplets; STAT3-linked reactivity; Ca^{2+} dysregulation; rising Aβ/tau; damaged mitochondrial release.	Altered recovery kinetics; signal variability; lipidomic abnormalities; GFAP/inflammatory markers; emerging Aβ/tau changes.	Mild progressive decline; instability under cognitive load; reduced tolerance to sustained demand.
4. Self-amplifying decompensation	Chronic buffering failure and spreading instability.	Severe mitochondrial dysfunction; impaired support; disrupted astrocyte-neuron coupling; lipid/inflammatory amplification; widespread insufficiency.	Hypometabolism; network instability; strong fluid biomarker abnormalities; marked electrophysiological recovery deficits.	Persistent cognitive impairment; reduced recoverability; poor resilience to repeated demand.

Legend: Summary of the hypothesised progression from reduced energetic margin to self-amplifying decompensation. The framework predicts that early dysfunction may be more detectable through load-dependent instability, impaired recovery, astrocytic metabolic stress and spatially localised support failure than through static baseline impairment alone.

Abbreviations: MPC: Mitochondrial Pyruvate Carrier.

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3. Limitations of the proposed model system

Our proposed model has several limitations, there has been limited evidence shown through GWAS studies that genes that solely influence metabolism within cells contribute to the development of AD. Within our model environmental exposure is key to the development of the later stages of progression, as without the astrocyte being subjected to metabolic stress through factors such as aging, the development of cardiovascular disease or infection, the energetic margin will not be reduced or challenged. This may explain the lack of evidence of specific metabolic gene causes of AD in GWAS work [64]. Evidence to support stage 1 of the model is limited, and difficult to assess experimentally due to the prolonged timeframe these changes are likely to occur over, and the fact that we propose that metabolism and brain function overall at this stage is essentially unchanged. There are limited studies on cellular metabolism in mild cognitive impairment cohorts who are biomarker positive for Alzheimer disease which in part explains this lack of evidence for stage 1.

The establishment of the different stages of the model is likely to be dependent or synergistic with the accumulation of amyloid or lack of clearance of this protein. As a result we have to consider how our perspective adds to or is distinct from the amyloid hypothesis. As discussed above, several energetic changes are seen to cells outside the nervous system in AD which are not influenced by amyloid accumulation, and hence suggest an underlying metabolic fragility in those that go on to develop the condition. There is also emerging evidence that organ systems with low cell turnover, such as skeletal muscle, do manifest mitochondrial and metabolic changes associated with AD, again without the presence of amyloid [65,66]. Therefore we would argue that our proposal of reduction in energetic margin in astrocytes caused by changes to mitochondrial efficiency and metabolic dysfunction give the conditions within the brain which allow the amyloid hypothesis to become manifest.

4. Conclusion

AD is often described as a disorder of accumulation. We suggest that its earliest functional consequences may also reflect a staged loss of energetic recoverability. Astrocytes normally buffer fluctuating neuronal demand through glycogen mobilisation, glycolysis, lactate handling, ion and glutamate clearance, neurovascular signalling, mitochondrial ATP regeneration, lipid homeostasis and, in some settings, mitochondrial transfer. Under repeated stress, this buffering may shift from efficient recovery to chronic compensation, reducing reserve capacity and increasing vulnerability to further perturbation.

In this framework, mitochondria are not simply collateral victims of AD pathology. They are limiting variables that help determine whether astrocytic buffering remains dynamically sufficient. Aβ and tau then act both as canonical pathological hallmarks and as amplifiers of a system whose energetic stability margin has already narrowed. Testing this model requires moving beyond static baseline measures toward dynamic assays of load, recovery, spatial architecture and resilience.

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