Mens sana in corpore sano: lifestyle changes modify astrocytes to contain Alzheimer's disease

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Alzheimer`s disease (AD) is the widespread and the most feared neurodegenerative disorder leading to dementia in the elderly. AD, by eliminating intelligence, diminishes a man to helpless body, places an unbearable strain on patients, families, and fuels socio-economic healthcare crises around the world. The main histopathological hallmarks of AD are the accumulation of extracellular amyloid depositions known as senile plaques and intracellular neurofibrillary tangles, together with severe dysfunctional synaptic connectivity and neuronal death leading to brain atrophy.

Whether accumulation of plaques and tangles is causal to the disease remains debatable, yet the widespread and progressive molecular and cellular impairments define AD clinical evolution, which spans over decades. According to the Braak staging system, AD pathology starts in the transentorhinal and entorhinal cortex (stages I and II), with subsequent spread to the hippocampus (stage III and IV) and cortex (stages V and VI), resulting in cognitive decline and failure of basic body functions (Braak et al., 2011). Clinically, the mild cognitive impairment associated with Braak stages I to IV is associated with declarative memory deficits and depressive symptoms, although the pathology remains compensated and individuals can retain independence. With progression of symptoms, extra care becomes necessary due to the more prominent deficit in memory, learning, reasoning, and general behavior. Finally, in the severe dementia (Braak stages V and VI), patients become fully malfunctional and require continuous observation and nursing.

Despite a substantial scientific effort employed to delay, prevent or mitigate the AD progression, no effective pharmacological treatment of the disease, or even its major symptoms have been developed. Alternative strategy, associated with improved lifestyle, including mental engagement, physical exercise, social interaction, visual and sensory stimulation emerges as a non-pharmacological option to preserve or improve cognitive conditions of AD patients with consequent improvement of their quality of life. Both physical exercise and enriched environment are known to boost brain health, improving cognitive functions, memory and reasoning abilities. At a cellular level, exercise and enriched environment stimulate adult neurogenesis thus modulating hippocampus-dependent tasks such as memory and cognition. At a molecular level, exercise and enriched environment induce release of growth factors such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF-1) and nerve growth factor (NGF) with critical roles in synaptic plasticity and metabolic supply, which ultimately modulate cognitive processes and behaviors (Mendiola-Precoma et al., 2016).

The neurological and cognitive outcome of AD, similarly to other neuropathologies, is directly linked to cognitive reserve. The latter is defined by (i) neuronal reserve reflecting the functional structure of the brain attained during life-time experience and learning and (ii) neuronal compensation, which reflects the defensive and regenerative capacity of the brain. In humans, daily physical exercise is associated with a reduced risk of AD (Buchman et al., 2012) by increasing cognitive reserve through improvement of neuronal density and synaptic plasticity (Mendiola-Precoma et al., 2016). Besides exercise and cognitive challenge, brain-friendly dieting and caloric restriction prolong cognitive longevity. All these changes in lifestyle reduce β-amyloid burden and misphosphorylated tau in old adults with cognitive deficits (Mendiola-Precoma et al., 2016). In summary, complex modifications of lifestyle are instrumental in delaying AD progression and, even more importantly, in ameliorating cognitive decline with consequent improvement of quality of life.

Astrogliopathology in AD: The defensive and self-protective capacity of the brain tissue, which defines the neuronal compensation, is, in its major part, a function of neuroglia and, in particular, of astrocytes. Astrocytes are multi-tasking neural cells involved in numerous critical central nervous system (CNS) functions from development to ageing. Astroglial cells regulate neuronal metabolism, neurotransmitter uptake and turnover, ions and water homeostasis. Through synaptic cradle, formed by leaflet-like perisynaptic processes, astrocytes regulate synaptic transmission being instrumental for synaptogenesis, synaptic maintenance and synaptic elimination, thus contributing to cognitive, behavioral and neuropathological processes (Augusto-Oliveira et al., 2020). Astrocytes respond to CNS insults through an evolutionary conserved programme of reactive astrogliosis to protect the brain against lesion and assist in post-lesion regeneration.

Astrogliopathology in AD is complex and is changing in the course of the disease. At the early stages of the disease characterised by a mild cognitive impairment (Braak I–IV), the emerging β-amyloid plaques attrach astrocytes and instigate reactive astrogliosis; most of the plaques are surrounded by reactive astrocytes and activated microglia (Verkhratsky et al., 2015). Astrogliosis in AD belongs to the anisomorphic type without any significant overlap of astroglial territorial domains. Inhibition of astroglial reactivity by genetic deletion of intermediate filaments glial fibrillary acidic protein (GFAP) and vimentin exacerbate β-amyloid pathology (Kraft et al., 2013), indicating defensive potential of reactive astroglia in AD. The clinical switch between mild cognitive impairment and dementia, which reflects progression to Braak V–VI, coincides with (and arguably is facilitated by) decline in astroglial reactivity as shown by positron emission tomography with astroglial marker deprenil (Verkhratsky et al., 2015). Besides reactive remodelling, the AD brain is characterized by an early accumulation of atrophic astrocytes. This morphological atrophy is associated with loss of homeostasis, including decrease in expression of glutamine synthetase, the key enzyme behind glutamate (GABA)-glutamine shuttle that is indispensable for neurotransmission and inhibitory/excitatory balance. Decrease in glutamine synthetase may also facilitate astroglial synthesis of GABA, which further adds to the imbalanced neurotransmission in the AD-disturbed brain. Atrophic astrocytes also lose defensive capabilities as they cannot mount reactive response to AD pathology in several brain regions including entorhinal cortex, known to be the most vulnerable part of the brain engulphed by AD pathology at the very early stages of the disease. In summary, complex pathological metamorphoses of astrocytes define the temporal progression of AD, while astroglial paralysis lies behind the switch from mild cognitive impairment to clinical dementia (Verkhratsky et al., 2015).

Lifestyle and astrocytes in AD context: The use of personalized holistic polytherapy has demonstrated beneficial effects in AD, preventing or even reversing cognitive decline in patients with relatively advanced stages of the disease (Bredesen, 2014). Underlying mechanisms and cellular targets however remain poorly understood. Astrocytes are likely to be the cellular elements translating environmental enrichment into an increased capacity of the brain tissue to withstand and compensate neurodegenerative lesions.

Physical exercise and environmental enrichment emerge as potent astroglial modulators. Astrocytes are affected by environmental stimulation, which impacts on astrocytic morphology, transcriptional activity and function. As shown by number of observations, subjecting of animals to enriched environment, which often includes physical exercise, visual and sensory stimulation and social engagement, makes astrocytes larger and more complex. These astrocytes demonstrate an increase in number and length of astrocytic processes compared to astrocytes from animals dwelling in standard environment. These cellular changes of astroglia are paralleled with improved memory and learning. Keeping mice for 4 weeks on treadmill and running increased synaptic density in the hippocampus, elevated BDNF (at both mRNA and protein levels), substantially increased size and complexity of astrocytes which develop longer processes projected toward granular cells, and increased astrocytic TrkB (Fahimi et al., 2017). Considering that astrocyte-derived growth

factors such as BDNF and transforming growth factor-β (TGF-β) improve memory deficits, increase spine density and strengthen synaptic connectivity, these findings highlight the role of astrocytes in translating physical activity into modified neural networks, which arguably increases their resistance to neurodegenerative disorders. In AD animal models, enriched environment and physical exercise for six months fully restored morphology of atrophic astrocytes, which arguably also increased astroglial homeostatic and neuroprotective support (Verkhratsky et al., 2015). At the same time physical exercise inhibits amyloidogenic pathway, by decreasing β-site amyloid precursor protein cleaving enzyme 1 and presenilin-1 (Zhang et al., 2018). Besides exercise and environmental stimulation, high intake of calories and fats represent a potential risk factor for AD. On the other hand, caloric restriction attenuates amyloid-β deposition in the brain. Similarly to enriched environment and physical exercise, food intake impacts upon astroglial morphology and synaptic plasticity. Caloric restriction induces morphological remodelling of hippocampal astrocytes with subsequent enhancement in synaptic plasticity, possibly improving memory (Popov et al., 2020).

Astrocytes also affect the brain health and cognitive longevity through the glymphatic system. This system relies on aquaporin-mediated water fluxes from perivascular space to brain parenchyma; aquaporins (of AQP4 variety) are specifically concentrated on astroglial endfeet that form *glia limitans perivascularis* which represents parenchymal portion of blood-brain barrier. The main function of the glymphatic system is to remove waste hence preserving functional cleanness of the brain tissue. In ageing, and even more so in neurodegeneration, the glymphatic system is seriously compromised because of the migration of AQP4 channels away from endfeet. Again, changes in lifestyle such as physical exercise increase the efficiency of glymphatic system through increased expression and endfeet polarisation of AQP4. An improvement of glymphatic system operational capacity coincided with improved performance in water-maze cognitive test (He et al., 2017). The glymphatic clearance is more effective during the sleep, and sleep disorders are intimately related to neurodegenerative pathologies; hence normalization of sleep is of paramount importance for cognitive longevity. Finally, low to moderate doses of alcohol similarly increase the efficacy of glymphatic clearance (Lundgaard et al., 2018).

In conclusion, the failure of monotherapies for AD seem rather obvious; to the very high likelihood a single "magic bullet" style molecule, effectively curing AD (as well as other neurodegenerative disorders) may never be discovered. The alternative lies with holistic polytherapies aimed at preservation or improvement of the whole human body, including normalization of metabolism and hormonal landscape. Healthy lifestyle is an important part of this holistic approach: intellectual engagement and physical exercise, good sleep and healthy brain-friendly diet, which deliver not only calories but also pleasure, are proven to prolong cognitive ageing. Astrocytes, the brain homoeostatic cells, are positively modulated by lifestyle changes; these modifications of astrocytes increase the support and protection of neurones, improve synaptic connectivity and enhance waste clearance ultimately increasing cognitive reserve and delaying senility (**Figure 1**).

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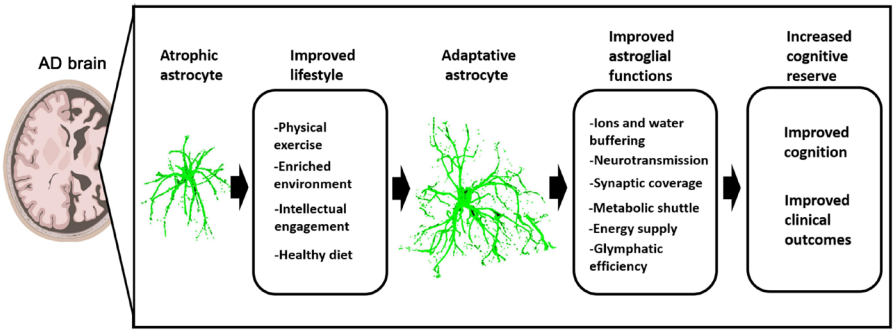

Figure 1 | **Astroglial remodeling through lifestyle changes contributes to longevity.**
Astroglial atrophy and failure of astrogliosis in late stages of Alzheimer's disease (AD) compromise astroglial homoeostatic support and neuroprotection, hence contributing to the decline of major brain functions, resulting in severe cognitive deficits. Lifestyle changes represent a holistic way to restore astroglial form and function leading to an improvement of neuronal survival and synaptic connectivity with consequent increase in quality of life and prolongation of cognitive longevity.

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