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Research report

Astrocytic face of Alzheimer's disease

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HIGHLIGHTS

- Astrocytes are main homoestatic and defensive cells of teh central nervous system.
- Astrocytes are endowed with morphological plasticity.
- Astroglial coverage defines, to a large extend, synaptic connectivity.
- Pathological remodelling of astroglia contributes to neurodegeneration.

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ABSTRACT

Ageing of the central nervous system (CNS) is the major risk factor for Alzheimer's disease (AD), a type of neurodegeneration that is associated with deficits in cognition and memory and clinically manifested as severe senile dementia. Numerous mental processes underline cognition, including attention, producing and understanding language, learning, reasoning, problem solving, decision making and memory formation. In the past, neurones or their parts have been considered to be the exclusive cellular sites of memory and cognitive processes. However, it has become evident that astrocytes, the major homeostatic glial cell of the CNS, provide an essential contribution to memory formation, and astroglial failure may promote cognitive decline in AD. In response to the network reset mechanisms mediated by the noradrenergic projections of neurones located in the locus coeruleus, astrocytes get excited and participate in the morphological remodelling associated with synaptic plasticity, otherwise thought to represent a cellular mechanism of learning and memory. Astroglial morphological plasticity is an energy-demanding process requiring mobilisation of glycogen, which, in the CNS, is almost exclusively stored in astrocytes. Astroglia exhibit cytoplasmic excitability that engages ions (such as Ca^{2+} and Na^{+}) and second messengers (such as cAMP). These ions/molecules contribute to the reception of extracellular signals and coordinate the secretion of glio-signalling molecules, including peptides such as apolipoporotein E, which participates in lipid transport between glia and neurones. In this setting, astrocytes are positioned as spatio-temporal integrators of neural network coordination, which disintegrates during progression of AD.

"All in all recaptured, we apparently appear to have in front of us a peculiar disease process. In recent years, such peculiar disease processes have been detected in growing numbers. This observation will have to suggest to us that we should not let ourselves satisfied with trying to include—with mobilisation of many an effort—any clinically unclear illness case into one of the diagnostic entities known to us. There are without any doubt many more psychic illnesses than listed in our textbooks. In some of these instances a later histological examination will subsequently reveal peculiarities of the specific case. Then, we will gradually arrive at a stage, when we will be able to separate

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out individual disease from the large illness categories of our textbooks; to delineate them clinically more accurately."

1. Neuroglia facets of Alzheimer's disease

The most common cause of dementia in the elderly is Alzheimer's disease (AD), a progressive, multistage, ultimately fatal neurodegenerative disease with preclinical phase of a decade or longer [1]. Many features appear at different stages of AD, but the most familiar one, presenting at a late stage, is linked to the histopathological presence of extracellular deposits of fibrillar β-amyloid peptide (Aβ), and intraneuronal accumulation of aggregates of hyper-phosphorylated Tau protein [2]. Degeneration and loss of synapses preceding neuronal death also occur [3,4]. Neurodegeneration occurs gradually and dementia may reflect the end stage of an accumulation of pathological changes that may start to develop decade(s) before the onset of the clinical symptoms [5,6].

The nature of the preclinical stages of AD remains obscure. Although the current view is that neurodegeneration in AD reflects neurone-specific deficits, it is possible that preceding or concomitant changes in neuroglia may also contribute to this process [1,6–9]. Neuroglia sustain brain homoeostasis at the organ, cellular, micro-architectural, vascular, metabolic, neurotransmitter and ion levels [10–15] and, by definition, homeostatic failure results in disease [7]. The role of neuroglia in dementia was recognised by Alois Alzheimer, who found glial cells in close contact with damaged neurones: "The glia have produced abundant fibres; concurrently many glia show large fatty sacks" [16–18]. In post-mortem tissue from patients with AD, astroglial hypertrophy (reflecting reactive astrogliosis accompanied by increased levels of glial fibrillary acidic protein (GFAP) and S100, a calcium binding protein) is often observed, particularly in astrocytes associated with senile plaques [19–23]. Consistent with a recent study in patients with AD [6], distinct time- and brain-specific morphological alterations were reported in an animal mouse model of familial AD, i.e. astroglial atrophy in addition to hypertrophy was detected in certain brain areas [24–27]. Astroglial asthenia preceded the appearance of senile plaques and appeared first in the entorhinal cortex, the region earliest affected by AD pathology [26]. Although the pathological developments associated with AD are of particular interest, studies in humans are difficult. Some facets of this pathology can be, to some extent, reproduced in animal models, where the evolution time of AD-like peculiarities is shorter and hence more amenable for experimentation. Thus, the aforementioned mouse models of AD offer certain opportunities for studying AD-related neuropathology. Besides mice, there are many other animal models of AD including nematodes, *Drosophila* flies, rabbits, canines, and non-human primates, and each model recapitulates different aspects of AD to some extent (reviewed in [28]).

In addition to the accumulation of peptides, such as Aβ, and morphological alterations of neuroglia, AD progression is also associated with brain tissue remodelling, which is often defined as neuroinflammation, because the accumulation of misfolded proteins provokes an innate immune response in the central nervous system (CNS) [1]. This response is in part associated with the Aβ deposits, because hydrophobic proteins may bind apolipoprotein E (ApoE), a major cholesterol carrier in the CNS that is synthesized and released mainly by astrocytes [29–31]. Polymorphic alleles of ApoE are the main genetic determinants of sporadic AD; individuals carrying the ε4 allele are at increased risk of AD compared with those carrying the more common ε3 allele, whereas the ε2 allele decreases the risk of developing the disease [32]. The mechanism(s) by which the particular alleles are associated with AD are unknown, but they may be related to the capacity of the respective ApoE isoforms to prevent neuroinflammation. It has been claimed that the ApoE lipoprotein isoform function associated with neuroinflammation arises from differential binding to hydrophobic proteins, such as Aβ, regulating their aggregation and clearance in the brain [33].

ApoE-mediated effects may also be related to a general deregulation of cell metabolism and fundamental failure in neuronal–glial interaction [34]. The key mechanism of neuronal damage by reactive oxygen species and mitochondrial dysfunction in *Drosophila* was associated with impaired lipid metabolism in glia before or at the onset of neurodegeneration. This likely indicates impairment in lipid traffic, carried by ApoE or similar carriers, between glia and neurones, a primary defect that leads to neurodegeneration. This was further supported by experiments in which human amyloid precursor protein (APP) was expressed in neuronal cells of *Drosophila*, which promoted neurodegeneration; the latter could be attenuated with mimetic ApoE peptides [35]. Before neurodegeneration, lipid droplet accumulation was shown to be present in the astrocytes of an animal model of neurometabolic disorder (Leigh's disease) that affects the CNS. *Ndufs*$^{-/-}$ mutant mice exhibit mitochondrial dysfunction, which further implies impairment of brain lipid metabolism in the early stages of neurodegeneration [34]; the *Ndufs4s* gene otherwise encodes a nucleus-encoded accessory subunit of the mitochondrial membrane respiratory chain NADH dehydrogenase (complex I, or NADH:ubiquinone oxidoreductase). The ApoE-mimetic peptides derived from the receptor-binding region of ApoE were selected based on their ability to mimic the functional anti-inflammatory and neuroprotective effects of the intact ApoE protein seen in different animal models of neurological diseases [36].

ApoE as a cholesterol-carrying protein likely contributes to cholesterol brain homeostasis. The brain is the most cholesterol-rich organ in the body [37]. Due to the blood–brain barrier, there is little uptake of cholesterol by circulating lipoproteins. However, cholesterol synthesis (which occurs mainly in glia [38]), takes place in the brain. In addition to de novo synthesis, cholesterol homeostasis in the brain also includes its enzymatic conversion to 24(*S*)-hydroxycholesterol [37], which readily crosses the blood–brain barrier; this represents the major route for elimination of cholesterol from the brain. It is appealing to speculate that neurodegeneration may be initiated by defects in components of cell metabolism at a very early stage of AD.

2. Failure of the locus coeruleus network reset system in Alzheimer's disease

Neurones in the locus coeruleus (LC) degenerate at the early stages of AD [39]. These neurones are the primary source of noradrenaline (NA), which is known to be a generic inhibitor of neuroinflammation [40]. Thus, deficient noradrenergic innervation in the CNS may affect the progression of AD through reduced inhibition of neuroinflammation, engaging a rather diffuse innervation of the brain provided by the LC as elaborated below.

The LC localized in the brainstem contains noradrenergic neurones, which project to most, if not to all, areas in the CNS [41]; cortical areas receive more abundant innervation [42]. The function of these diffuse projections lies in the synchronous activation of target neural ensembles, acting thus as a functional reset [43,44]. Activation of LC projections is associated with a variety of processes, such as arousal, attention and memory, the sleep–wake cycle, behavioural flexibility, behavioural inhibition and stress, cognitive control, emotions, neuroplasticity, posture and balance [41]; presumably these processes would be affected via activation of specific subgroups of LC projections. Simultaneous activation of all the LC projections [44] is likely reflected by gamma waves on an electroencephalogram [43].