Astrocytes in Ageing and Alzheimer’s Disease

or

Neuroglial origins of neurodegeneration?

Ageing of astrocytes: GFAP

Ageing of astrocytes: s100β
Ageing of astrocytes: glutamine synthetase


Astroglia in ageing brain
Physiology

Whole cell recordings from astrocytes in aged brain slices


NMDA induces glycine-sensitive current response in isolated astrocytes

Astroglial NMDA receptors are weakly Mg$^{2+}$-sensitive and have lower Ca$^{2+}$ permeability

ATP-induced currents in cortical astrocytes

Ionotrophic receptors and glutamate transporter mediate GSC in the neocortex
Spontaneous glial synaptic currents

Ageing modifies astroglial postsynaptic currents

Ageing modifies expression of glutamate and purinergic receptors in astroglia

Ageing modifies receptor-mediated calcium signalling
Astrocyte atrophy drives early stages of Alzheimer’s Disease?

Dementia is the ultimate scourge of mankind, being generally absent in every other animal species; and as such it may be considered as the most appalling and horrible disease because it effectively robs human beings from their intelligence and turns them into helpless bodies.

Carolus Horn 1921-1992, German painter

Initial stages

Severe AD

Terminal stage

Shortly before death

Maurer & Fröhlich. (2000): Insights in Alzheimer’s Disease online. 6 (2).

Neurodegeneration – neurone-centric view

Neurodegeneration is the progressive loss of function and structure of neurones, including death of neurones

The process in which neurons die

A varied assortment of central nervous system disorders characterised by gradual and progressive loss of neural tissue

Progressive loss of neurologic functions.

Alzheimer: activated glial cells associate with damaged neurons (1910)

Alois Alzheimer (1864-1915)

Alzheimer: Glial cells form the neuritic plaque (1910)


Animal models of AD

Lesion (focal injections)
- Specific regions: Nucleus basalis magnocellularis
- Neurotoxins: Quinolinic ac. Ibotenic ac.

Transgenic models:
Expressing various combinations of mutant genes isolated from family AD (APP, PS, tau)

Triple transgenic model expresses PS1M146V, APPSwe, and tauP301L transgenes

GFAP accurately visualise astroglial domain in hippocampus

The number of hippocampal astrocytes does not change with age in WT and 3xTG-AD brains

Morphological atrophy of hippocampal astroglia in 3xTG-AD animals


Age-dependent decrease in number of GS containing astrocytes in hippocampus of 3xTG animals


Decrease in glutamine synthetase expressing astrocytes in hippocampus of 3xTg-AD animals

AD: Astroglial atrophy complements astrogliosis


Early astroglial atrophy in prefrontal cortex in 3xTg-AD mice


Morphological atrophy of astrocytes as revealed by glutamate synthetase immunoreactivity

Earlier Astroglial Atrophy in the Entorhinal Cortex

Yeh, Verkhratsky, Rodriguez (2011) ASN Neuro, 3, e00071
Amyloidosis in prefrontal cortex is not associated with astrogliosis


Formation of plaques does not trigger astrogliosis in entorhinal cortex

Yeh, Verkhratsky, Rodriguez (2011) ASN Neuro, 3, e00071

Amyloid-β differentially affects calcium signalling toolkit in astrocytes from different brain regions

Grolla, Sim, Lim, Rodriguez, Genazzani & Verkhratsky (2012): submitted
Astroglial atrophy in neurodegenerative diseases

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<th>Pathology</th>
<th>Astroglial atrophy</th>
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<td>Amyotrophic lateral sclerosis</td>
<td>Prominent astroglial degeneration and atrophy was found in the human(SOD1)_{105} transgenic mouse; this astrodegeneration preceded both neuronal death and the appearance of clinical symptoms. Incidentally, the ALS astrocytes (expressing SOD1) were specifically sensitive to glutamate, and contrary to healthy astrocytes displayed glutamate excitotoxicity.</td>
<td>Rossi &amp; Volterra, 2009, Brain Res Bull; 50: 224-232; Rossi et al. 2008 Cell Death Differ; 15: 1691-1700</td>
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Progression of astrogliodegeneration in AD

Enriched environment and physical activity reverse atrophy of astrocytes in the hippocampus of AD transgenic mice

Conclusions

Astrocytes are the central element of brain homeostatic system, which through their multiple functions provide for maintenance and defence of neural networks. Astroglial cells are specifically involved in various neurological diseases, determining their pathogenesis and outcome.

Astrocytes are involved in all types of neurodegenerative processes, and often display signs of degeneration at the early stages of pathology.

In AD early dystrophic changes in astroglia can represent an important step in initiation and progression of Alzheimer’s disease. These changes are region specific and absence of reactive gliosis may account for specific vulnerability of certain areas of the brain to the disease. Targeting of astroglia may provide a new principle for prevention and/or treatment of AD at the early stages of the disease.