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Principles of Astrogliopathology

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Pathological Potential of Neuroglia

The pathological potential of neuroglia was widely recognised and acknowledged by neurologists and neuroanatomists at end of the nineteenth and the beginning of the twentieth century. Contribution of neuroglia to the diseases was described, and numerous pathological morphological types of glial cells have been characterised in detail (Achucarro 1910; Alzheimer 1910; Frommann 1878; Nissl 1899). By 1920 the universal involvement of neuroglia in neuropathology was universally accepted; neurologists agreed that “the appearance of neuroglia serves as a delicate indicator of the action of noxious influences upon the central nervous system” (del Rio-Hortega and Penfield 1927); the concept of reactive gliosis has been formulated and generally recognised (del Río-Hortega and Penfield 1927; Penfield 1928b). The widespread role and importance of neuroglia in neurological and neuropsychiatric diseases were somewhat forgotten in the course of the twentieth century. However, the recently passed decade witnessed much revival in the interest in glia in neuropathology as the neuroglial cells are firmly considered as key players in pathophysiology of all disorders of the nervous system (both central and peripheral), and neuropharmacology regards neuroglia as a legitimate target for new therapeutic strategies (Burda and Sofroniew 2014; Ferrer 2018; Giaume et al. 2007; Parpura et al. 2012; Pekny et al. 2016; Sofroniew 2014b; Verkhratsky et al. 2012b, 2016a, 2017; Verkhratsky and Parpura 2016; Zeidan-Chulia et al. 2014).

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Astrogliopathology: General Principles

Astrocytes are primary homeostatic cells of the central nervous system (CNS; see previous chapter); in addition, astrocytes contribute to brain defence. Astrocytic contribution to neuropathology can be primary (when cell-autonomous changes drive the pathologic progression) or secondary, when astrocytes respond to lesions or to various pathological changes in the nervous tissue. Current classification (Fig. 1) distinguishes the following forms of astrogliopathology: (i) reactive astrogliosis, (ii) astrocytic atrophy with loss of function, (iii) pathological remodelling of astrocytes and (iv) astrodegeneration (Fig. 1, (Verkhratsky et al. 2017). These pathological groups cover multiple pathological phenotypes which are yet to be fully characterised; furthermore pathological changes in astrocytes can occur together or in isolation; they are sometimes specific to disease stages and they are affected by age and systemic pathologies.

Reactive Astrogliosis

Reactive astrogliosis is a specific and evolutionary conserved (from arthropods to humans) response of astrocytes to polyaetiological brain lesions, from trauma and infection to neurodegeneration. Reactive astrogliosis is a process whereby, in response to pathology, astrocytes launch genetic programmes that result in biochemical, morphological, metabolic and physiological remodelling (Escartin et al. 2021). This remodelling leads to either gain or loss or modification of astrocytic functions, all aimed at neuroprotection and preservation of the nervous tissue integrity. Astrogliotic remodelling of astrocytes leads to an emergence of multiple context-specific reactive phenotypes, characteristic for particular, age, type of pathology and brain region. These multiple phenotypes differ in specific molecular profile, functions and distinct impact on diseases (Pekny et al. 2016; Sofroniew 2014a; Sofroniew 2020; Verkhratsky et al. 2017). Reactive astrogliosis is flexible to adapt functional and biochemical reprogramming of astrocytes to the nature and strength of the insult with an ultimate goal to mount maximal protection. Within the framework of the same pathology and even within the same affected areas, astrocytes remain heterogeneous in their expression of transcription factors, inflammatory agents and signalling molecules, arguably associated with distinct reactive phenotypes (Garcia et al. 2010; Herrmann et al. 2008).

Reactive astrogliosis contributes to many neurological diseases. In particular, prominent astrogliosis occurs in disorders associated with direct lesion to the nervous tissue by physical, biological or chemical agents. These conditions include neurotrauma (Burda et al. 2016; Faulkner et al. 2004), systemic inflammation and sepsis (Shulyatnikova and Verkhratsky 2019; Tremblay et al. 2020), microbial or viral neuroinfection (Soung and Klein 2018; Zorec et al. 2019), toxic encephalopathies (Li et al. 2021; O'Callaghan et al. 2014), autoimmune inflammation of the nervous tissue including multiple sclerosis (Voskuhl et al. 2009; Wheeler and Quintana 2019), cancerous growth (Henrik Heiland et al. 2019) and neurodegenerative diseases (Verkhratsky et al. 2010). Histopathologically reactive astrogliosis is characterised by morphological hypertrophy, changes in the thickness of processes, sometimes associated with retraction of distal leaflets (Plata et al. 2018); furthermore, reactivity is manifested by an up-regulation of two major cytoskeletal

intermediate filaments, glial fibrillary acidic protein (GFAP) and vimentin (Hol and Pekny 2015; Pekny and Pekna 2014; Sofroniew 2014a).

There are several classifications of reactive astrogliosis (Fig. 2). According to morphological changes, astrogliosis is classified into isomorphic and anisomorphic astrogliosis. In isomorphic astrogliosis, astrocytes become hypertrophic; however, they do not move and do not proliferate and the reach of their individual territorial domains remains unchanged (Escartin et al. 2021; Wilhelmsson et al. 2006). Isomorphic astrogliosis is fully reversible, and after the resolution of pathology, astrocytes return to physiological morphology; the isomorphic astrogliosis is indispensable for post-lesion regeneration (Anderson et al. 2016). In anisomorphic astrogliosis astrocytes start to proliferate, and they migrate towards the site of lesion, assemble into astroglial palisades and form the glial scar (Pekny et al. 2016; Sofroniew 2020). Another classification divides astrogliosis according to the severity of changes. According to this classification astrogliosis is classified into (i) mild to moderate astrogliosis, (ii) severe diffuse astrogliosis and (iii) severe astrogliosis with compact scar formation (Sofroniew 2009, 2014a). Although morphological presentation of reactive astrocytes can be similar in different pathological contexts generally following the above classification, their molecular signatures are quite distinct and disease-specific. Different astrocytic transcriptomes associate with different conditions and diseases including neurotrauma (Anderson et al. 2016), stroke (Zamanian et al. 2012), animal models of multiple sclerosis (Itoh et al. 2018) or neurodegenerations; in the latter group astrocytes in Huntington's disease (Al-Dalahmah et al. 2020) are distinct from astrocytes in Alzheimer's disease (Kamphuis et al. 2015). Similarly, astrocytic reactive phenotypes can be different in different stages of the same disease (Wheeler et al. 2020; Zamanian et al. 2012).

Fundamentally, astrogliosis is a defensive response of astrocytes aimed at (i) neuroprotection and trophic support of neural cells tissue, (ii) isolation of the lesioned area, (iii) reconstruction of the compromised blood-brain barrier and (iv) facilitating the post-lesion regeneration of the nervous tissue (Sofroniew 2020). The ultimate result of severe astrogliosis, the scar formation, is essentially defensive reponse to isolate the damaged part of the nervous tissue and save the whole at the expense of its part (Pekny et al. 2016; Verkhratsky et al. 2017; Verkhratsky and Butt 2013). Inhibition of astroglial reactivity often exacerbates the damage to the nervous tissue and worsens neurological outcomes (Pekny et al. 2016). For example, suppression of astrogliotic response increases the size of the traumatic lesions and augments neurological deficit (Okada et al. 2006). Genetic deletion of GFAP and vimentin, both of which are critical for mounting reactive astrocyte remodelling, facilitates the evolution of brain ischaemia (Li et al. 2008) and potentiates posttraumatic synaptic loss (Pekny et al. 1999). Furthermore, inhibition of astroglial reactivity results in higher accumulation of β-amyloid and reduced microglial association with senile plaques in the animal model of Alzheimer's disease (AD); all these changes seem to exacerbate AD-type pathology (Kraft et al. 2013).

Reactive astrogliosis is instigated by multiple factors. Conceptually, astrocytes may sense and integrate numerous molecular cues that signal the damage and provide some information about the nature of this damage. Such molecular cues can have multiple origin and nature. They can be released by damaged cells, they can be associated with accumulation of

pathological material (β-amyloid being a well-known example), they can be blood-borne (blood cells or proteins, such as albumin or thrombin) and they can be associated with invading pathogens (bacteria, viruses or prions) or systemic immune factors. Astrogliosis can also be stimulated by certain neurotransmitters and hormones (Fig. 3; (Pekny et al. 2016, Sofroniew 2020)). Conceptually, all factors associated with the instigation of astrogliosis can be classified into (Tang et al. 2012) damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs). The DAMPs are molecules released from immune-responsive microglia or other stressed, damaged or dying cells or factors coming from the circulation through the compromised blood-brain barrier. These factors may include cytokines, chemokines, endothelins, blood-borne proteins, etc. Astrocytes express a wide pattern of receptors that can be activated by DAMPs (Verkhratsky and Nedergaard 2018). The archetypal DAMP is represented by ATP, which is massively released from damaged cells; in pathological contexts, ATP mainly acts on astrocytes through activation of $P2X_7$ purinoceptors, although other classes of purinoceptors may also contribute (Franke et al. 2012). The PAMPs are exogenous agents associated with pathogens such as bacteria, viruses or prions; these factors stimulate Toll-like receptors (TLRs) widely expressed in astrocytes (Jack et al. 2005; Kielian 2006). In addition, astrocytes express nucleotide-binding oligomerisation domain (NOD)-like receptors (NLRs), double-stranded RNA-dependent protein kinase, scavenger receptors, mannose receptor and receptors for complement components and mediators, such as CXCL10, CCL2, interleukin-6 and B-cell-activating factor of the TNF family, all of which are contributing to the regulation of reactive astrogliosis (Farina et al. 2007).

Intracellularly, initiation of reactive astrogliosis is associated with Ca^{2+} signalling. This signalling is an important part of astrocytic intracellular excitability, mediated by cytosolic ions and second messengers (Verkhratsky et al. 2020b, c). Exposure of astrocytes to various DAMPs and PAMPs is frequently associated with initiation of Ca^{2+} signals mainly originating from Ca^{2+} release from the intracellular endoplasmic reticulum (ER) Ca^{2+} store. This release is mediated by inositol-1,4,5,-trisphosphate ($InsP_3$) receptor type 2, which is predominant in astrocytes (Verkhratsky et al. 2012a). Similarly, pharmacological inhibition of Ca^{2+} release from the ER suppressed astrocytic reactivity in response to β-amyloid (Alberdi et al. 2013)

Despite being an intrinsically defensive response, reactive astrocytes may, in certain conditions, acquire maladaptive features which may exacerbate or even cause damage to the nervous tissue (Pekny et al. 2016; Sofroniew 2020). First, astrocytic reactivity may interfere and downregulate essential homeostatic functions such as K^+ buffering or glutamate homeostasis. In particular, failure of glutamate homeostasis seems to be a converging point in the pathophysiology of various neurological diseases, such as toxic encephalopathies (Li et al. 2021), hepatic encephalopathy (Montana et al. 2014; Obara-Michlewska et al. 2015), epilepsy (Bedner et al. 2015) or amyotrophic lateral sclerosis (Rossi et al. 2008; Valori et al. 2014). In addition, reactive astrocytes may be associated with the release of potentially damaging molecules through pathological gain of function, when existing homeostatic cascades start to overproduce particular agents. For example, in Alzheimer's disease astrocytes overexpress monoamine oxidase-B (MAO-B) to produce GABA from puterscin; this overproduction of GABA counteracts neuronal hyperexcitability

closely associated with AD progression (Garaschuk and Verkhratsky 2019; Ghatak et al. 2019). Increase in MAO-B activity, however, results in overproduction of hydrogen peroxide that initiates neuronal damage and death (Chun et al. 2020). Similarly, astrocytic overproduction of complement C3 (which otherwise is a legitimate physiological ligand) leads to morphological and functional neuronal defects (Lian et al. 2015).

To summarise, reactive astrogliosis is an intrinsic physiological astrocyte programme aimed at neuroprotection, at maintenance of tissue homeostasis and at preservation of integrity of nervous tissue. In certain conditions, however, and in particular in conditions of chronic and severe stress, reactive astrocytes may acquire maladaptive properties contributing to the damage of the CNS. In both conditions, reactive astrocytes remain an important part of disease progression often defining the neurological outcome of neuropathological process.

Pathological Remodelling of Astrocytes

The second group of astrogliopathologies is represented by pathological remodelling of astrocytes. This class of pathological changes covers astrocytic abnormalities associated with an acquisition of aberrant molecular cascades or functional properties, which drive pathology (Ferrer 2018; Pekny et al. 2016). The best examples of pathological astrocytic remodelling are represented by primary genetic astrogliopathies linked to expression of mutated genes. Alexander disease, a genetic leukomalacia, stems from astrocytic expression of sporadically mutated GFAP gene, which affects, in a yet unknown way, astrocyte function which ultimately results in severe damage to the white matter (Messing et al. 2012). Another example of pathological remodelling of astrocytes occurs in Duchenne muscular dystrophy (DMD) associated with expression of mutated dystrophin gene. Although major clinical presentation of DMD is associated with muscular weakness and cardiomyopathy, most of the patients show psychosocial abnormalities and impaired cognitive abilities. In the CNS dystrophin is expressed mainly in astrocytes (Hendriksen et al. 2016), and its mutations are linked to aberrant CNS cytoarchitecture, abnormalities in dendrites and loss of neurones. All these cytopathologies cause a general detrimental neurobehavioural profile, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders and obsessive-compulsive disorder (Anderson et al. 2012; Hendriksen et al. 2018; Ricotti et al. 2015). At the cellular level, expression of mutant dystrophin gene resulted in an aberrant cytoskeleton arrangement and deficient homeostatic capabilities of astrocytes derived from stem cells isolated from DMD patients. In particular, glutamate clearance was severely affected in these astrocytes (Patel et al. 2019). Astroglial pathological remodelling is also central for several other leukodystrophies including vanishing white matter disease, megalencephalic leukoencephalopathy with subcortical cysts and Aicardi-Goutières syndrome (Brignone et al. 2014; Dooves et al. 2016; Jorge and Bugiani 2019). Finally, pathological remodelling of astrocytes has been suggested to occur in mesial temporal lobe epilepsy, characterised by aberrant astrocytic morphology, reduced gap junctional coupling and downregulation of $K_{ir}4.1$ channel expression; all these changes converge into deficient K^+ homeostasis that facilitates generation of seizures (Bedner et al. 2015).

Astroglial Atrophy, Asthenia and Loss of Function

This class of pathological changes includes cell-autonomous astrocytic changes, which do not involve reactivity (i.e. they are not instigated by lesion to the CNS) while being associated with diminished astrocytic function. First, this astrocytic insufficiency is linked to cellular atrophy manifested by decrease in astrocytic morphological profile, with corresponding decrease in astrocytic territorial domain and diminished astrocytic synaptic coverage. This morphological atrophy associated with decrease astrocytic homeostatic support is observed in numerous neuropathological contexts. In particular, morphological atrophy of astrocytes has been detected in diseases of cognition such as neurodegenerative diseases (Heneka et al. 2010; Rodriguez et al. 2009; Verkhratsky et al. 2010) and psychiatric diseases (Dietz et al. 2020; Verkhratsky et al. 2014; Verkhratsky and Parpura 2016; Windrem et al. 2017). Major neuropsychiatric disorders, such as schizophrenia, major depressive disorder and addictive disorders are all associated with reduction of astrocytic density and decrease in astrocytic morphological profiles as revealed by multiple markers (Cotter et al. 2001; Czeh and Di Benedetto 2013; Czeh and Nagy 2018; Miguel-Hidalgo 2009; Rajkowska et al. 2002; Rajkowska and Stockmeier 2013; Scofield et al. 2016). Another pathological feature, the astrocytic asthenia, which is manifested by failures of astroglial homeostatic cascades, is also frequently present in diseases of the brain. In particular, severe decrease in glutamate clearance due to ~80% decrease in expression of astrocytic plasmalemmal glutamate transporters is a leading cause of Wernicke-Korsakoff encephalopathy, associated with massive excitotoxic neuronal death (Hazell 2009; Hazell et al. 2009). Deficits in astroglial glutamate clearance and failure in glutamate-glutamine/GABA shuttle are likely responsible for abnormal neurotransmission as well as for excitotoxic neuronal death, both resulting in psychotic symptoms (Sanacora and Banasr 2013). Decreased expression of plasmalemmal glutamate transporters and decreased glutamate clearance from the extracellular space/synaptic cleft are common features of many addictive disorders, with astrocytic plasmalemmal glutamate transporters representing a promising drug target (Roberts-Wolfe and Kalivas 2015). Neuronal death in amyotrophic lateral sclerosis similarly reflects astrocytic loss of function being a consequence of insufficient astroglial function in extracellular glutamate clearance (Rossi et al. 2008; Valori et al. 2014).

Atrophy of astrocytes linked to decreased synaptic connectivity and synaptic efficacy contributes to cognitive deficiency in both normal ageing and senile dementia. Ageing is the main risk factor for neurodegenerative diseases underlying senile dementia, including Alzheimer’s disease. At the same time normal physiological brain ageing with mostly preserved cognitive capacity differs fundamentally from neurodegenerative pathology: in the former the number of neurones is largely preserved, whereas in the latter neurones undergo massive death, which underlies severe cognitive impairment (Pakkenberg and Gundersen 1997; Verkhratsky et al. 2004; von Bartheld et al. 2016; West 1993). Astrocytic numbers seem to be preserved in physiological ageing, whereas the data on astrocytic morphology are controversial and detailed analysis of astrocytic profiles is scarce (Olabarria et al. 2010; Pakkenberg and Gundersen 1997; Verkhratsky et al. 2020a). Most of our knowledge of the state of astrocytes in the ageing brain rests on the analysis of the expression of GFAP, the presumed universal marker of astrocytes (Hol and Pekny 2015). Expression of GFAP is generally increased in the aged brain, which was considered as

a sign of astrogliosis and age-dependent inflammation (David et al. 1997; Goss et al. 1991; Hardy et al. 2018; Nichols et al. 1993). Morphometry of aged astrocytes, however, revealed rather contradictory results with both increase and decrease in size and complexity of GFAP-positive astrocytic profiles being observed (see Verkhratsky et al. (2020a) for details and references). All these results, however, need a critical revisit, because GFAP is not an ideal marker of astrocytes (see Verkhratsky and Nedergaard (2018) for detailed discussion). First, in a healthy brain, the majority of astrocytes do not express GFAP at the level of immunocytochemical detection. Second, the proportion of GFAP-positive cells depends on age and brain region. Third, increases in GFAP immunorecativity does not necessarily report reactive changes; in the suprachiasmatic nucleus and the intergeniculate leaflet, for example, GFAP expression undergoes substantial circadian changes (Moriya et al. 2000). Fourth, GFAP labels only cytoskeleton associated with primary astrocytic processes; the peripheral leaflets are always GFAP-negative, and therefore GFAP cannot accurately reveal astrocytic morphology. Finally, GFAP expression changes under various types of environmental stimulation: physical exercise or environmental enrichment increases GFAP-positive profiles, and this increase is beneficial for nervous tissue (Diniz et al. 2016; Rodriguez et al. 2013; Sampedro-Piquero et al. 2014). Thus, age-dependent changes in GFAP expression and GFAP-positive profiles do not reveal much about astrocytic ageing.

Labelling of astrocytes with other markers showed more complex age-dependent changes. Staining of astrocytes with Golgi black reaction did not identify age-dependent morphological changes (Castiglioni Jr. et al. 1991). Immunohistochemical analysis of astroglial profiles labelled with antibodies against GFAP, glutamine synthetase and protein s100β demonstrated complex region- and marker-dependent and age-dependent changes ranging from atrophy to hypertrophy (Rodriguez et al. 2014). The GFAP-labelled astrocytes showed hypertrophy in the CA1 region and in the dentate gyrus of old hippocampus but marked atrophy in the entorhinal cortex (EC). Astrocytes positive for glutamine synthetase were smaller in old hippocampus but larger in the old entorhinal cortex, while s100β-positive profiles from old animals demonstrated an increase in the entorhinal cortex and almost no change in the dentate gyrus and no changes in the CA1 region (Fig. 4).

Morphology of astrocytes probed with intracellular injection of the fluorescent dye Alexa Fluor® 594 revealed age-dependent changes in astrocytic morphology. Two-photon imaging with subsequent 3D reconstruction of astrocytes perfused with the dye showed a significant increase in the size and complexity of astrocytes in development from youth to adulthood, whereas astrocytes in the old brains were smaller and less complex and significant decrease in size and complexity of astrocytes in old animals, with substantial reduction on the volume of peripheral processes (Fig. 5, (Popov et al. 2020)). These changes in peripheral processes affected synaptic coverage and synaptic homeostasis; in particular, astrocytic extracellular glutamate and K^+ clearance are both compromised in old animals, leading to depression of long-term potentiation reflecting on deficient memory (Popov et al. 2020).

Astrocytic atrophy is also present in neurodegenerative diseases. In AD, atrophic astrocytes appear in the brain together with reactive astrocytes. Subpopulations of atrophic astrocytes have been found in transgenic AD mouse models (Beauquis et al. 2013; Olabarria et al. 2010) and confirmed in stem cell-derived astrocytes from AD patients in vitro (Jones et al.

2017; Mohamet et al. 2018) and in vivo in derived astrocytes grafted in the mouse brain (Preman et al. 2020). In AD mouse models the total number of astrocytes does not change with age (Olabarria et al. 2010, 2011). At the same time at the early, pre-plaque, stages, astrocytes in entorhinal and prefrontal cortices and hippocampus demonstrate morphological atrophy (Beauquis et al. 2013; Kulijewicz-Nawrot et al. 2012; Olabarria et al. 2010; Yeh et al. 2012). There is a specific temporal pattern in the emergence of atrophic astrocytes in mouse AD models (Rodriguez et al. 2016; Verkhratsky et al. 2019). First, atrophic astrocytic profiles (as visualised by antibodies against GFAP, s100β or glutamine synthetase) appear in the entorhinal cortex (they are present already in 1-month-old mice); subsequently, atrophic astrocytes appear in the prefrontal cortex (3–4 months of age) and finally in the hippocampus (in 6- to 9-month-old animals). Appearance of atrophic astrocytes thus precedes formation of β-amyloid deposits.

At the later stages (12- to 18-month-old animals) of AD, the emergence of β-amyloid plaques in the hippocampus instigates astrogliotic remodelling; reactive astrocytes migrate towards and surround senile plaques and β-amyloid infested blood vessels; at the same time atrophic astrocytes are positioned distantly to β-amyloid depositions (Olabarria et al. 2010; Verkhratsky et al. 2016b). Conversely, in entorhinal and prefrontal cortices, extracellular β-amyloid depositions are not accompanied with astroglial reactivity (Verkhratsky et al. 2016b). Failed astrogliosis represents a loss of function, which defines vulnerability of different brain regions to AD pathology. Indeed, in humans AD starts in entorhinal and prefrontal cortices before this disease spreads to the hippocampus.

Astrocytic atrophy and loss of function can contribute to AD pathophysiology being responsible for early synaptic dysfunction and cognitive deficits. Atrophic astrocytes provide diminished synaptic coverage, which translates in decreased support of synapses by astroglial cradle. First and foremost, this affects K^+ buffering and glutamate homeostasis which both are critical for normal synaptic connectivity. In addition, astrocytes are fundamental for synaptogenesis not only in the developing but also in the adult brain, and astrocytic atrophy may impair the formation of new synapses associated with learning and neuronal plasticity. Early stages of AD are associated with synaptopathy (Coleman et al. 2004; Terry 2000), which might be directly linked to diminished astrocytic support. Astroglial asthenia and loss of function may also account for deficient support associated with the lactate shuttle. Finally, a failure of astrogliotic defence together with a loss of homeostatic capacity of astrocytes (the glial paralysis) can be directly linked to neuronal death and brain atrophy clinically manifested as senile dementia (Verkhratsky et al. 2015).

Astrodegeneration or Clasmatodendrosis

Insults to the brain as well as chronic brain pathologies stress astrocytes, which can undergo degenerative changes and necrotic or apoptotic death. Morphologically, astrodegeneration is manifested by clasmatodendrosis (from Greek “κλάσμα”, fragment, “δένδρον”, tree, “ωσις”, process). This process has been initially characterised by Alois Alzheimer and also described and named by Santiago Ramón y Cajal (Penfield 1928a). Clasmatodendrosis appears as fragmentation of astroglial processes, vanishing of distal processes, and swelling and vacuolisation of the cell body. Clasmatodendrosis has been visualised in vitro and

in tissue, and it was observed in several forms of neuropathology including ischaemia, infectious encephalopathies, stroke, dementia and psychiatric diseases (Hulse et al. 2001; Sahlas et al. 2002; Tachibana et al. 2019). Clasmatodendrotic astrocytes have been also identified in the brains of old mice (Mercatelli et al. 2016).

Envoi

We have outlined the presently ascribed roles of astroglia in nervous system pathology. As per human need to organize and stratify, we pigeonholed the roles into the present-day classification of astrogliopathology. While we have no doubt that this classification will develop further, likely by the time one reads these lines as the volume gets published, we deem it necessary and sufficient for further discussion of more detailed chapters that follow in this volume and delve into the role of astroglia in a variety of psychiatric conditions and diseases.

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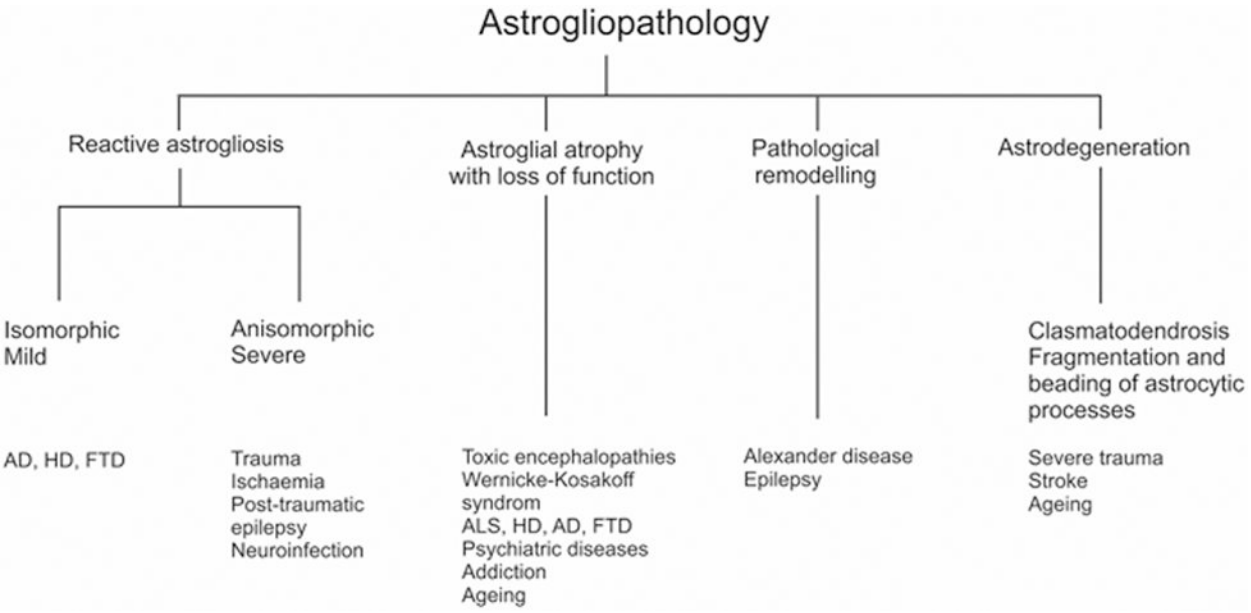

Fig. 1.

Classification of astrocytic pathological changes. AD Alzheimer's disease, ALS amyotrophic lateral sclerosis, FTD fronto-temporal dementia, HD Huntington's disease

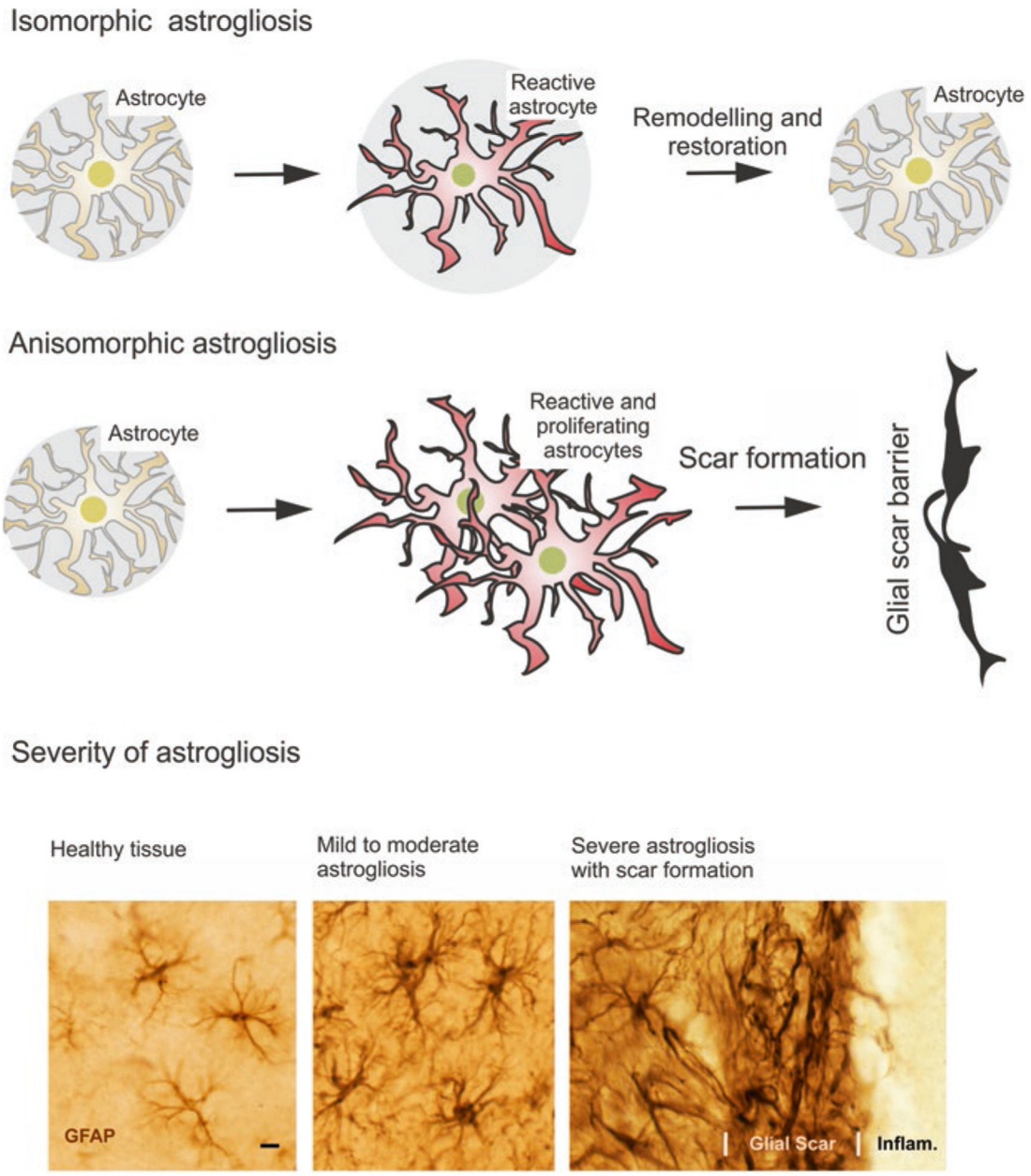

Fig. 2.

Classification of reactive astrogliosis; see text for explanation. (Modified from Verkhratsky and Butt (2013) and Sofroniew (2009))

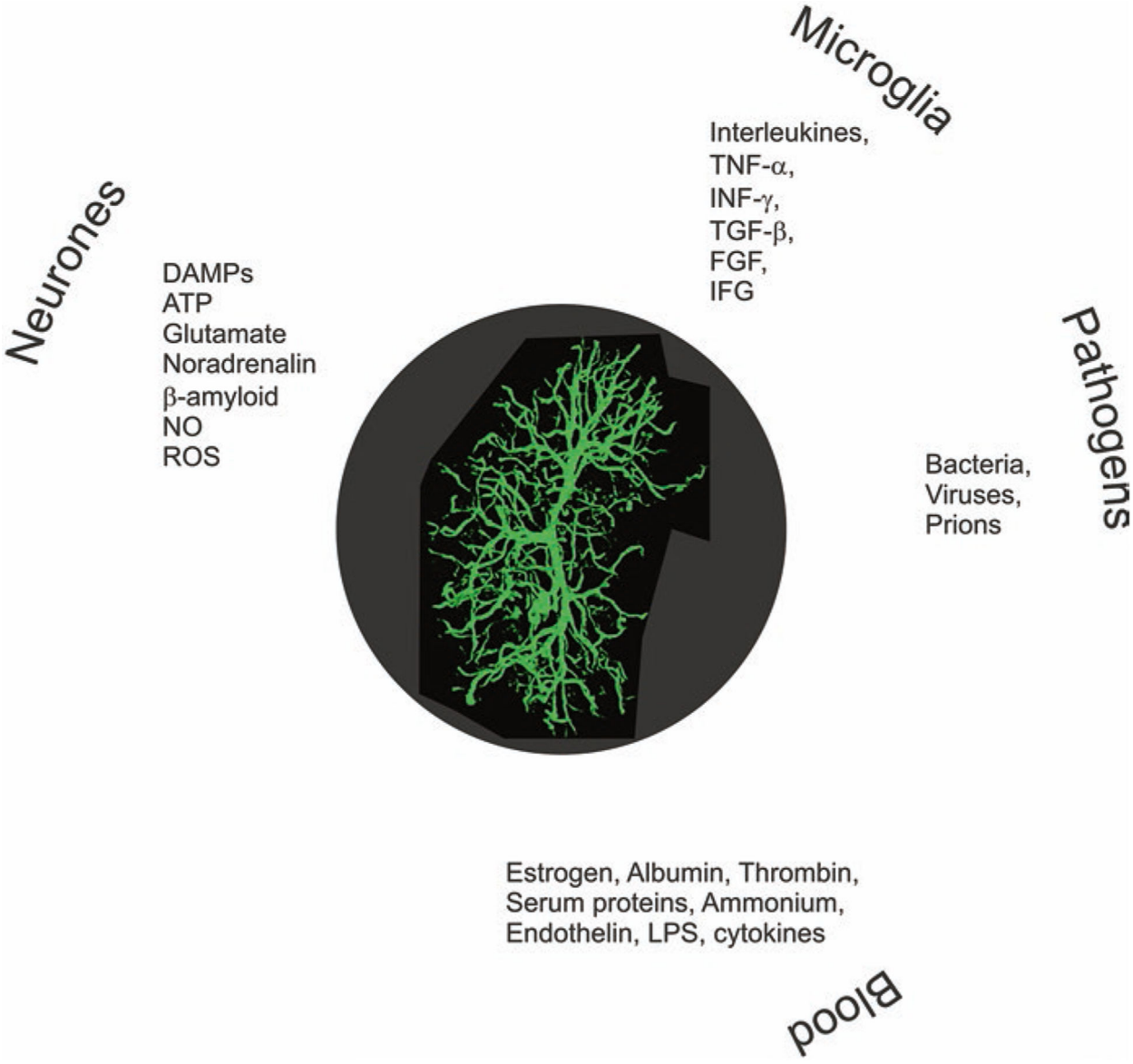

Fig. 3.

Instigators of reactive astrogliosis. Numerous agents, including damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPS, pathogens), the former originating from various cells in the nervous tissue or from blood. All these agents can activate various astrocytic receptors which launch astrogliotic programmes. Abbreviations: TNF-α tumour necrosis factor α, INF-γ interferon γ, TGF-β transforming growth factor β, FGF fibroblast growth factor, IFG insulin growth factor, NO nitric oxide, ROS reactive oxygen species, LPS lipopolysaccharide

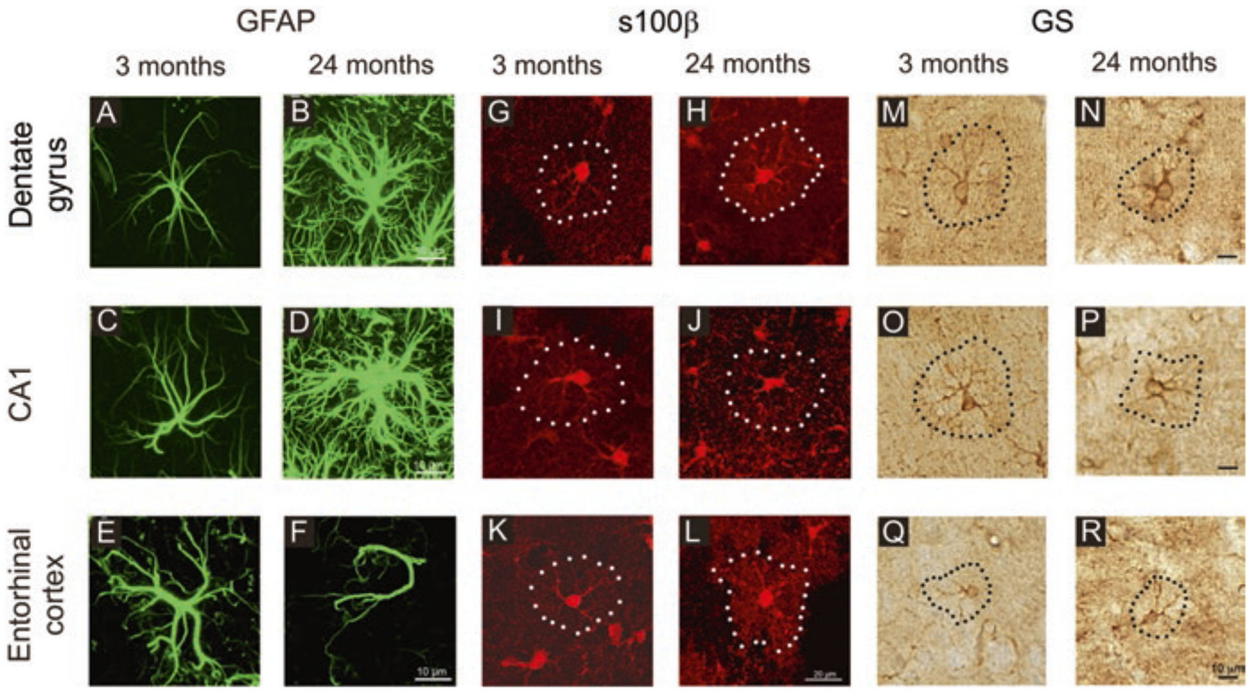

Fig. 4.

Age-dependent remodelling of astroglial profiles in different brain areas. Confocal images showing glial fibrillary acidic protein (GFAP) (A to F), s100β (G to L) and glutamine synthetase (GS) (M to R) immunolabelled astrocytes in the dentate gyrus and CA1 hippocampal areas as well as in the entorhinal cortex of mice at 3 and 24 months. (Reproduced, with permission from Verkhratsky et al. (2020a))

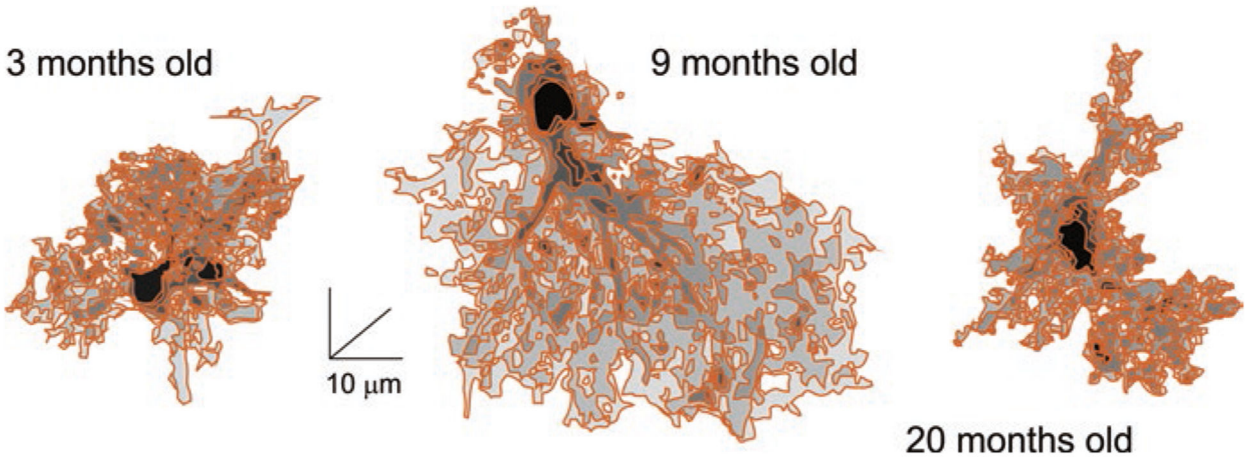

Fig. 5.

Reconstructions of hippocampal protoplasmic astrocytes from young, adult and old mice. (Reproduced, with permission from Verkhratsky et al. (2020a))