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Astrocytes: a central element in neurological diseases

--Manuscript Draft--

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Corresponding Author:	Milos Pekny University of Gothenburg Gothenburg, SWEDEN
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Gothenburg
Corresponding Author's Secondary Institution:	
First Author:	Milos Pekny
First Author Secondary Information:	
Order of Authors:	Milos Pekny
	Alexei Verkhratsky
	Marcela Pekna
	Albee Messing
	Christian Steinhäuser
	Jin-Moo Lee
	Vladimir Parpura
	Elly Hol
	Michael Sofroniew
Order of Authors Secondary Information:	
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Abstract:	The neurone-centred view of the past disregarded or downplayed the role of astroglia as a primary component in the pathogenesis of neurological diseases. As this concept is changing, so is also the perceived role of astrocytes in the healthy and diseased brain and spinal cord. We have started to unravel the different signalling mechanisms that trigger specific molecular, morphological and functional changes in reactive astrocytes that are critical for repairing tissue and maintaining function in CNS pathologies, such as neurotrauma, stroke, or neurodegenerative diseases. An increasing body of evidence shows that the effects of astrogliosis on the neural tissue and its functions are not uniform or stereotypic, but vary in a context-specific manner from astrogliosis being an adaptive beneficial response under some circumstances to a maladaptive and deleterious process in another context. There is growing support for the concept of astrocytopathies in which the disruption of normal astrocyte functions, astrodegeneration or dysfunctional/maladaptive astrogliosis are the primary cause or the main factor in neurological dysfunction and disease. This review describes the multiple roles of astrocytes in the healthy CNS, discusses the diversity of astroglial responses in neurological disorders and argues that targeting astrocytes may represent an effective therapeutic strategy for Alexander disease, neurotrauma, stroke, epilepsy and Alzheimer's disease as well as other neurodegenerative diseases.

Dear Professor Paulus,

Please find enclosed the revised version of our manuscript "Astroglial responses as a central element in neurological diseases: towards novel therapeutic targets". We have addressed all the comments and concerns of the reviewers (see below) and we trust that the review is now acceptable for publication in Acta Neuropathologica.

We look forward to hearing from you.

Yours sincerely,

Milos Pekny and Alex Verkhratsky
On behalf of the authors

Editor's comments:

…. please carefully consider the following technical requirements:

(1) Figures should be of high resolution (at least 300 dpi)
Done.
(2) Figure parts should be identified with lower case roman letters on figures and throughout text including legends (a, b, c etc, not A, B, C etc).
Done.
(3) Number of references should ideally be reduced to less than 200.
We have not reached below 200, but only essential references are given.
(4) The abstract should include more specific terminology so that readers can find the paper more conveniently using PubMed etc, such as names of diseases covered.
We completely agree, and we have now done so.

Reviewer #1:
1. This is a comprehensive review of astrocyte pathology in a number of neurological diseases and a review of the nature of astrocyte "gliosis." The main issue with this review is that the reader expects much more in terms of ideas for treating astrocytes in these diseases and ideas about how treating astrocytes will improve the clinical or pathological aspects of the diseases. Yet the authors give little attention to this issue and suggest few specific ideas. The review would be greatly strengthened by a primary focus on potential strategies for treatment. This focus would provide novelty to this review, since descriptions of astrocyte pathology in many neurological diseases have been given in many papers and reviews.

We agree with this comment and we have now revised the manuscript with the proposed angle in mind, moreover, we have included a table with examples of potential treatment strategies targeting astrocytes.

2. There are a great many correlations between reactive astrocytes and other pathologies or clinical signs and symptoms (GFAP expression and dementia, for eg. (p.17)), but there are few clear causal relationships. This issue will be important to sort out when thinking of treatments that involve astrocyte function. The authors should discuss this.

We agree; this is a rather complex matter, because indeed in many pathologies the casual relationship between GFAP expression and the neurological outcome is not yet clarified. When more is known (for example in Alexander disease) we provide the reader with the hard data; in other chapters we discuss the relations between failed astroglial homeostatic function and disease progression, which we feel is particularly relevant in the context of epilepsy, AD and HD (for example compromised glutamate uptake as a mechanism for neuronal death). Therefore - and as suggested by this reviewer - we have now stated in the text "The causal relationship of these important associations needs to be addressed on a molecular level."

3. The different neurological diseases discussed affect quite different parts of the CNS. Astrocytes are a heterogeneous population, so the authors should discuss what is known about the nature of astrocytes in these various areas with respect to the astrocyte pathology that occurs in those different parts of the CNS.

We agree with this reviewer, but the available information is still too limited to give a reasonably comprehensive and useful picture of this in the current review. However, as the molecular characterization of astrocytes proceeds, we hope that this highly relevant issue of astrocyte heterogeneity (further amplified in a disease context, and definitely disease-specific) could soon be addressed.

4. A description of GFAP null and/or Vimentin null mice doesn't really add too much to the discussion of potential treatments.

We politely disagree, because the data on the null mice demonstrate that the absence of GFAP and vimentin affects the pathology and hence these molecules are legitimate therapeutic targets. We have now made this angle more clear by including GFAP and vimentin in the new Table among the examples of potential treatment strategies targeting astrocytes.

5. There is little reason to describe the well-known features of AD and HD.

We removed the general introductions as suggested

6. How has astrocyte pathology been causally related to changes in BBB in disease?

At present, we are not aware of direct experimental data indicating that damage to BBB can originate from astrocytes.

7. In many of the neurodegenerative diseases one sees neuronal and astrocyte and microglial pathologies. How much of the astrocyte pathology is primary to the disease itself and how much is secondary? However, even in a secondary pathology, astrocyte dysfunction could exacerbate the underlying pathological changes, in neurons, for example.

We completely agree and want to thank the reviewer for bringing up this angle, which was not sufficiently stressed in the review. It is indeed so important that we have now integrated it both in the review and in the conclusion section, which we have re-written. We must however state that our review is specifically dedicated to astrogliopathology, and we feel that, to maintain the focus, we cannot go into the detail of pathology of other glia, namely oligodendroglia, NG2 cells and microglia.

Reviewer #2:
This paper is a comprehensive very detailed review of what is known about the role of astrocytes and their contribution to the neuropathology of major neurological disorders. The topic is without doubt of great interest and the authors have done a very comprehensive review of the available literature . In its present form the paper is however difficult to follow. It would be helpful if it could be more synthetic outlining concepts and limiting to some extent the detailed description of results of single papers. The numbers of references is excessive. Figures at times do not necessarily add clarity (see figure 4).

We appreciate that this reviewer finds the review to be comprehensive, very detailed and on a topic that will be of great interest. We have followed this reviewer's suggestions and shortened some descriptive paragraphs, have re-written both the abstract and the conclusions for better clarity, and added a new segment on potential treatment strategies targeting astrocytes. We have also improved the clarity of Figure 4 by re-writing the figure legend.

Reviewer #3:
I have mainly minor suggestions for improvement but their number is rather large. They are detailed below.

It would benefit the paper if the existing literature that is relevant to the concept of "sick glia" would be mentioned. This literature probably started with Papp-Lantos inclusions in MSA, sick microglia in prion disease (J Neuropathol Exp Neurol. 1998 Mar;57(3):246-56) and the concept of primary gliodegeneration was introduced in this journal (Acta Neuropathol. 2006 Nov;112(5):517-30). Use of conventional nomenclature increases readability. Thus, primary should be distinguished from secondary astroglial involvement. Furthermore, the long-standing controversy about astrocytes as important CNS antigen presenting cells, which seems to have been finally settled, should at least be mentioned. In addition, the rather widespread

formation of submicroscopic astrocytic lamellar processes by (reactive) astrocytes (there are numerous physiological as well as pathological conditions) should be referenced. The term neuroinflammation (vide infra) should be defined or omitted. There are a number of small language problems (listed below).

We are grateful for all these suggestions, and tried to accommodate them in the revised paper.
1. The concept of "sick glia": the paper by Eitzen at al., 1998, to which this referee refers, indeed introduces a concept of pathologically injured microglia as a substantial part of the pathological progression in the context of Creutzfeldt-Jakob disease. We fully appreciate the importance of this observation, and yet our paper is specifically focused on astrocytes, and hence we do not feel we may go into detailed descriptions of microglial pathology. The term "sick glia" has not become common and hence we prefer not to use it.

2. We did overlooked the original paper by Croisier E, Graeber MB outlining the concept of gliodegeneration, and we are grateful to this referee for his/her criticism; we now cite this paper.

3. We cannot agree more about the usage of the term "neuroinflammation" and in fact we tried to avoid it; the revised text does not contain this term at all.

The title would be more original without the fashionable translational lingo, "towards novel therapeutic targets".

We have changed the title accordingly, albeit after some hesitation: most of us have a clinical background and thus do not consider the translational angle of this review "fashionable" but simply reflecting our ambition to connect the existing body of knowledge about reactive astrogliosis to respective disease situations. But we self-critically admit that we are only at the beginning of the hunt for new therapeutic targets and have therefore reserved the qualifier "towards novel therapeutic targets" for one of the next reviews.

Page 4 There is increasing evidence for a concept of astrocytopathies *in support of

We agree, and have re-written the abstract.

Page 4 We argue that a full concept of astrocytopathology *sounds odd, especially with respect to the functional astrocytic syncytium

We agree, and have re-written the abstract.

Page 5 The synaptic assembly also includes a process of microglial cell that frequently tests the synapse status [114, 239]. *Reference 114 is quite self-serving; Kettenmann in particular failed to recognize the importance of the concept for quite some time - there are earlier review articles that should be cited

We additionally cited the review by Tremblay (2010).

Page 5 Insults to the CNS, regardless their aetiology, strain the organ homeostasis and these are astrocytes which through dedicated molecular cascades protect neurones against *check for completeness and style

We have revised the sentence in question.

Page 5 Defensive function of astrocytes is manifested in reactive astrogliosis, *teleological statement

We have modified the sentence accordingly.

Page 6 Astrocytes also regulate the number of synapses after injury and inhibition of astrogliosis intensifies synaptic loss in the hippocampus of mice in the acute phase (4 days) after injury [249]. Incidentally, in the same mice with suppressed astroglial response the synaptic recovery was improved, with the numbers reaching the levels on the uninjured side 14 days after lesion [249]. *This discrepancy is confusing, please explain

We have now re-written this part for better clarity.

Page 7 This neurone-centricity is now being challenged and neuroglia begin to be regarded as a central element of neuropathology [32, 172, 194, 234, 236]. *Neuropathology has been far less neuron-centric than the authors realise as it has been recognised since Alzheimer's and Spielmeyer's time that neuropathology is glial pathology to a significant extent. Neurobiologists unaware of the glial changes in pathology introduced the recent literature bias.

We agree with this completely; indeed we referred to early observations of Alzheimer (page 13 for example). It is hard to deny however that modern neurology is very much neurone-centric and we tried to confront this.

Page 7 Astroglial component of neuropathology is highly variable and is disease-specific. *It certainly is not always disease-specific

We modified the sentence by adding "it is often".

Page 7 ... major depressive disorders *please explain further

The sentence in question states: "Decrease in the astroglial numbers as well as astroglial atrophy has been detected in schizophrenia, in temporal lobe epilepsy, and in major depressive disorders and loss of astrocyte-dependent control over glutamatergic transmission is considered as one of the principal mechanisms of abnormal synaptic connectivity in these major psychiatric disorders." The matter of astroglia loss in numbers

and function has been extensively covered by existing literature and we provide relevant references. We do not feel that it is appropriate to go into detailed description of astroglial changes in psychiatric diseases in the context of this review.

Page 8 ... hypertrophy of astrocyte processes *missing: lamellar specialisations (see above)

We are somewhat confused with this query - we do not clearly see what we should discuss about lamellar specializations in the context of broad definition of astroglial reactivity. We acknowledge that is a very important feature of astrocytes and relates to their structural and functional subdomains. However, their relevance for pathophysiological situations still remains to be established.

Page 8 ... a proportion of reactive astrocytes proliferate *explain proportion

This has now been re-formulated.

Page 8 ... astrocytes do not migrate *this is contradicted later (see below)

We want to thank this reviewer for pointing out this contradiction. It has now been resolved.

Page 8 ... neuroinflammation *please define

We are now more specific in the text, and we do not use the term neuroinflammation.

Page 9 ... astrocyte migration *see above

We want to thank this reviewer for pointing out this contradiction. It has now been resolved.

Page 9 ... analysis at the single cell in vivo *please check for completeness

We wish to thank this reviewer for identifying this missing word. It has now been corrected.

Page 10 ... which up-regulation happens *please check for completeness

We have now used a better formulation.

Page 13 ... missense variations, *not a widely used term

We wish to thank this reviewer for identifying this typo.

Page 13 (Bedner et al., 2015) *check citation format

Done.

Page 15 ... glial-mediated and propagated inflammation has been shown to exacerbate amyloid plaque pathogenesis *carefully define inflammation in this context; typical inflammation is a multicellular process involving cells of the peripheral immune system; up-regulation of a cytokine doesn't equal inflammation, cf. Estes, M. L., & McAllister, A. K. (2014). Alterations in Immune Cells and Mediators in the Brain: It's Not Always Neuroinflammation! Brain Pathology, 24(6), 623-630. doi:10.1111/bpa.12198

This sentence has been removed.

Page 15 In addition, further studies in transgenic mouse models suggested that inflammation and glial activation may be a much more complex process than previously thought. *see above comments regarding (neuro)inflammation

The text has been modified.

Page 16 ... astrocytes migrated *see above

We have adjusted this statement and want to thank the reviewer for bringing it up.

Page 16 Therefore, enhancing lysosomal function in astrocytes is an effective strategy to restore adequate -amyloid removal and counter amyloid plaque pathogenesis in AD. *Lysosomes are not a leading feature of astrocytes; this should be mentioned

We are introducing the topic in the sentence "Astrocytes are capable of taking up b-amyloid, via endocytosis or macropinocytosis and subsequent trafficking and degradation via the lysosomal pathway [14, 129]."

Page 17 ... the failure of the latter may further exacerbate astrodegeneration in AD. *Fragmentation of microglia in AD is now a well recognised phenomenon; the comparable (?) changes in astrocytes remain unclear

We agree.

Page 17 This is in contrast with an AD mouse model, in which the earliest sites of ?-amyloid depositions are associated with both reactive astrocytes and microglia [105, 107]. *The mouse model really doesn't matter much in this context; the human tissue is the reference of interest

We agree, we mention it only to imply that care should be exercised when drawing inference to humans.

Page 17 ... neuropathological Braak stages *what precisely are the authors referring to, Alzheimer's or Parkinson's disease?

It refers to the former - we have now clarified it in the text.

Page 18 Obviously, this type of plasticity is lost in AD patients. *This is not obvious

We agree and we removed this statement completely.

Page 18 Furthermore, amyloid precursor protein, one of the causal genes for AD, is highly expressed in astrocytes *the protein is not the gene

We have corrected the text.

Page 19 ... imperative to include the molecular and cellular changes of glia as well as neurones into account when trying to decipher the exact processes that lead to dementia in AD. *Check grammar

We have corrected the text accordingly.

Page 19 ... cell-autonomous change *this is a confusing term which should be explained or omitted

We have modified the text accordingly.

Page 20 Astroglia represents the homeostatic, controlling and defensive arm of the CNS. *Controlling neurons? That seems unlikely. Microglia represent the CNS defence system. 'Defensive arm' applied to astrocytes sounds like an overstatement.

We have re-written the conclusion section with the corresponding modifications.

Page 38 Astroglial cradle *strange wording (raises unrelated and thus distracting connotations)

This is the term introduced in 2012 which has been the subject of several reviews and has been accepted by at least a part of glial community. The Fig 1 is modified from the very paper that discusses this concept.

Page 38 Classification of pathological changes in astroglia. *See comment regarding primary and secondary above

We have now addressed the issue of primary vs. secondary changes in astroglia both in the review and in the conclusion section.

Page 38 Reactive astrocytes receive and send diverse molecular instructions. *Teleological statements

We agree and we have re-written the whole figure legend.

Acta Neuropathologica

Astrocytes: a central element in neurological diseases

Milos Pekny[1,2,3], Marcela Pekna[1,2,3] , Albee Messing[4], Christian Steinhäuser[5], Jin-Moo Lee[6], Vladimir Parpura[7], Elly M. Hol[8,9,10], Michael V. Sofroniew[11] & Alexei Verkhratsky[12,13,14]

[1]Center for Brain Repair and Rehabilitation, Department of Clinical Neuroscience and Rehabilitation, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, SE-405 30 Gothenburg, Sweden;
[2]Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia
[3]University of Newcastle, New South Wales, Australia;
[4]Waisman Center, 1500 Highland Avenue, University of Wisconsin-Madison, Madison, WI 53705, USA;
[5]Institute of Cellular Neurosciences, Medical faculty, University of Bonn, Germany;
[6] Department of Neurology, The Hope Center for Neurological Disorders Washington University School of Medicine, St. Louis, USA;
[7] Department of Neurobiology, Civitan International Research Center and Center for Glial Biology in Medicine, Evelyn F. McKnight Brain Institute, Atomic Force Microscopy & Nanotechnology Laboratories, 1719 6th Avenue South, CIRC 429, University of Alabama at Birmingham, Birmingham, AL 35294, USA;
[8]Department of Translational Neuroscience, Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands;
[9]Netherlands Institute for Neuroscience, an Institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands;
[10]Swammerdam Institute for Life Sciences, Center for Neuroscience, University of Amsterdam, The Netherlands;
[11] Department of Neurobiology, University of California, Los Angeles, CA 90095, USA;
[12] Faculty of Life Sciences, The University of Manchester, Manchester, M13 9PT, UK
[13] Achucarro Center for Neuroscience, IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain & Department of Neurosciences, University of the Basque Country UPV/EHU and CIBERNED, Leioa, Spain;
[14]University of Nizhny Novgorod, Nizhny Novgorod 603022, Russia

Running title: Astrocytes: a central element in neurological diseases

Address for correspondence:

Professor Milos Pekny
Center for Brain Repair and Rehabilitation,
Department of Clinical Neuroscience and Rehabilitation,
Institute of Neuroscience and Physiology,
Sahlgrenska Academy at the University of Gothenburg,
SE-405 30 Gothenburg, Sweden
email: Milos.Pekny@neuro.gu.se

OR

Professor Alexei Verkhratsky
The University of Manchester,
Oxford Road, Manchester, M13 9PT, UK.
Telephone +44 (0)161-2757324,
E-mail: Alexej.Verkhratsky@manchester.ac.uk

Abstract

The neurone-centred view of the past disregarded or downplayed the role of astroglia as a primary component in the pathogenesis of neurological diseases. As this concept is changing, so is also the perceived role of astrocytes in the healthy and diseased brain and spinal cord. We have started to unravel the different signalling mechanisms that trigger specific molecular, morphological and functional changes in reactive astrocytes that are critical for repairing tissue and maintaining function in CNS pathologies, such as neurotrauma, stroke, or neurodegenerative diseases. An increasing body of evidence shows that the effects of astrogliosis on the neural tissue and its functions are not uniform or stereotypic, but vary in a context-specific manner from astrogliosis being an adaptive beneficial response under some circumstances to a maladaptive and deleterious process in another context. There is growing support for the concept of astrocytopathies in which the disruption of normal astrocyte functions, astrodegeneration or dysfunctional/maladaptive astrogliosis are the primary cause or the main factor in neurological dysfunction and disease. This review describes the multiple roles of astrocytes in the healthy CNS, discusses the diversity of astroglial responses in neurological disorders and argues that targeting astrocytes may represent an effective therapeutic strategy for Alexander disease, neurotrauma, stroke, epilepsy and Alzheimer's disease as well as other neurodegenerative diseases.

Key words: astrocytes, astroglial cells, reactive astrogliosis, reactive gliosis, astrocytopathies, neurotrauma, stroke, epilepsy, Alzheimer's disease, Alexander disease, Huntington disease, neurological diseases

To help and protect: The warden astrocytes

Evolution of the nervous system progressed through specialisation and division of function, with neural cell networks being composed from electrically excitable neurones and electrically non-excitable glia. Neuronal specialization is in firing action potentials that propagate to axonal terminals and initiate synaptic transmission, whereas glia are optimized for housekeeping, control and neural tissue protection. The multipartite synapse of the CNS represents a striking example of such a specialization (Fig. 1), with pre- and post-synaptic membranes being packed with exocytotic machinery, neurotransmitter receptors and proteins responsible for plasticity, whereas all "homeostatic" molecules (i.e. transporters and enzymes responsible for ion and transmitter homeostasis in the synaptic cleft, for transmitter catabolism, for metabolic support etc.) being localized in the perisynaptic astroglial processes [229]. The synaptic assembly also includes a process of microglial cell that frequently tests the synapse status [112, 223, 236]. Already at this elementary level of CNS organisation, the cellular functions are divided. Neuronal compartment assures fast information flow whereas glial elements ascertain synaptic functional isolation and support, maintain synaptic operation through regulation of homeostasis and control synaptic survival or elimination depending on the network demands.

The very same specialisation is observed at all levels of CNS organization. Neurones fire and establish multiple contacts whereas neuroglia control local microenvironment and protects neural tissue. In the grey matter, astrocytes divide (through the process known as tiling that starts in late embryogenesis) the parenchyma into relatively independent units traditionally known as neurovascular units, and recently often called astroglio-vascular units, that integrate, within an individual astroglial territorial domain, neural and vascular elements [33, 94, 151]. By employing a wide array of molecular mechanisms such as exocytosis, diffusion through plasmalemmal channels or membrane transporters, astrocytes secrete numerous neurotransmitters, neurohormones and trophic factors [140, 164] that regulate synaptic fields, neuronal groups and signal to other cellular elements (e.g. microglia, oligodendroglia, pericytes, endothelial cells). At the level of the whole brain, astrocytes form *glia limitans* and regulate emergence and function of brain-blood and brain-cerebrospinal fluid barriers and contribute to overall brain metabolism being the sole producers and repository of glycogen.

The homeostatic function of astroglia is linked to their neuroprotective capabilities, as indeed astrocytes are principal elements of CNS defence. Insults to the CNS, regardless their aetiology, strain the organ homeostasis and these are astrocytes, which, through dedicated molecular cascades, protect neurones against glutamate excitotoxicity, extracellular K^+ overload, reactive oxygen species, and these are also astrocytes that supply stressed neurones with energy substrates [230]. The loss of these critical astroglial functions permits and exacerbates progression of various diseases, of which amyotrophic lateral sclerosis, toxic encephalopathies or neurodegeneration are prominent examples [228, 231]. Defensive function of astrocytes is manifested as reactive astrogliosis, a multicomponent and complex remodelling of astroglia triggered by lesions to the CNS [30, 165, 171, 205]. Astrogliosis is an important component of cellular pathophysiology and its suppression often aggravates neuropathology.

To learn and to remember: Astroglia in adaptive and regenerative CNS plasticity

Astrocytes are fundamental elements of the adaptive plasticity of the nervous system, essential for experience-dependent learning and functional regeneration after injury. Adaptive plasticity involves dendritic and axonal arborisation, spine density, synapse number and size (structural synaptic plasticity) as well as changes in receptor composition and density, and regulation of neurotransmitter release involving individual synapses (Hebbian synaptic plasticity) or resetting the strength of all the synapses in a particular neurone (homeostatic synaptic scaling). In some brain regions such as the hippocampus and olfactory bulb, adaptive plasticity involves also changes in neuronal numbers. These structural and functional changes in neuronal networks underlie also the activity-dependent re-arrangements of cortical maps, which together with the involvement of the contra-lesional hemisphere and contra-lesional axonal remodelling also contribute to the compensation and recovery of function after injury [166].

Astroglia derived factors induce synapse formation and maturation [148]. Thrombospondin (TSP) 1 and 2, extracellular glycoproteins secreted by astrocytes, induce excitatory synapse formation during development [39] by acting through the neuronal receptor α2δ-1 [56]. Similarly, astrocytes support synaptogenesis in the regenerating post-lesioned neural tissue. Expression of TSP 1 and 2 is increased after ischemia and TSP 1 and 2 deficient mice exhibited reduced synaptic density and axonal sprouting associated with impaired motor function recovery after stroke [130]. Another thrombospondin, TSP 4, controls protective astrogenesis in the adult subventricular zone after neurotrauma [19]. Astrocyte were also reported to secrete hevin protein that stimulates synaptogenesis; conversely the protein SPARC (secreted protein acidic and rich in cysteine), also secreted by astroglia, inhibits synaptogenesis both *in vitro* and *in vivo* [118]. Astroglia-derived glypican-4 and 6 induce functional synapse maturation by increasing the number of AMPA receptors on synapses [5]. Astrocytes also regulate the number of synapses after injury and attenuation of reactive astrogliosis in mice led to a more prominent synaptic loss in the hippocampus in the acute phase (4 days) after injury, but led to a complete synaptic recovery by 14 days after lesion [246]. These findings indicated that while reactive astrogliosis is protective at the acute stage, if it persists, regenerative responses might be inhibited.

In the developing CNS, astrocytes acting in concert with microglia play a critical role in the elimination of supernumerary synapses and this process, called synaptic pruning, is delayed in mice in which microglial migration is suppressed due to the lack of CX3CR1 chemokine receptor [163]. Synaptic pruning in the dorsal geniculate nucleus of the thalamus is dependent on the expression of the complement protein C1q in the retinal ganglion cells [189, 216], which in turn is regulated by transforming growth factor (TGF)-β secreted by immature astrocytes in the retina [23]. The C1q activates the classical complement pathway leading to the tagging of the thalamic synapses of these cells with complement-derived C3b fragment; the tagged synapses are subsequently eliminated by microglia in a manner that requires the complement receptor 3, CR3 [189, 216]. In glaucoma, one of the most common neurodegenerative diseases, microglia upregulate C1q at an early stage of the disease, and mice deficient in C1q are protected against glaucoma [91]. In line with these observations, mice lacking C3, from which C3b is generated by proteolytic removal of a small peptide known as C3a, have a larger number of synapses in the hippocampal CA1 [173]. Notably, these mice do not show any spontaneous epileptiform activity, conceivably due to compensatory reduction in release probability of glutamate from the presynaptic terminals [173]. The complement system also contributes to axotomy-induced elimination of synapses on spinal cord motoneurones, albeit in a C1q-independent manner [20]. Remarkably, while basal levels of C3a are required for normal synaptic function, dendritic extension and neuronal maturation of neural progenitor cells [129, 199], excessive astroglial release of C3 in

response to e.g. activation by β-amyloid disrupts neuronal morphology and function [129]. Astrocytes also actively engulf and eliminate synapses in the developing and adult brain. This process is governed by neuronal activity, and requires expression of phagocytic receptors MEGF10 and MERTK [40]. After ischemic injury, ephrin-A5 expressed by reactive astrocytes inhibits axonal sprouting and motor recovery [161]. Finally, astroglial cells are instrumental in controlling neuronal numbers through adult neurogenesis. Neural stem cells in the subventricular zone and in the dentate gyrus of the hippocampus, the two neurogenic regions of the adult brain, express glial fibrillary acidic protein (GFAP) and it has been proposed that many of these GFAP-positive astrocytes possess stem cell properties [28, 50, 53, 54]. Astrocytes also regulate the local microenvironment in the neurogenic regions through secreted as well as membrane-bound factors [131, 209, 245].

Astrogliopathology: Classification and general concept

Fundamentally, all diseases, naturally including neurological disorders, can be broadly defined as homeostatic failures within tissue, organ or a system. For a long time neuropathology was dominated by the neurone-centric views when all conceptualisation of brain pathology was focused on neurones, on their survival or death. This neurone-centricity is now being challenged and neuroglia begin to be regarded as a central element of neuropathology [30, 171, 192, 231, 233]. Astroglial component of neuropathology is highly variable and is often disease-specific. Distinct astrogliopathic changes may co-exist or emerge sequentially in the progression of neurological disorders. Here we propose a classification of astrocytopathies that is based around functional cellular response (Fig. 2). We broadly classify astrocytopathies into astroglial atrophy with loss of function, astroglial pathological remodelling and astrogliosis.

The concept of gliodegeneration in neuropathology was introduced by Emilie Croisier and Manuel Graeber in 1996 [45]. Astroglial atrophy, functionally manifested by loss of function contributes to pathological progression of a surprising variety of neurological disorders. Decrease in the astroglial numbers as well as astroglial atrophy has been detected in schizophrenia, in temporal lobe epilepsy, and in major depressive disorders and loss of astrocyte-dependent control over glutamatergic transmission is considered as one of the principal mechanisms of abnormal synaptic connectivity in these major psychiatric disorders [15, 152, 178, 232]. Astrodegeneration and down-regulation of astroglial glutamate uptake plays a leading role in excitotoxicity in amyotrophic lateral sclerosis, in Korsakoff-Wernicke syndrome and in toxic encephalopathies [85, 185, 232]. Atrophic changes in astroglia are observed in several types of neurodegeneration.

Pathological remodelling of astrocytes can be a causal factor in homeostatic failures of the brain such as a severe leukoencephalopathy seen in Alexander disease, in which astroglial expression of mutant GFAP leads to profound deficits in the white matter [141]. Aberrant increase in the astroglial synthesis of kynurenic acid induced by infection of astrocytes with *Toxoplasma gondii* is considered as a risk for schizophrenia [190]. Astrogliosis represents a multifactorial and complex remodelling of astrocytes, generally characterised by an increase in expression of GFAP and vimentin as well as a profound changes in astrocytic biochemistry and physiology associated with a secretion of numerous neuroprotective and pro-inflammatory factors.

Astrocyte reactivity and reactive astrogliosis

When and where can astrocyte activation be detected and why has it evolved? Molecular and morphological features of reactive astrocytes responding to an injury or other CNS pathologies include hypertrophy of astrocyte processes and up-regulation of GFAP, the key constituent of astrocyte intermediate filaments, both of these being hallmarks of reactive astrocytes in human pathologies such as neurotrauma, stroke, perinatal asphyxia, brain haemorrhage, CNS infections, epilepsy, or Alzheimer's disease (AD) (Fig. 3). Cytokines, such as transforming growth factor (TGF)-α, ciliary neurotrophic factor (CNTF), interleukin (IL)-6, leukaemia inhibitory factor (LIF), oncostatin M all were shown to induce astrocyte activation [10, 90, 115, 177, 213, 247]. Astrocyte activation seems to be also mediated by gp-130/activator of transcription 3 (STAT3) signalling pathway, phosphorylation and nuclear translocation of STAT3, either in astrocytes themselves [213] or, indirectly, via microglia, neurones or endothelial cells. Extensive (also known as anisomorphic) reactive astrogliosis results in glial scarring, which involves not only astrocytes but also other cells types, including pericytes that were recently proposed to be key contributors to glial scars [71].

Functionally, astrogliosis is aimed at: (i) increased neuroprotection and trophic support of insult-stressed neurones; (ii) isolation of the damaged area from the rest of the CNS tissue, (iii) reconstruction of the compromised blood-brain barrier; and (iv) in some situations, possibly at the facilitation of the remodelling of brain circuits in areas surrounding the lesioned region. Within the framework of remodelling, the neural circuits reactive astrocytes may acquire properties of stem cells [181]. The overall result of these functional reactions is clearly beneficial for the nervous tissue, since experimental removal of reactive astrocytes increases the degree of tissue damage and neuronal death [181, 208].

Reactive astrocytes that form a demarcating border between a focal lesion and the surrounding tissue (e.g. in ischemic or traumatic lesions or around amyloid plaques in AD) provide the means to demarcate the lesion and separate it from the rest of the CNS [180, 235]. Such a sequestering of a lesion might favour clinical stabilization and allow survival, but it might negatively affect the regenerative responses at a later stage [200]. Factors reducing astrocyte activation (as measured e.g. by the expression of GFAP) have not been sufficiently studied. Recently, complement activation-derived C3a has been shown to reduce the expression of GFAP in astrocytes subjected to ischemia while promoting their survival [198]. As the positive effect of C3a on astrocyte survival was equally strong in astrocytes lacking GFAP and vimentin, these data point to differential regulation of cell survival and GFAP expression in astrocytes in response to ischemic stress [198].

In response to injury, some reactive astrocytes proliferate and this increases the number of astrocytes at the lesion site [29, 205, 208]. Contrary to what was previously thought, recent live imaging data suggest that astrocytes do not migrate towards the side of injury [11]. Many astrocytes in the injured brain cortex become hypertrophic and up-regulate GFAP, however they stay within their tiled domains, among which only a limited overlap can be found [11, 244]. Some astrocytes become polarized or can proliferate, with the latter ones often being associated with blood vessels [11]. Such proliferating blood vessel-associated astrocytes might regulate migration and proliferation of pericytes involved in the glial scar formation [11, 71].

Are reactive astrogliosis and corresponding changes in the astrocyte network disease-specific and do they have disease-specific consequences? Recent data suggest that reactive astrogliosis has both common and unique cellular and molecular features in individual neuropathologies. Comparisons of gene expression profiles of reactive astrocytes between ischemic stroke and endotoxin-induced astrocyte activation revealed that at least half of altered gene expression

was disease-specific [256].

Elimination of dividing subpopulation of reactive astrocytes in transgenic mice suggested that reactive astrocytes play a positive role at the acute posttraumatic stage and limit the extent of neurodegeneration after neurotrauma [31, 59, 207]. Manipulation of reactive astrogliosis around focal lesions by ablation in astrocytes of STAT3 transcription factor, which is a transducer of signals for cytokines such as IL-6, LIF and CNTF [111, 213, 250] inhibited both astrocyte migration and lesion demarcation and resulted in larger lesions and increased functional deficit [87, 154, 241]. In contrast, ablation of Socs3, a negative feedback molecule of STAT3 [66, 144], reduced the lesion area and resulted in a better functional recovery [154].

As suggested by the above, changes associated with astrogliosis range from reversible alterations in astrocyte gene expression and cell hypertrophy with preservation of cellular domains and tissue structure, to long lasting scar formation that involves cell proliferation and permanent rearrangement of tissue structure. Multiple lines of molecular and cellular research indicate that astrogliosis is not a simple all-or-none stereotypic program triggered by a simple on/off regulatory switch, but instead is a finely gradated continuum of changes that occur in a context-dependent manner and that can be independently regulated by a multitude of specific molecular signalling events that mediate different specific responses [205, 208]. There is growing evidence for and interest in the potential for heterogeneity among reactive astrocytes not only across different CNS regions, but locally within the same [7]. For example, adjacent to focal traumatic or ischemic lesions there is topographic heterogeneity of astrogliosis as regards astrocyte proliferation, morphology and gene expression with respect to distance from the insult [205, 241]. In addition, analysis at the single cell level *in vivo* shows that intermingled reactive astrocytes can exhibit different expression levels of (i) chemokines or cytokines [81], (ii) signalling molecules such as pSTAT3 [87], or (iii) transcription factors that regulate sonic hedgehog signalling (SHH) [68].

As outlined above, astrogliosis can be induced, regulated or modulated by a wide variety of extracellular molecules ranging from small molecules such as purines, transmitters and steroid hormones, to large polypeptide growth factors, cytokines, serum proteins or neurodegeneration-associated molecules (Fig. 4). These instructive signals can derive from many different sources and can be released by cell damage or cell death, or via specific signalling mechanisms and act via receptors that initiate intracellular second messenger signalling cascades as reviewed elsewhere [107, 168, 170, 205, 208]. Many cell types can release molecular regulators of astrogliosis, including (i) local neural and non-neural cells intrinsic to CNS tissue such as neurones, microglia, oligodendrocyte lineage cells, endothelia, pericytes, fibromeningeal cells and other astrocytes, as well as (ii) non-neural cells that gain entry into the CNS, such as bone marrow derived leukocytes, fibrocytes, and microbial infectious agents, and (iii) cells outside of the CNS that produce serum proteins, cytokines, steroid hormones or microbial endotoxins such as lipopolysaccharides [30].

There is now substantial information about extra- and intra-cellular signalling molecules that regulate astrogliosis (Fig. 4A). Some aspects of astrogliosis can be regulated by multiple signalling cascades, while other aspects are regulated more selectively. For example, expression of intermediate filament proteins such as GFAP or vimentin can be induced by intracellular signalling pathways associated with cAMP, STAT3, NFkB, Rho-kinase, JNK, calcium and others [65, 143, 168, 170]. Similarly, astrocyte proliferation can be regulated by various extracellular signals including EGF, FGF, endothelin 1, sonic hedgehog, the serum proteins thrombin and albumin and others, and by intracellular regulators such as Olig2, JNK pathway and many more [63, 125, 203, 205] Other aspects of astrogliosis are regulated more selectively. For example, certain pro- and anti-inflammatory functions of astrocytes are

regulated separately. Deletion or disruption of NFkB or SOC3 signalling pathways in astrocytes diminishes recruitment of inflammatory cells after traumatic injury and autoimmune disease [26, 27, 154]. In contrast, deletion of STAT3 or its associated membrane receptor GP130, markedly increases the spread of inflammation after traumatic injury, autoimmune disease or infection [55, 82, 87, 154, 241]. Deletion of estrogen receptor alpha, but not estrogen receptor beta, selectively from astrocytes diminishes the anti-inflammatory and neuroprotective effects of estrogen on autoimmune inflammation [211, 212]. In addition, certain microRNAs (miR) such as miR-21 and miR-181, and miR regulatory enzymes, such as Dicer, can modulate astrogliosis and its functions, adding yet another level of potential regulation and specification of functions [22, 93, 218]. Thus, different signalling mechanisms regulate different aspects of pro- or anti-inflammatory functions of reactive astrocytes.

In response to the many incoming instructive signalling events described above, reactive astrocytes can release a wide variety of instructive molecular signals that are targeted at diverse kinds of surrounding cells, including multiple types of inflammatory cells, vasculature and other non-neural cells, as well as neural cells including neurones, synapses and oligodendroglia (Fig. 4B). Substantial evidence, as revealed in particular by *in vivo* transgenic loss-of-function studies, indicates that via these multiple molecular signals astrogliosis exerts numerous critical functions. For example, transgenic ablation or prevention of astrogliosis or astrocyte scar formation causes increased inflammation and tissue damage and worsens functional outcome in all CNS insult models studies thus far, including traumatic injury, ischemic injury (stroke), infection, autoimmune inflammation and neurodegenerative disorders [32, 55, 59, 82, 87, 127, 139, 147, 150, 235, 241]. Nevertheless, transgenic studies also reveal the potential for certain aspects of astrogliosis to exacerbate inflammation after traumatic injury or autoimmune challenge [26, 27, 211, 212]. Large scale gene expression evaluations also show that inflammatory mediators can drive astrocyte transcriptome profiles towards pro-inflammatory and potentially cytotoxic phenotypes [81, 256] that may be beneficial in microbial infection but may be detrimental if triggered during sterile (uninfected) tissue responses to trauma, stroke, degenerative disease or autoimmune attack [206]. Thus, transgenic loss-of-function studies point towards the potential for astrocytes to contribute to regulation of CNS inflammation in different ways, both by attracting inflammatory cells that take part in debris clearance, but also by forming scars that act as functional barriers that protect adjacent neural parenchyma from the spread of neurotoxic inflammation [30] Together, such observations provide compelling evidence that astrogliosis exerts a variety of beneficial functions that are essential for limiting tissue damage and preserving neurological function after CNS insults but that astrogliosis also has the potential to exert detrimental effects as determined by specific signalling mechanisms.

Ablation of astrocyte intermediate filament (nanofilament) system as an experimental modulation of reactive astrogliosis

Several approaches to study the function of reactive astrocytes utilized genetic ablation of the intermediate filament proteins, the up-regulation of which represents a hallmark of reactive astrogliosis. The intermediate filament system of reactive astrocytes is composed of GFAP, vimentin and nestin, and in some astrocytes it also includes synemin [100, 172, 214]; combined deficiency of GFAP and vimentin in *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice results in a complete absence of intermediate filament in reactive astrocytes [167]. Mice with *GFAP*$^{-/-}$*Vim*$^{-/-}$ genome show reduced reactive gliosis and glial scarring, slower healing with an increased loss of neuronal synapses following neurotrauma [167, 246], with decreased resistance of the CNS tissue to mechanical stresses [138, 226]. Astrocytes around the CNS lesion in *GFAP*$^{-/-}$ *Vim*$^{-/-}$ mice are present in normal numbers and form normally tiled domains [246], but do not

develop the typical hypertrophy of the main cellular processes [244, 246]. Ischemic stroke induced in *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice results in larger infarcts [127] with the astrocyte intermediate filament system being linked to astrocyte motility [125], viscoelastic properties, which might affect cell migration [136], vesicle trafficking [175, 176, 224], activation of Erk and c-fos [149], response to hypo-osmotic and oxidative stress and neuroprotective properties [47, 52], and the efficiency of glutamate transport and astrocyte gap junctional communication [127], all of which may play roles in CNS trauma or ischemia. The causal relationship of these important associations needs to be addressed on a molecular level.

Numerous negative consequences of reactive astrogliosis were also demonstrated, in particular when it does not get resolved in time, and can thus become maladaptive [183]. The inhibition of chondroitin sulphate proteoglycans that are expressed by oligodendrocyte precursor cells and astrocytes after CNS injury, is linked to improved axonal regeneration after trauma [24, 25, 123, 197, 240, 254]. Ephrin-A5, expressed by reactive astrocytes after injury was shown to limit axonal sprouting and functional recovery [161]. Genetic attenuation of reactive astrogliosis in *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice also has some positive outcome, albeit it is associated with more extensive tissue damage in the initial acute posttraumatic or post-ischaemic stage [127]. These include improved synaptic regeneration after entorhinal cortex lesion [246], improved post-traumatic regeneration of the optic nerve in the early postnatal period [36, 38] and improved regenerative response and functional recovery after spinal cord trauma [42]. Both basal and post-traumatic hippocampal neurogenesis are increased in *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice and it was proposed that the negative control of neurogenesis by astrocytes via Notch signalling to NSC/NPSs depends on GFAP and vimentin [245]. *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice exposed to neonatal hypoxic-ischemic injury develop normal size infarcts but show increased number of newly born cortical neurones [99]. Adult *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice support better integration of neural grafts in the retina [114] and neuronal and astrocyte differentiation of adult NSC/NPCs transplanted in the hippocampus [243]; it remains unknown whether this is caused by attenuated reactive gliosis or by altered interactions between the grafted cells and the recipient's astrocytes. Thus, the benefits of reactive astrogliosis at the acute stress-handling phase of neurotrauma or ischemic lesions might be counterbalanced by restricted regenerative potential at a later stage.

Astroglia in neurological diseases

Genetic astrogliopathy: Alexander Disease

Mutations in the astrocyte intermediate filament protein, GFAP, are causative for Alexander disease (AxD), a protein aggregation disorder in which the hallmark pathology consists of cytoplasmic aggregates known as Rosenthal fibres (RFs) that accumulate in the cell body, processes, and distal endfeet of astrocytes [141]. As such this disorder offers a fascinating window on the spectrum of effects that astrocyte dysfunction may have on the CNS. Clinically, patients present with a wide range of onsets from foetal through the seventh decade and varied symptomatology. Many patients exhibit some degree of white matter deficit (perhaps a combination of hypomyelination or demyelination depending on age of onset) that is typically bilaterally symmetrical and most severe in the fontal lobes but less severe or even absent in the later onset patients. A subset of patients displays focal lesions that are sometimes confused with neoplasia, especially in the brain stem. Why only certain areas of the nervous system are so vulnerable to the effects of mutations in a gene that is widely expressed, and in a cell type that is present throughout the entire nervous system, is far from clear.

One question that remains a topic of investigation is the composition of RFs and their role in disease. Early studies identified GFAP and the small heat shock proteins aB-crystallin and Hsp27 as major components of the fibres [96]. More recently this list has expanded to include vimentin, nestin, plectin, the 20S proteasome subunit, p-JNK, p62, and synemin [142, 172, 220, 257], although the exact proportions of these various components in the fibres remains to be elucidated. A lingering question is what prompts formation of the fibres in the first place. Initial studies implicated accumulation above a critical threshold as the key, since over-expressing even wild type GFAP to sufficient levels in mouse models leads to aggregates that are morphologically and biochemically indistinguishable (except for the absence of mutant protein) from those found in Alexander disease [142]. What the critical threshold is remains uncertain, with data from experiments using a knock-in mouse model showing that fibres appear with a five-fold change in total brain levels [76]; experiments on similar though not identical transgenic model suggesting a much lower threshold of only 30% excess to be sufficient [217]. In addition, no one has yet established whether RFs are protective or toxic, although evidence from the recently developed *Drosophila* model is compatible with the latter property [239].

In addition to the formation of RFs, a consistent downstream effect of both mutant GFAP and the accumulation of GFAP to excess is the activation of multiple stress pathways within the astrocyte. Some of these stress pathways may actually be protective, which if amplified in the proper way could be useful as therapeutic strategies. Such a role is already suggested for alphaB-crystallin from both the mouse and fly models [78, 239], and for the transcription factor Nrf2 from the mouse model [121]. Increased expression of GFAP itself can also be considered a type of stress response, as indicated from studies demonstrating transactivation of the *Gfap* gene promoter as an early event in evolution of disease [98]. Of course increasing expression of the very protein that starts the entire disease process in motion is not helpful, and more needs to be learned about how this promoter activation takes place.

Ultimately what aspects of astrocyte function are impaired via expression of mutant GFAP is still not known. Some data exists for an interference with expression of glutamate transporters, but whether this has functional significance in vivo has not yet been proven [221]. Recently, Walker et al. [237] demonstrated that the DNA and RNA binding protein TDP-43, clearly causative and widely implicated in other neurodegenerative disease, mis-localizes to the cytoplasm of astrocytes and becomes abnormally phosphorylated. Given the large number of genes and genetic pathways that are regulated by TDP-43, the cascade of effects initiated by GFAP mutations has the potential to quickly expand in multiple directions.

While most attention in Alexander disease research naturally has focused on astrocytes, it is worth remembering that other cells express GFAP as well, both developmentally and into adulthood. Indeed, the R236H mutant mouse suffers from a striking deficit in adult neurogenesis in the hippocampus [77]. In theory, this deficit could arise either from dysfunction of mature astrocytes in the hippocampus which are known to influence the stem cell population [12, 209], or directly from dysfunction of the stem cells themselves which also express GFAP [67, 194]. In rodents, at least, the integration of new neurones into the dentate gyrus contributes to contextual learning, spatial memory, and pattern separation [1, 49, 113, 187]. Similar claims have been made for human hippocampus [43]. The existence of this hippocampal phenotype opens an entirely new perspective and set of possibilities for studying the cognitive impairments that are frequently observed in patients with Alexander disease. Given the increasing recognition of neurogenesis as a property of the adult human central nervous system [210], it is especially valuable to have a single gene disease model in which to study the significance of adult neurogenesis.

Pathological remodelling of astroglia in epilepsy

Epilepsy is a condition of the brain characterised by the unpredictable occurrence of seizures, affecting at least 2% of the population world-wide [89]. The vast majority of epileptic cases are of idiopathic origin with their underlying mechanisms being undefined. This disorder is generally considered to reflect neuronal malfunction, and the search for antiepileptic drugs has largely concentrated on compounds that affect neurones. The efficacy of these drugs, old and newly created, has not improved substantially over the past decades. All known antiepileptic drugs merely suppress symptoms without treating the underlying disorder, and at least one third of patients are refractory to pharmacological treatment. There is, therefore, an urgent need for developing more efficacious medications. Accordingly, recent critical reviews call for alternative concepts to identify new targets for improved therapeutic approaches [64, 135, 201].

Emerging evidence suggests that astrocytes might represent such new targets. These cells are now recognized as active communication partners in the CNS. Among many homeostatic functions, astrocytes provide energetic metabolites to neurones [186], regulate K^+ and glutamate homeostasis [238, 258] and synchronize neuronal firing [8, 60]. Because neurosurgical specimens from patients presenting with mesial temporal lobe epilepsy (MTLE) demonstrate marked reactive gliosis, it is conceivable that astrocytes also have a role in seizure generation and/or seizure spread. In support of this view, various membrane channels, receptors and transporters in astrocytic membranes are altered in the epileptic brain [193].

Decreased expression and function of inwardly rectifying K^+ (K_{ir}) channels characterizes astrocytes in human sclerotic hippocampus surgically resected from patients with MTLE, which indicates impaired K^+ clearance and increased seizure susceptibility (reviewed by [16]; Fig. 5). Astrocytes predominantly express the $K_{ir}4.1$ channel [191], and support for an anti-epileptic function of $K_{ir}4.1$ came from conditional $K_{ir}4.1$ knockout mice, which display an epileptic phenotype [37, 79]. Similarly, missense mutations, loss-of-function mutations or single nucleotide polymorphisms in the genes encoding Kir4.1 (and, incidentally, the water channel AQP4 usually co-localised with $K_{ir}4.1$ channels in astroglial processes) are associated with human epilepsy [16].

In the adult brain, astrocytes are connected to each other through gap junctions mainly composed of connexin Cx43 and Cx30, allowing intercellular exchange of ions, amino acids and energy metabolites. This astrocytic network has important functions, including spatial buffering of K^+ [238], delivery of energy metabolites to neurones [186] and regulation of adult neurogenesis [120]. In epilepsy, enhanced, reduced or unaltered expression of Cx43 and Cx30 has been reported [69, 215]. However, altered expression of connexins does not allow conclusions about functional coupling, and functional coupling studies in epilepsy are virtually absent. According to the spatial buffering concept, the astrocytic network is expected to exert anti-epileptic effects because decreased coupling would lead to accumulation of extracellular K^+, neuronal depolarization and hyperactivity (Fig. 5). In accord with this idea, mice with coupling-deficient astrocytes, due to genetic deletion of Cx30 and Cx43, display impaired clearance of K^+ and glutamate as well as epileptiform activity [162, 238]. However, spread of Ca^{2+} waves and energy supply to neurones are also reduced in the absence of astrocytic coupling, suggesting that the networks might play a dual, pro- and anti-epileptic role. These findings further emphasize the need for functional studies to unravel the role of coupling in epilepsy. Functional properties of astrocytes were recently investigated in neurosurgical hippocampal specimens from MTLE patients with and without sclerosis,

combining patch clamp recording, K^+ concentration analysis, EEG/video-monitoring, and fate mapping analysis [15]. The authors reported that the hippocampus of MTLE patients with sclerosis is completely devoid of *bona fide* astrocytes and gap junction coupling, while coupled astrocytes were abundantly present in non-sclerotic specimens (Fig. 5). To decide whether these glial changes represented cause or effect of the disease, a mouse model was established that reproduced key features of the human disease. In this model, uncoupling impaired K^+ buffering and temporally preceded neuronal death and generation of spontaneous seizures. Uncoupling was induced *in vivo* through injection of LPS, prevented in Toll-like receptor4 knockout mice and reproduced *in situ* through acute IL-1β, TNFα or LPS incubation. Fate mapping confirmed that in the course of MTLE with sclerosis, astrocytes acquire an atypical functional phenotype and lose coupling [15]. The study suggested that astrocyte dysfunction might be a prime cause of the disease and identified novel targets for anti-epileptogenic therapeutic intervention.

Enhanced extracellular glutamate concentrations are observed in human epileptic tissue, which is thought to induce hyperactivity and neuronal death [70]. Whether dysfunctional glial glutamate transporter (EAAT1, EAAT2) contribute to the impaired glutamate homeostasis in epilepsy is under discussion because experimental findings are inconsistent [193]. For effective removal of excess extracellular glutamate, the transmitter must be converted by the enzyme glutamine synthetase (GS) into the receptor-inactive molecule glutamine, and recent data suggested that in epilepsy, GS might represent the bottle neck for catabolism of the transmitter [44], (Fig. 5). Indeed, loss of GS was found in the sclerotic hippocampus of MTLE patients. GS is also down-regulated in the chronic phase of experimental epilepsy, and pharmacological inhibition generated seizures and a pathology resembling human hippocampal sclerosis. Besides disturbing glutamate uptake, loss of GS also impairs delivery of glutamine to neurones by reactive astrocytes, which results in decreased GABA release from interneurones and exacerbates hyper-excitability [160], (Fig. 5).

In conclusion, although research on astrocytes in epilepsy is still in its infancy, increasing evidence suggests a critical role of these cells in the disturbance of K^+ and transmitter homeostasis and seizure generation. These findings might eventually classify MTLE as a glial rather than a neuronal disorder, and identify astrocytes as promising new targets for the development of more specific antiepileptogenic therapeutic strategies.

Astroglia in AD: Reactivity, astrodegeneration and pathological remodelling

Reactivity

Astrogliosis has been reported to be an integral component of AD pathology since its first descriptions in the early 20th century [6]. Astrocytes surrounding amyloid plaques show a reactive phenotype characterised by increased GFAP expression with hypertrophied processes which envelop and penetrate into plaques. However, the precise role of astrocyte activation in disease pathogenesis has been controversial. Activated astrocytes elaborate a complex array of inflammatory mediators. *In vitro*, exogenous β-amyloid stimulates astrocytes to express IL-1β, IL-6, TNF-a, IFN-γ, and iNOS [126], which have been detected in activated astrocytes surrounding plaques in transgenic mouse models and the AD brain [146, 158]. The increased expression of pro-inflammatory mediators and cytotoxic molecules in astrocytes (and other glial cells) form the basis of the "inflammation hypothesis", which postulates that plaques activate glia and initiate a pro-inflammatory and cytotoxic cascade resulting in neurodegeneration [3].

In support of the specific role of astrocytes in mediating this effect, Furman et al [62] demonstrated that selective inhibition of inflammatory signalling in astrocytes via viral-mediated disruption of calcineurin/NFAT (nuclear factor of activated T-cells), reduced plaque pathology and improved cognitive function in a mouse model of AD. An adeno-associated virus (AAV) driving expression of VIVIT, a peptide targeting the interaction between calcineurin and NFAT, using a GFAP promoter, was injected into the hippocampi of APP/PS1 mice. After several months, amyloid plaque load was reduced by 25% compared to control AAV, and hippocampal-dependent active avoidance behaviour was improved. These results suggest that astrocytic inflammatory cascades regulated by calcineurin/NFAT play a critical role in exacerbating amyloid plaque pathogenesis with detrimental behavioural consequences [62].

The inflammation hypothesis gained support with early epidemiological studies which revealed that non-steroidal anti-inflammatory drug (NSAID) use was inversely correlated with the risk of AD incidence, suggesting a protective effect [137]. However, several subsequent randomized, blinded, placebo-controlled clinical trials did not confirm this beneficial effect [2, 179]. More recent studies suggest that different aspects of astrocyte function might also play a salutary role, reducing β-amyloid load during AD pathogenesis. A hallmark of astrocyte activation is the induction and assembly of the cellular intermediate filament network, consisting of GFAP and vimentin (among others), giving astrocytes the characteristic reactive phenotype [169]. Deletion of *GFAP* and *Vim* in mice result in astrocytes with peculiar phenotypes: under physiological conditions, astrocyte morphology is indistinguishable from wild type astroglia; however, following acute CNS injury (spinal cord injury, hippocampal deafferentation, or cerebral ischemia), $GFAP^{-/-}Vim^{-/-}$ astrocytes do not develop the characteristic morphologic changes associated with activation [127, 167, 246]. Similarly, gene deletion of *GFAP and Vim* in APP/PS1 mice resulted in alterations in the morphology of activated astrocytes. $GFAP^{-/-}Vim^{-/-}$ astrocytes in close proximity to plaques had the appearance of non-reactive astrocytes with fine processes that lacked interaction with plaques, in striking contrast to the typical hypertrophied processes with intimate invasion of amyloid plaques seen with wild type astrocytes [116]. Furthermore, the plaque load in $GFAP^{-/-}Vim^{-/-}$ mice was double that found in the APP/PS1 mice with wild type astrocytes. Of note, the finding on the amyloid plague load was not confirmed in another study with the APP/PS1 $GFAP^{-/-}Vim^{-/-}$ mice, although the changes of astrocytes morphology were present [102]. In addition, *GFAP and Vim* absence was associated with an increased load of dystrophic neurites - the swollen neuronal processes seen adjacent to plaques - providing evidence that activated astrocytes might exert neuroprotective effects on nearby neurones. *GFAP and Vim* gene deletion had remarkably little effect on the expression of key cytokines and chemokines in the APP/PS1 mice: IL-1β, IL-6, IL-10, TNF-α, TGF-β, and iNOS were unchanged. The number of astrocytes, and expression of GS and S100β were also unaltered, suggesting that the double knockout had no effect on astrocyte viability. Finally, the gene deletions had little effect on APP expression or processing. Thus, the major difference between the mice appeared to be the structural interface between the astrocyte and plaque [116].

The precise intermediate filament-dependent mechanism by which astrocytes reduce plaque accumulation in APP/PS1 mice is not known; however, several potential mechanisms have been described. Transcriptome profiling has revealed that astrocytes express genes involved in phagocytosis, including *Draper/Megf10* and *Mertk/integrin αvβ5* [34]. Wyss-Coray and colleagues cultured mouse astrocytes on the surface of plaque-laden brain slices derived from aged APP transgenic mice, and found that astrocytes degraded amyloid plaques [249]. Others have demonstrated that activated astrocytes release proteases, such as matrix metalloproteinase-9, capable of degrading β-amyloid and amyloid [252, 255]. Astrocytes are

capable of taking up β-amyloid, via endocytosis or macropinocytosis and subsequent trafficking and degradation via the lysosomal pathway [13, 128]. It has been hypothesized that age-dependent lysosomal dysfunction [46, 110, 248] may be an underlying mechanisms for accumulation of β- amyloid resulting from impaired degradation [61, 249]. Recent studies demonstrate that activation of ubiquitously expressed transcription factor EB (TFEB) stimulates lysosome biogenesis and cellular trafficking pathways to promote breakdown of lipids and proteins [195, 196, 251]; and remove abnormal aggregates in lysosome storage disorders [195]. The hypothesis was tested that enhancing lysosomal function in astrocytes with TFEB, would promote β-amyloid uptake and catabolism; and attenuate plaque pathogenesis. Exogenous TFEB localized to the nucleus with transcriptional induction of lysosomal biogenesis and function, *in vitro*. This resulted in significantly accelerated uptake of exogenously applied β-amyloid$_{42}$, with increased localization to and degradation within lysosomes in primary cultures of astrocytes. Stereotactic injection of AAV particles carrying TFEB driven by a GFAP-promoter was employed to achieve astrocyte-specific expression in the hippocampus of APP/PS1 transgenic mice. Viral gene transfer of TFEB to astrocyte enhanced lysosome function, resulting in reduced β-amyloid levels and shortened β-amyloid half-life in the brain interstitial fluid; and reduced amyloid plaque load in the hippocampus compared to control virus-injected mice [251]. Therefore, enhancing lysosomal function in astrocytes is an effective strategy to restore adequate β-amyloid removal and counter amyloid plaque pathogenesis in AD.

The above studies highlight the multiple facets of astrocyte activation in the setting of AD pathogenesis (Fig. 6). Astrogliosis results in the activation of a complex array of pathways involved in diverse functions, including changes in inflammation, metabolism, cytoarchitecture, and microenvironmental regulation. The activation of specific astroglial pathways (such as immune/inflammatory regulation) might exacerbate AD pathogenesis, while others (catabolic, proteolytic, and phagocytic function) might attenuate AD pathogenesis. Understanding these specific pathways as they related to disease pathogenesis will be critical for the potential identification of exploitable targets for intervention.

Astrodegeneration

Reduction in astroglial volume, surface area and in their morphological complexity has been observed in several AD transgenic mouse models [14, 119, 156, 253]. This reduction was quantified by analysing astroglial profiles labelled with antibodies against GFAP (which labels primary and possibly secondary processes) as well as with antibodies against GS and S100β (these latter stainings reveal much of astroglial arborisation including the finest processes, because both GS and S100β are cytosolic proteins whereas GFAP is associated with cytoskeleton). The total number of astrocytes labelled with these markers did not change with age in the triple transgenic model (3xTG-AD) under investigation [119, 156, 253].

The astroglial atrophy in 3xTG-Ad animals was region- and age-specific with the reduction in astroglial profiles first occurred in the entorhinal cortex (at 1 month of age); in the prefrontal cortex reduction in morphological profiles became significant at 3 months of age, whereas in the hippocampus atrophic astrocytes appeared much later at 9 - 12 months of age (see [182, 228] for systematic review). It is of importance to observe, that atrophic astroglia emerged in all these brain regions before an appearance of extracellular β-amyloid depositions.

Morphological atrophy of astrocytes coincides with a decrease in their territorial domains, and most likely results in a reduction of the astroglial coverage of synaptic contacts belonging to these domains. Furthermore, reduced astroglial coverage may also indicate compromised homeostatic support, which may have detrimental consequences for neuroprotection and for

synaptic strength and connectivity. All of this can result in decrease in the number of synapses which are known early pathological events observed in AD [41, 219]; of note a decrease in synaptic densities has been reported to correlate with the severity of dementia [48, 188]. Astrocytes support synaptic transmission through numerous coordinated mechanisms [229]; these mechanisms include regulation of ion concentrations in the synaptic cleft, shuttling lactate to active synapses, uptake of neurotransmitters and supplying neuronal terminals with glutamine, that is an obligatory precursor for glutamate and GABA. Naturally, decreased coverage of synapses by astroglial processes reduces homeostatic support and hence affect synaptic transmission.

Pathological atrophy of astroglia may also affect the neuro-vascular unit and reduce coverage of brain vessels with astroglial endfeet, thus contributing to vascular deficits manifest already in the early stages of AD [18, 259]. Brain metabolism is also compromised in AD and decreased glucose utilisation is often detected by functional brain imaging [145]. Astrocytes are the only cells in the brain containing and processing glycogen; and astroglial metabolism was shown to be affected by β-amyloid [4]. Early stages of AD are also characterised by a remarkable decrease in noradrenergic innervations of the brain due to an early degeneration of the locus coeruleus from which noradrenergic projections originate [35]. Astroglial function, including calcium signalling, metabolism, and morphological plasticity, and gap junctional connectivity, are all controlled by noradrenergic regulation [51, 88]; the failure of the latter may further exacerbate astrodegeneration in AD.

Pathological remodelling of astrocytes: can these contribute to cognitive decline and dementia?

In general, it is accepted that more astrocytes show an increased GFAP expression in the brains of AD patients and in AD mouse models. In the human brain reactive astrocytes have been observed closely to Aβ plaques, however not all Aβ plaques are surrounded by GFAP-expressing astrocytes, and reactive astrocytes also occur in areas without plaques [104, 202] . This is in contrast with an AD mouse model, in which the earliest sites of β-amyloid depositions are associated with both reactive astrocytes and microglia [103, 105]. This difference is likely due to the diversity in plaque pathology. In the human brain different plaques morphologies occur, i.e. dense core, neuritic and diffuse plaques, some of these might be very old plaques and thus the reactive astrocyte response might have subsided. In the mouse brain a steady build up of plaques occur and the diversity of plaque morphology as in human brains is not observed. A positive correlation between GFAP expression and the neuropathological Braak stages in AD has been observed in several studies [104, 202, 242].

Astrocytes are known to be involved in clearance of Aβ [106, 249], but can they also be involved in dementia? In the rodent CNS each astrocyte supports and modulates about 100,000 synapses and this number is even higher in the human CNS where up to 2 million synapses can be supported by a single astrocyte [153]. Astrocytes in glial networks form syncytia coupled through gap junctions [69]. This property enables them to organize K^+ homeostasis in the brain, an essential factor in neurone excitability (Fig. 5). Astrocytes are essential for neurotransmitter homeostasis and are actively involved in neuronal communication [80, 84]. They respond to neurotransmitters by calcium waves and release gliotransmitters to which in turn the neurones respond [9] (Fig. 5). It has been recently shown that release of D-serine from astrocytes is essential for long-term potentiation in the hippocampus [86], which is a mechanism that is thought to be critical for learning and memory. Interestingly, the appearance of reactive astrocytes in the human brain, as measured by GFAP expression, coincides with the occurrence of dementia [95, 109]. This suggests that

reactive astrocytes can be an important factor in the development of dementia. Furthermore, amyloid precursor protein, mutated in some forms of AD, is highly expressed in astrocytes [159], and in certain pathological conditions astrocytes can produce Aβ [225]; the Apolipoprotein E, which is the genetic risk factor for AD, is highly expressed in astrocytes [159]. A role for astrocytes in AD pathogenesis process is also supported by genome wide association (GWAS) studies as these have revealed that many genes within GWAS loci are highly expressed in astrocytes, such as clusterin (CLU) and sortilin-related receptor L (DLR Class), A repeats containing (SORL1) [108].

The functional consequences in reactive astrocytes are yet to be fully understood. It has been shown that GS is decreased in reactive astrocytes [155] resulting in a depletion of glutamine and consequently a reduction of synaptic GABA and a hyper-excitability of hippocampal neuronal circuits [160] (Fig. 5). In an AD mouse model a hyperactivity in intracellular calcium waves in astrocytes near Aβ plaques have been observed [117]; whereas β-amyloid was shown to alter astroglial Ca^{2+} signalling kit [73, 184], see also [133] for detailed overview of glial calcium signalling in AD. In another AD mouse model, an increase astrocyte coupling and an increase in glutamate sensitivity was reported [174]. Furthermore, a transcriptomic profiling study on acutely isolated astrocytes showed that these cells adopt a pro-inflammatory phenotype, including up-regulation of the immunoproteasome activity [157], and a reduction in genes involved in neuronal signalling a support [158]. Recently, it was shown that reactive astrocytes in AD mice show an abundant production of and an abnormal release of the inhibitory neurotransmitter GABA, due to an increase in the enzyme MAO-B, which leads to a memory impairment in the AD mice [101].

Genetic studies have revealed causative genes and genetic risk factors, but in the majority of the AD patients the exact cause of the disease is still unclear. The disease is in about 13% of the early-onset cases caused by autosomal recessive mutations in the genes for amyloid precursor protein (APP) and the presenilins (PSEN1 and PSEN2) [21]. ApoE is the main genetic risk factor for AD, and it has been calculated that 50% of the late onset AD patients have an ApoE4 allele [227]. Since 2009, more genetic risk factors have been identified with genome wide association studies, such as clusterin, CR1, SORL1, PICALM, BIN1, EPHA1, ABCA7, MS4A, CD33 and CD2AP [21, 108]. Despite of all this knowledge, it is still elusive which molecular and cellular mechanisms cause the actual dementia. In this respect it is important to note that not only neurones are affected in AD patient brains. Astrocytes are highly involved in neuronal communication, and therefore the transformation of these cells to a reactive phenotype can have detrimental effects on the tripartite synapse. Taken together, it is imperative to consider the molecular and cellular changes of glia as well as neurones when trying to decipher the exact processes that lead to dementia in AD.

Huntington disease: astroglial morpho-functional changes

In tissue of HD patients, there is a prominent astrogliosis [58, 234], which could be either primary and/or a response to neuronal dysfunction. This is characterized by a progressive increase in the number of reactive astrocytes, having hypertrophic somata and an increase in GFAP immunoreactivity and seen throughout the striatum; eventually, the blurring of the astrocytic tiling, i.e., the formation of overlapping domains between neighbouring astrocytes, occurs as the HD severity increases [58]. Similarly, astrogliosis in the striatum and cortex has been reported in many of the mouse models expressing mHTT [74, 75, 134], being more severe with animal ageing [58]. Reactive astrogliosis in HD may contribute to pericyte death, causing the reduction in pericyte coverage of cerebral blood vessels, which also could contribute to the disease progression [92].

Besides morphological changes in HD, astrocytes function is compromised as well leading to excitotoxicity, which is generally considered responsible for neuronal death [72]. There is a substantial decrease in the presence of astrocytic plasma membrane glutamate transporters EAAT2/GLT-1 along with a decrease in the astrocytic production of the antioxidant ascorbic acid [57]. The decrease in astrocytic expression of EAAT2/GLT-1 has been identified in post-mortem human tissue and in an HD mouse model [17, 58, 83, 132]. Consequently, the decreased efficacy of astrocytic glutamate uptake leads to elevated glutamate concentration in the brain, which is a leading factor in excitotoxicity and neuronal death [17, 58, 83, 132] (Fig. 5). An additional disorderly component of HD astrocytes is evident in the pathological glutamate release [124], which occurs as a result of an increased expression of the astrocyte-specific enzyme pyruvate carboxylase. As this enzyme is critical for *de novo* synthesis of glutamate, the resulting augmented glutamate production leads to an increased availability of cytosolic glutamate for vesicular packaging and, consequentially, pathologically high exocytotic release of this neurotransmitter from astrocytes. In addition, HD astrocytes in a different mouse model showed a decreased expression of $K_{ir}4.1$ K^+ channels resulting in a deficient K^+ buffering (Fig. 5), which may further contribute to the pathogenesis of HD [222]. Thus, astrogliosis and dysfunctional regulation of glutamate and potassium extracellular levels by astrocytes can contribute to HD pathology. However, it remains unclear whether EAAT2, pyruvate carboxylate and $K_{ir}4.1$ channels may represent targets for therapeutic interventions in HD.

Potential treatment strategies targeting astrocytes

Although much remains to be learnt about the specific involvement - primary or secondary - of astrocytes in neurological disorders, at least in some of them, astrocytes emerge as potential therapeutic targets. This was discussed above and examples of astrocyte-specific molecular targets are given in Table 1.

Conclusions

Astroglia represent the homeostatic and regulatory arm of the CNS and their dysfunction or maladaptive responses contribute to the pathogenesis of most, if not all, neurological diseases. Whether the astrocyte pathology is primary to the disease in question and how much of it is secondary is in most cases rather difficult to determine. However, even in the latter case, astrocyte dysfunction can profoundly affect and exacerbate the primary pathology. Astrocytes can contribute to neuropathology through multiple and complex pathways ranging from reactive astrogliotic response to astrodegeneration, or pathological remodelling with loss or modification of function. Astroglial reactivity is generally a defensive response aimed at containing the damage and facilitate regeneration. In certain conditions however, pathologically modified astrocytes can release neurotoxic factors, lose intercellular communication and exacerbate vicious progression. Astrocytes therefore should be considered as targets for cell-specific therapy, which may open new avenues in treatment or even prevention of neurological disorders.

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Table 1. Examples of potential treatment strategies targeting astrocytes

Disease	**Subcellular/Molecular target**	**Mode of action**	**Reference**
Epilepsy	gap junction protein Cx3	inhibition	[15]
Stroke/neurotrauma	Ephrin-A5	inhibition	[161]
Alexander disease	GFAP	downregulation	[217]
ALS	TDP-43	misfolding inhibition	[97]
Ischemic stroke	C3a receptor	activation	[198]

Desired effect	**Subcellular/Molecular target**	**Mode of action**	**Reference**
Improved integration of transplanted stem cells	GFAP and vimentin	downregulation	[114, 243]
Increased neurogenesis	GFAP and vimentin	downregulation	[122, 245]

Figure Legends

Figure 1. Astroglial cradle and homeostatic support of the multi-partite synapse in the CNS.

The majority of synapses in the brain and in the spinal cord are multi-partite being composed of (i) the presynaptic terminal; (ii) the postsynaptic dendritic compartment; (iii) the perisynaptic process of the astrocyte; (iv) the process of neighbouring microglial cell that periodically contacts the synaptic structure and (v) the extracellular matrix (ECM) present in the synaptic cleft and also extended extra-synaptically. Astroglial perisynaptic membrane contains numerous transporters that control homeostasis in the synaptic cleft.

Abbreviations: EAAT - excitatory amino acid transporters 1 (SLC1A3) and 2 (SLC1A2); NKA - the Na^+/K^+ ATP-ase or ATP-dependent Na^+/K^+ pump, the $\alpha 2$ subtype (ATP1A2) is predominantly expressed in astrocytes; NKCC1 - the Na-K-Cl co-transporter (SLC12A2); NCX - the sodium-calcium exchanger expressed in 3 isoforms (SLC8A1, SLC8A2 and SLC8A3); NAAT - the Na^+-dependent ascorbic acid transporter (SLC23); NBC - the sodium-bicarbonate co-transporter (SLC4A4); CNT2 - the high-affinity Na^+-dependent concentrative adenosine transporter (CNT2); ASCT2 - the alanine-serine-cysteine transporter 2; MCT-1 - the monocarboxylase transporter 1 (SLC16A1); $K_{ir}4.1$ - inward rectifier $K_{ir}4.1$ channels; NHE - the sodium-proton exchanger 1 (SLC9A1); GAT - GABA transporters 1 (SLC6A1) and 3 (SLC6A11); SN1,2 - Na^+/H^+ dependent sodium coupled neutral amino acid transporters 1 (SLC38A3) and 2 (SLC38A5); GlyT1 - glycine transporter 1 (SLC6A9).

Figure 2. Classification of pathological changes in astroglia.

Figure 3 Reactive astrogliosis is the term used for responses of activated astrocytes seen in many neurological diseases. As a rule reactive astrogliosis is a defensive reaction (which is often disease-specific) in times of acute stress that aims at restoring the tissue homeostasis and restricting the damage. Persisting reactive astrogliosis has a potential of turning maladaptive and inhibit neural plasticity and other regenerative responses. Modified from [65, 143, 168, 170].

Figure 4. Reactive astrocytes interact with multiple cell types. (A) Reactive astrocytes can receive diverse molecular signals from neurons, synapses, inflammatory cells, such as microglia and white blood cells (wbc), as well as blood vessel (bv) endothelia and pericytes. Incoming molecular signals include neurone-derived growth factors and transmitters, or inflammatory cell derived cytokines, or blood borne molecules, which then activate specific intracellular signaling pathways. (B) Conversely, reactive astrocytes can send diverse molecular signals that can influence all of these same cell types in context specific manners via specific intracellular signaling pathways. Astrocyte released molecules include numerous growth factors, neurotransmitters, cytokines and chemokines. The functional implications of the diverse and complex signaling interactions of reactive astrocytes with multiple cell types are poorly understood and only beginning to be elucidated. Dissecting the functional interactions of reactive astrocytes is a next major challenge and holds much promise for improving understanding of many aspects of pathophysiology. Modified from [204].

Figure 5. Astrocytic dysfunction in MTLE. (1) Seizure activity leads to an increase in extracellular K^+ concentration. Down-regulation of K_{ir} channels was observed in astrocytes in human and experimental epilepsy. (2) Gap junctions mediate spatial redistribution of K^+ and energy metabolites. Loss of gap junction coupling in human and experimental MTLE entails

impaired K^+ buffering and hyperactivity. (3) Dislocation of water channels contributes to impaired K^+ buffering. (4) Astrocytes accomplish glutamate uptake. Reduced expression of the astrocytic transporters (EAAT1, EAAT2) was observed in human epileptic hippocampus. Elevated extracellular glutamate decreases the threshold for seizure induction. (5) Glutamate is converted into glutamine through GS. In chronic epileptic hippocampus, loss of GS impaired extracellular glutamate clearance and glutamine supply to neurones, resulting in decreased GABA release and hyperactivity. Modified from [193].

Figure 6. Astrocytic Multiple facets of reactive astrocytosis in Alzheimer's disease. Schematic diagram illustrating both detrimental and salutary effects of reactive astrocytes on amyloid plaque pathogenesis. Astrocyte surrounding plaques become activated, elaborating pro-inflammatory mediators and free radicals, and may contribute to neurodegeneration. Concomitantly, astrocytosis induces catabolic, proteolytic and phagocytic pathways that might attenuate plaque pathogenesis.

figure 1

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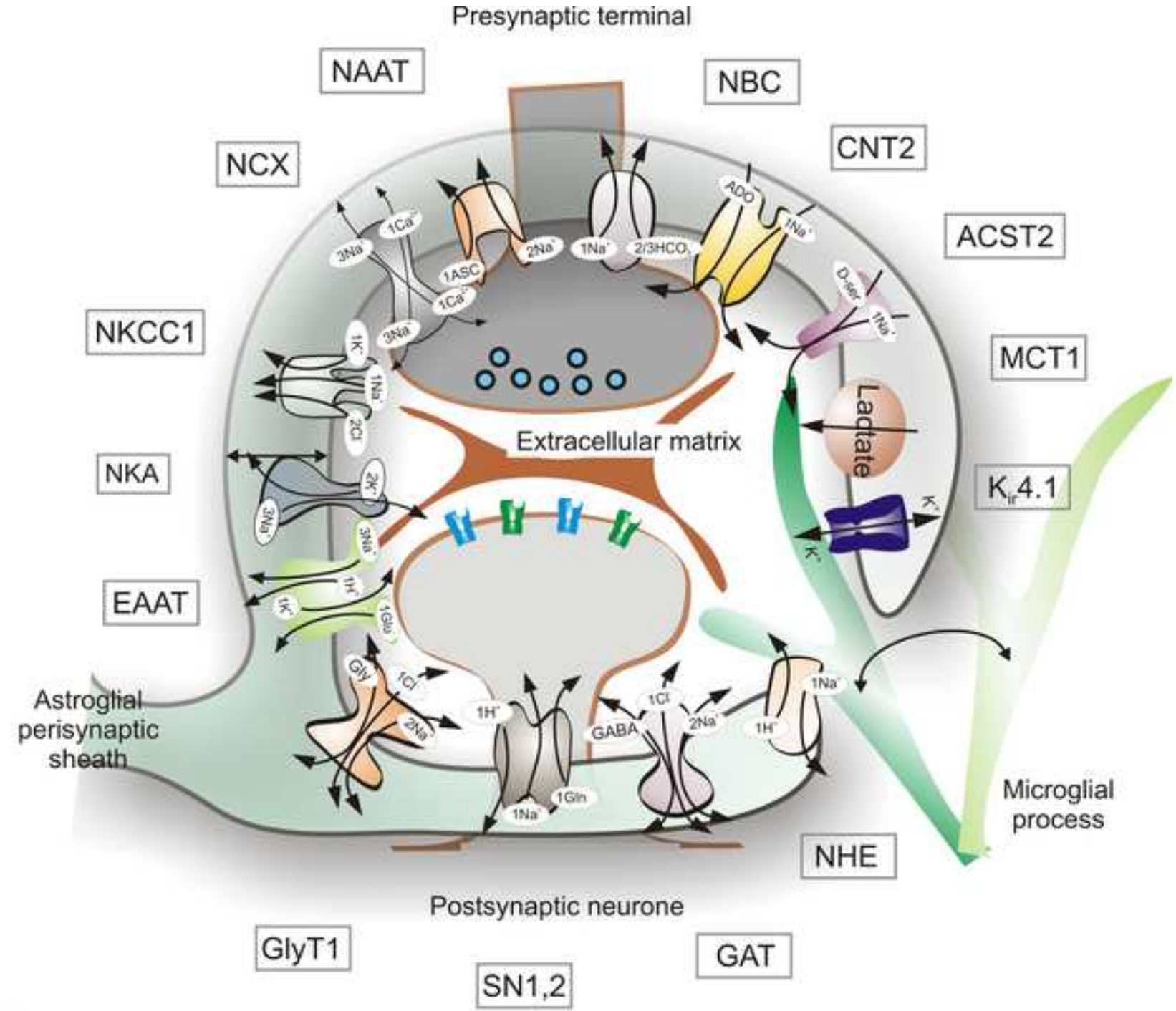

Fig. 1

figure 2

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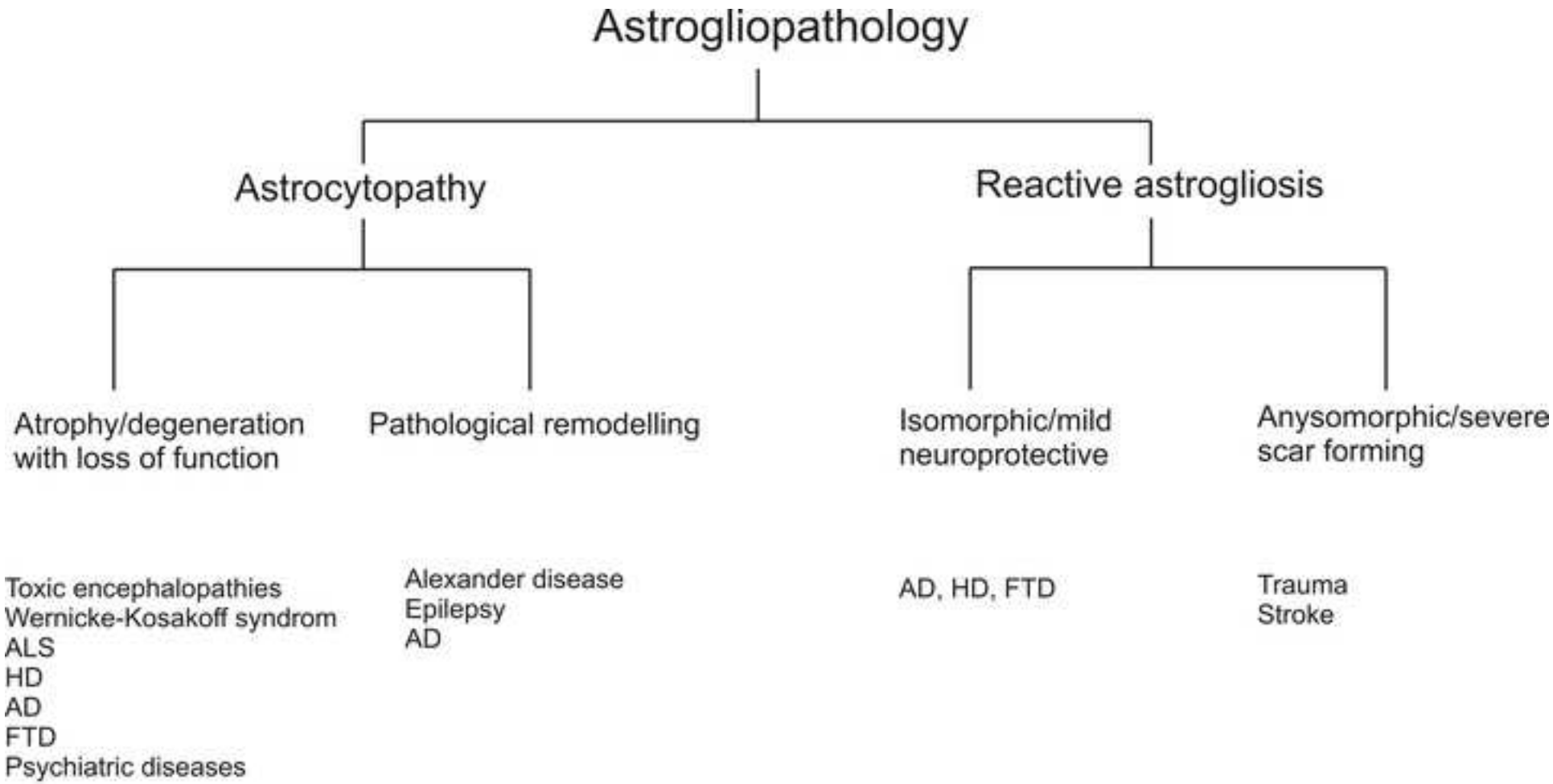

Fig. 2

figure 3

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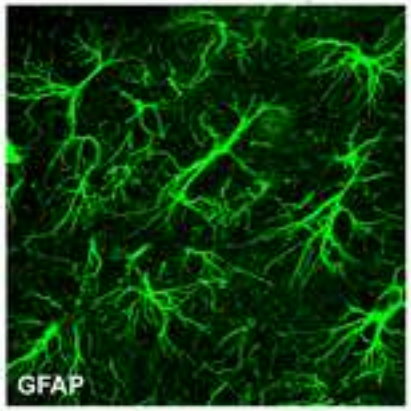
Healthy CNS

Diseased CNS

In many (but not in all) diseases of CNS (for example in neurotrauma, stroke or in neurodegenerative diseases) astrocytes acquire reactive phenotypes, hallmarks of which are increase in GFAP expression and hypertrophy of processes.

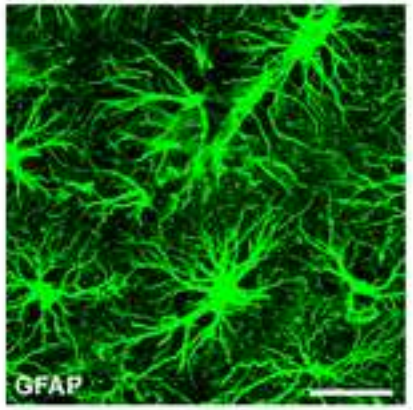


Molecular triggers:
ATP, β-amyloid, TNF-α
IL-6, LIF, CNTF, etc.

→

Reactive astrogliosis

limits the acute stress
and tissue damage,
and restores homeostasis



Physiological functions of astroglia

Neurogenesis
Synaptogenesis
Synaptic plasticity
Formation of astroglio-vascular unit
Ion homeostasis
Neurotransmitter homeostasis and metabolism
Water transport
Regulation of local blood flow

Reactive astrogliosis

Disease-specific
Multiple phenotypes
Isomorphic vs. anisomoprhic
Mild to severe (scar formation)
Focal to diffuse
Protective vs. maladaptive

Persisting reactive astrogliosis can be maladaptive
Maladaptive astrogliosis can be a therapeutic target

figure 4

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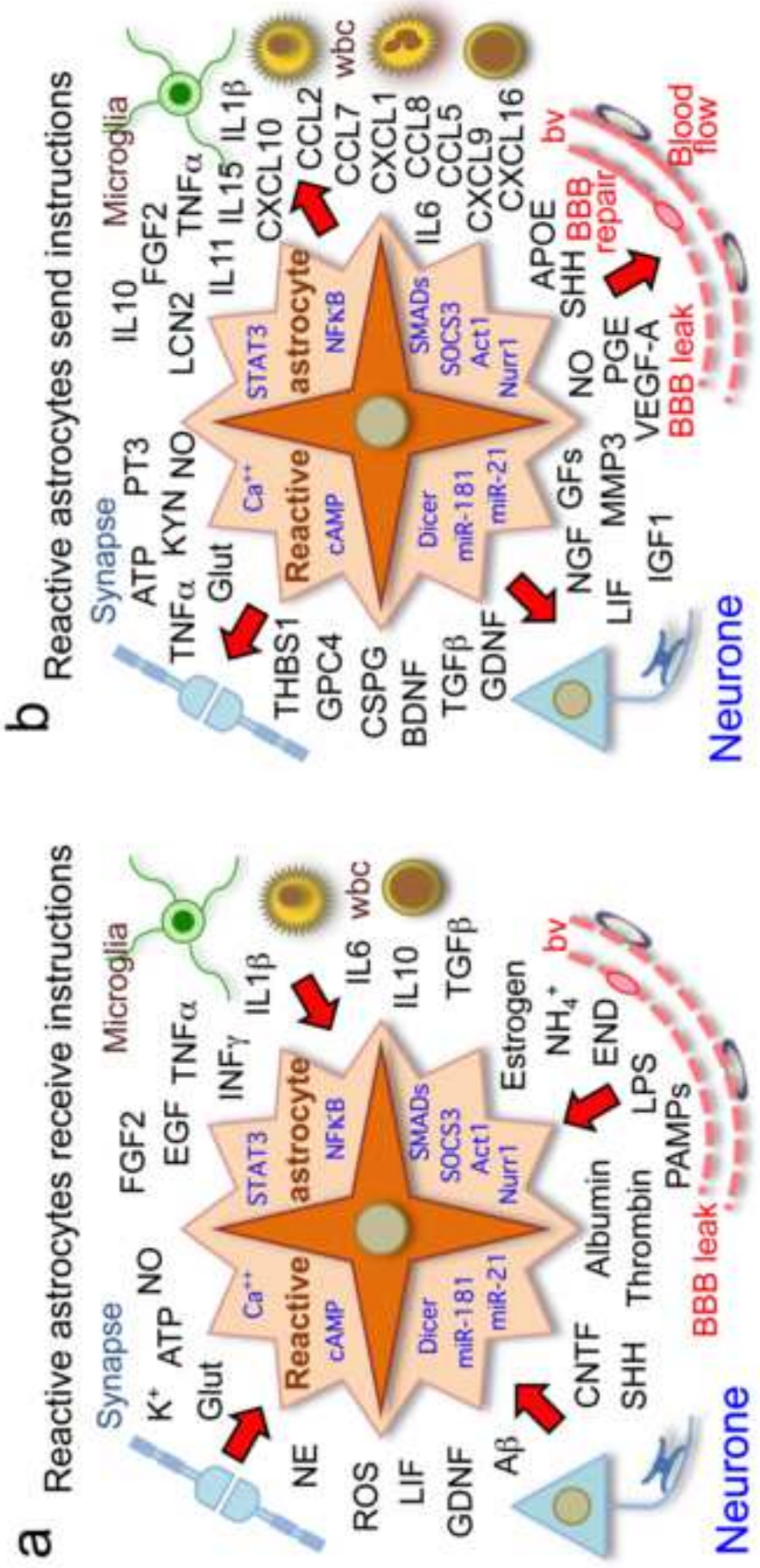

figure 5

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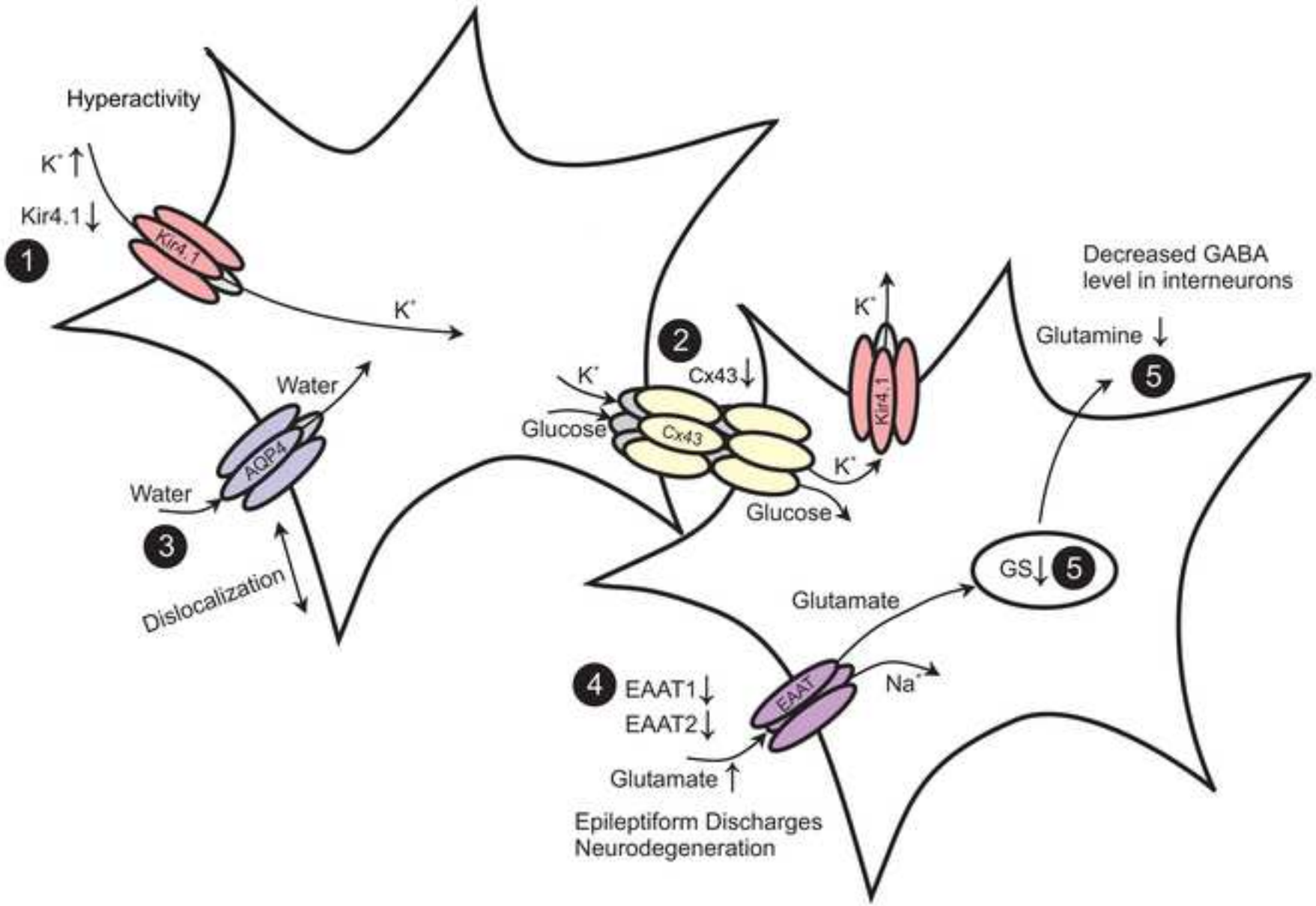

figure 6

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