Progress in Neurobiology 144 (2016) 48–67

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Astrocytes as new targets to improve cognitive functions

Glenn Dallérac *, Nathalie Rouach *

Neuroglial Interactions in Cerebral Physiopathology, Center for Interdisciplinary Research in Biology, Collège de France, Centre National de la Recherche Scientifique UMR 7241, Institut National de la Santé et de la Recherche Médicale U1050, Labex Memolife, PSL Research University, Paris, France

ARTICLE INFO

Article history:
Received 18 September 2015
Received in revised form 7 January 2016
Accepted 24 January 2016
Available online 8 March 2016

Keywords:
Astroglial network
Neuroglial interactions
Memory
Neurodegenerative diseases
Psychiatric diseases
Alzheimer
Huntington
Parkinson
Depression
Schizophrenia
Bipolar disorder
Autism spectrum disorder
Fragile X
Rett syndrome
Epilepsy

ABSTRACT

Astrocytes are now viewed as key elements of brain wiring as well as neuronal communication. Indeed, they not only bridge the gap between metabolic supplies by blood vessels and neurons, but also allow fine control of neurotransmission by providing appropriate signaling molecules and insulation through a tight enwrapping of synapses. Recognition that astroglia is essential to neuronal communication is nevertheless fairly recent and the large body of evidence dissecting such role has focused on the synaptic level by identifying neuro- and gliotransmitters uptaken and released at synaptic or extrasynaptic sites. Yet, more integrated research deciphering the impact of astroglial functions on neuronal network activity have led to the reasonable assumption that the role of astrocytes in supervising synaptic activity translates in influencing neuronal processing and cognitive functions. Several investigations using recent genetic tools now support this notion by showing that inactivating or boosting astroglial function directly affects cognitive abilities. Accordingly, brain diseases resulting in impaired cognitive functions have seen their physiopathological mechanisms revisited in light of this primary protagonist of brain processing. We here provide a review of the current knowledge on the role of astrocytes in cognition and in several brain diseases including neurodegenerative disorders, psychiatric illnesses, as well as other conditions such as epilepsy. Potential astroglial therapeutic targets are also discussed.

Contents

Abbreviations: AAV, adeno-associated viral vectors; ALS, amyotrophic lateral sclerosis; ApoE, apolipoprotein E; AQP4, aquaporin-4; AD, Alzheimer's disease; ASD, autism spectrum disorders; BBB, blood brain barrier; BD, bipolar disorder; Ca^{2+}, calcium; CALHM1, calcium homeostasis modulator 1; CUS, chronic unpredictable stress; Cx, connexin; DAAO, D-amino acid oxidase; DBS, deep brain stimulation; Disc1, disrupted-in-schizophrenia; EAAT2, excitatory amino acid transporter; ECS, electroconvulsive stimulation; EC-SOD, extracellular SOD; FXS, Fragile X syndrome; GFAP, glial fibrillary acidic protein; GJ, gap junction channel; GLT, glutamate transporter; GPCs, glial progenitor cells; GPx, glutathione peroxidase; GR, glucocorticoid receptors; GST, glutathione-S-transferase; HD, Huntington's disease; HO-1, heme oxygenase 1; IP3R2, inositol triphosphate receptor 2; K^+, potassium; Kir4.1, inward rectifier K^+ channel 4.1; L-AAA, L-α-aminoadipate; LDH, lactate dehydrogenase enzyme; MCT, monocarboxylate transporters; LTD, long-term depression; LTP, long-term potentiation; MD, major depression; MeCP2, methyl-CpG-binding protein-2; MSNs, medium spiny neurons; mPFC, medial prefrontal cortex; NAAMFs, neuronal activity associated magnetic fields; NCX, sodium/calcium exchangers; NFAT, nuclear factor of activated T-cells; NG2, nerve-glia antigen 2; NO, nitric oxide; NOR, novel object recognition; NT-3, neurotrophin-3; O_2^-, superoxide; OHC, hydroxycholesterol; $ONOO^-$, peroxynitrite; PD, Parkinson's disease; PLC, phospholipase C; RTT, Rett syndrome; ROS, reactive oxygen species; SOC, store operated channels; SOD, superoxide dismutase; SWA, slow wave sleep activity; TeNT, tetanus neurotoxin; TNFα, tumor necrosis factor α; TMS, trans-magnetic stimulation; TRPC, transient potential channels; UPS, ubiquitin-proteasome degradation system; VGCC, voltage-gated calcium channels.

* Corresponding authors.
E-mail addresses: glenn.dallerac@college-de.france.fr (G. Dallérac), nathalie.rouach@college-de-france.fr (N. Rouach).

http://dx.doi.org/10.1016/j.pneurobio.2016.01.003
0301-0082/

1. Introduction

Brain information processing is traditionally perceived as a neuronal performance. Recent data nevertheless point to an important role of astrocytes in behavioral states, cerebral pathologies and cognitive functions, including learning and memory (Fields et al., 2013; Halassa and Haydon, 2010; Halassa et al., 2009; Pannasch and Rouach, 2013; Pereira and Furlan, 2010; Scuderi et al., 2013). This explains the increasing interest within the neuroscience community, in the relatively underexplored area of neuroglial interactions. Astrocytes are indeed now viewed as crucial elements of the brain circuitry which regulate the formation, maturation, activity and plasticity of neuronal networks involved in processing of sensory, emotional or cognitive information. Astrocytes not only modulate neuronal excitability, synaptic activity and plasticity, but also rhythm generation and neuronal network patterns (Dallérac et al., 2013; Fellin et al., 2009; Lee et al., 2014; Sasaki et al., 2014; Wang et al., 2012a). In particular, astrocytes have been reported to contribute to slow oscillations (Fellin et al., 2009; Poskanzer and Yuste, 2011), gamma oscillations (Lee et al., 2014) and sleep (Halassa and Haydon, 2010; Halassa et al., 2009), in part through modulations of excitatory synaptic activity by releasing gliotransmitters such as glutamate or adenosine. Indeed, numerous astroglial factors and properties are thought to regulate neurotransmission and plasticity. How do astrocytes operate?

Astrocytes are dynamic signaling elements of the brain (Bernardinelli et al., 2014; Haber et al., 2006). They can sense neuronal inputs through membrane ion channels, transporters and receptors. They can also respond by transduction pathways, involving for instance calcium (Ca^{2+}) signaling, and modulate in turn adjacent neuronal elements by various mechanisms, including uptake or release of neuroactive factors, contact-mediated signaling or plastic physical coverage of neurons (Araque et al., 2014; Bernardinelli et al., 2014; Clarke and Barres, 2013; Dallérac et al., 2013). In particular, astrocytes can regulate the formation and stability of synapses, receptor trafficking and the moment-to-moment synaptic activity by releasing for instance gliotransmitters such as glutamate, ATP or D-serine, acting on pre- or postsynaptic receptors (Araque et al., 2014). They can also modify efficacy of synapses by controlling extracellular glutamate concentration *via* clearance through their transporters (Dallérac et al., 2013; Oliet et al., 2001; Pannasch et al., 2014, 2011) or by changing the extracellular space volume as a result of plastic physical coverage of neurons (Piet et al., 2004). However, comprehensive molecular description of such regulations, their occurrence and impact during physiological or pathological conditions remains to be further described. Indeed, deciphering the specific and direct contribution of astrocytes to neuronal activity and cognitive functions is challenging, due to the scarcity of tools interfering selectively with astroglial pathways. In fact, a major technical limit to the study of neuroglial interactions is to act selectively on astrocytes, as they possess many receptors, transporters and transmitters identical to the neuronal ones. Consequently, elucidating the nature, molecular mechanisms and significance of astroglial contribution to cognitive functions represents an emerging and promising field of research. Unraveling how astrocytes control the activity of neuronal circuits is important, not only to advance our comprehension of cognitive function, but also to provide a novel framework for identifying dysfunction underlying neurological disorders as well as alternative therapeutic targets. Indeed astrocyte degeneration has been described in several pathological conditions such as depressive disorders or dementia (Rodriguez et al., 2009). In particular, reactive astrogliosis and dystrophy accompany these diseases, events which may directly contribute to early alterations in synaptic transmission and cognitive processes that occur prior to neurodegeneration. In addition, astroglial cell loss described at later stages of several neurodegenerative diseases is also likely to indirectly alter neuronal function and survival by compromising glial physiological support and modulation of neuronal activity, and may thereby accelerate the course of pathologies (Rossi et al., 2008; Rodriguez et al., 2009; Martorana et al., 2012).

Here, we review recent findings on the role of astrocytes in cognitive functions, focusing on their novel neurophysiological and behavioral roles, as well as the experimental approaches used. In addition, future directions and prospects in unraveling the physiological and pathological relevance of astrocytes in cognitive functions are also discussed.

2. Astroglial contribution to cognitive functions

Evolutionary advanced brains are endowed with information processing abilities that enable them to perform decision making, planning, learning as well as storage of memories. These highly developed cognitive functions have recently been defined as the competence of "thinking and knowing" (Heyes, 2012). The physiology behind such complex processes has been investigated at different levels of complexity, from the interactions between brain areas to specific neuronal network activities and involvement of synaptic plasticity. Research in cell physiology unveiling astrocytes as active partners of neurotransmission processes has recently drawn attention to the role that astroglial networks undertake in higher integrated brain functions. Indeed, a wealth of investigations now shows that astrocytes regulate processes considered as cellular substrates for handling information and memory formation. Basal synaptic transmission and synaptic plasticity, which are believed to be at the root of information processing and mnesic function, depend on the astrocytes ability to control extracellular levels of neurotransmitters and ions, in