ASN NEURO COMMENTARY

ASN NEURO 1(5):art:e00023.doi:10.1042/AN20090049

Filming the glial dreams: real-time imaging of cannabinoid receptor trafficking in astrocytes

Alexei Verkhratsky[1]
Faculty of Life Sciences, The University of Manchester, Manchester M13 9PT, U.K.

Cite this article as: Verkhratsky A (2009) Filming the glial dreams: real-time imaging of cannabinoid receptor trafficking in astrocytes. ASN NEURO 1(5):art:e00023.doi:10.1042/AN20090049

ABSTRACT

How does the brain process incoming information and produce thoughts? These questions represent, to all likelihood, the most challenging matters ever faced by natural sciences, matters which may never be fully comprehended. The evolution of the nervous system that, in about billion of years, brought into existence the human brain progressed through an ever-increasing complexity of neural networks. This evolution began from the diffuse nervous system, in which primordial neurons were able to sense the environmental inputs and convey them to effector organs and to the neighbouring neurons. At the next evolutionary stage the conglomerates of neuronal cell bodies, the ganglia, appeared, thus forming the primitive centralized nervous system. The developments which ensued went through a continuous increase in complexity of neuronal conglomerates, which eventually formed the central nervous system, which attained maximal perfection in mammals. In this issue of *ASN NEURO*, Osborne et al. have described details of real-time imaging of cannabinoid receptor trafficking in astrocytes, a technique that will help to elucidate the role of these receptors in the ever-increasing complex neural networks.

Key words: actin, acutely isolated astrocyte, cannabinoid receptor, microtubule, vesicular trafficking.

The development of the CNS (central nervous system) necessitated an increase in cell specialization, so that neurons, although perfecting sophisticated machinery for rapid propagation of information through electrically excitable membrane and synaptic contacts, lost their metabolic independence. This became possible by a parallel phylogenetic advance of the neuroglia, which assumed the function of a primary brain homoeostatic and defence cellular system (Giaume et al., 2007; Reichenbach and Pannicke, 2008). At the later evolutionary stages, in the primates and human brain, the neuroglia became specifically developed. Indeed, both the number and structural complexity of the astrocytes (the principal neuroglial cells in the grey matter) is substantially higher in primates as compared with other species; astrocytes in the human brain are the most numerous and complex among the whole of the animal kingdom (Oberheim et al., 2006; Sherwood et al., 2006; Oberheim et al., 2009; Verkhratsky, 2009).

The processes of astroglia form excessively intricate arborizations, which, by virtue of tiny appendages and membranous expansions (Grosche et al., 1999), provide a tight coverage for a majority of synapses in the CNS, thus forming the tripartite synaptic structure (Araque et al., 1999; Perea et al., 2009). On average a single astrocyte in the brain of rodents covers ~100 000 synapses, whereas the human astrocyte embraces up to 2 000 000 synaptic contacts (Oberheim et al., 2006). As a result, a single astrocyte perceives and most likely integrates the massive synaptic input. The signalling input to the astroglia is mediated by numerous receptors expressed in astrocytes, the expression being greatly heterogeneous in different astroglial cells, and being finely tuned by the immediate neurotransmitter environment (Verkhratsky et al., 1998; Verkhratsky and Steinhauser, 2000). The functional relevance of astroglial information processing for higher cognitive functions is virtually unknown, yet its importance for brain homoeostasis is fundamental. Indeed the astrocytes are central elements of the neurovascular unit, and astrocytes couple the neuronal activity with local blood flow and metabolic support of neuronal networks (Zonta et al., 2003; Magistretti, 2006).

An increase in complexity of neural networks evolved in parallel with intercellular signalling, which relies upon neurotransmitters and neuromodulators. The primitive forms of extracellular signalling had already appeared in prokaryotes, in

[1] email alex.verkhratsky@manchester.ac.uk

Abbreviations: CB1R, cannabinoid receptor 1; CNS, central nervous system; GPCR, G-protein-coupled metabotropic receptor.

which two main extracellular transmitter molecules, ATP and glutamate, acted as danger signals (Burnstock and Verkhratsky, 2009). Further developments led to an ever-increased variety of neurotransmitter molecules and neurotransmitter receptors, and their functional segregation between brain regions.

Astroglial receptors are many; astrocytes express both ionotropic and GPCRs (G-protein-coupled metabotropic receptors). The functional role of ionotropic astroglial receptors remains somewhat obscure, as indeed their activation hardly can have electric consequences, and is probably mediated by localized ion fluxes with subsequent formation of cytosolic domains of high Ca^{2+} or Na^{+}. The glial metabotropic receptors, in contrast, are directly connected to the glial Ca^{2+} excitability mediated through intracellular signalling cascades and Ca^{2+}-release channels of the endoplasmic reticulum membrane (Verkhratsky et al., 1998; Verkhratsky, 2006). The metabotropic signalling is controlled by a balance between plasmalemmal and intracellular distribution of the GPSRc, which can be dynamically shifted, thus affecting the efficacy of the signalling chain. Furthermore, a remarkable complexity of astroglial processes, which come into contact with multiple synapses, calls for a precise control of allocation of various receptors, which can rapidly change depending on the levels of synaptic input. All of the above contemplations are, however, in a purely speculative realm, because of the absence of specific approaches allowing real-time tracking of receptor movements in glial cells. In this issue of *ASN NEURO*, Osborne et al. (2009) have presented a new and fundamentally important technique of real-time imaging of receptor movements inside astroglial cells. They chose to genetically label the CB1R (cannabinoid receptor 1) with green fluorescent protein, which, upon expression in cortical astrocytes, can be imaged with fluorescent videomicroscopy. The CB1Rs are typical GPCRs that are constitutively expressed in astroglia and are involved in various forms of signalling in neuronal–glial circuits (Navarrete and Araque, 2008).

The fluorescent CB1R chimeras were concentrated in the intracellular vesicles, some of which were actively transported to the plasmalemma with the help of cytoskeletal elements. This transport can be of fundamental importance, as it may dynamically enrich the specific regions of the astroglial processes [e.g. the end-foot structures where CB1Rs are preferentially located (Rodriguez et al., 2001)], with the receptors thus providing a mechanism for controlling local signalling events. The obvious perspective developments are the insertion of chimeric fluorescently labelled receptors of various kinds in glial cells *in vivo*, which opens a whole range of new possibilities for dynamic imaging of receptor distribution and trafficking, and the role of these processes in controlling information processing in neuronal–glial networks.

REFERENCES

Araque A, Parpura V, Sanzgiri RP, Haydon PG (1999) Tripartite synapses: glia, the unacknowledged partner. Trends Neurosci 22:208–215.

Burnstock G, Verkhratsky A (2009) Evolutionary origins of the purinergic signalling system. Acta Physiol (Oxf) 195:415–447.

Giaume C, Kirchhoff F, Matute C, Reichenbach A, Verkhratsky A (2007) Glia: the fulcrum of brain diseases. Cell Death Differ 14:1324–1335.

Grosche J, Matyash V, Moller T, Verkhratsky A, Reichenbach A, Kettenmann H (1999) Microdomains for neuron–glia interaction: parallel fiber signaling to Bergmann glial cells. Nat Neurosci 2:139–143.

Magistretti PJ (2006) Neuron–glia metabolic coupling and plasticity. J Exp Biol 209:2304–2311.

Navarrete M, Araque A (2008) Endocannabinoids mediate neuron–astrocyte communication. Neuron 57:883–893.

Oberheim NA, Wang X, Goldman S, Nedergaard M (2006) Astrocytic complexity distinguishes the human brain. Trends Neurosci 29:547–553.

Oberheim NA, Takano T, Han X, He W, Lin JH, Wang F, Xu Q, Wyatt JD, Pilcher W, Ojemann JG, Ransom BR, Goldman SA, Nedergaard M (2009) Uniquely hominid features of adult human astrocytes. J Neurosci 29:3276–3287.

Osborne KD, Lee W, Malarkey EB, Irving AJ, Parpura V (2009) Dynamic imaging of cannabinoid receptor 1 vesicular trafficking in cultured astrocytes. ASN NEURO 1(5):art:e00022.doi:10.1042/AN20090040

Perea G, Navarrete M, Araque A (2009) Tripartite synapses: astrocytes process and control synaptic information. Trends Neurosci 32:421–431.

Reichenbach A, Pannicke T (2008) Neuroscience. A new glance at glia. Science 322:693–694.

Rodriguez JJ, Mackie K, Pickel VM (2001) Ultrastructural localization of the CB1 cannabinoid receptor in μ-opioid receptor patches of the rat caudate putamen nucleus. J Neurosci 21:823–833.

Sherwood CC, Stimpson CD, Raghanti MA, Wildman DE, Uddin M, Grossman LI, Goodman M, Redmond JC, Bonar CJ, Erwin JM, Hof PR (2006) Evolution of increased glia-neuron ratios in the human frontal cortex. Proc Natl Acad Sci USA 103:13606–13611.

Verkhratsky A (2006) Calcium ions and integration in neural circuits. Acta Physiol (Oxf) 187:357–369.

Verkhratsky A (2009) Neuronismo y reticulismo: neuronal–glial circuits unify the reticular and neuronal theories of brain organization. Acta Physiol (Oxf) 195:111–122.

Verkhratsky A, Steinhauser C (2000) Ion channels in glial cells. Brain Res Brain Res Rev 32:380–412.

Verkhratsky A, Orkand RK, Kettenmann H (1998) Glial calcium: homeostasis and signaling function. Physiol Rev 78:99–141.

Zonta M, Angulo MC, Gobbo S, Rosengarten B, Hossmann KA, Pozzan T, Carmignoto G (2003) Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. Nat Neurosci 6:43–50.

Received 19 October 2009; accepted 12 November 2009

Published as Immediate Publication 12 November 2009, doi 10.1042/AN20090049