Please cite this article in press as: Rose CR, Chatton J-Y. Astrocyte sodium signaling and neuro-metabolic coupling in the brain. Neuroscience (2015), http://dx.doi.org/10.1016/j.neuroscience.2015.03.002

Neuroscience xxx (2015) xxx–xxx

ASTROCYTE SODIUM SIGNALING AND NEURO-METABOLIC COUPLING IN THE BRAIN

C. R. ROSE [a]* AND J.-Y. CHATTON [b]

[a] *Institute of Neurobiology, Faculty of Mathematics and Natural Sciences, Heinrich-Heine-University Düsseldorf, Universitätsstrasse 1, D-40225 Düsseldorf, Germany*

[b] *Department of Fundamental Neurosciences, University of Lausanne, rue du Bugnon 9, CH-1005 Lausanne, Switzerland*

Abstract—At tripartite synapses, astrocytes undergo calcium signaling in response to release of neurotransmitters and this calcium signaling has been proposed to play a critical role in neuron–glia interaction. Recent work has now firmly established that, in addition, neuronal activity also evokes sodium transients in astrocytes, which can be local or global depending on the number of activated synapses and the duration of activity. Furthermore, astrocyte sodium signals can be transmitted to adjacent cells through gap junctions and following release of gliotransmitters. A main pathway for activity-related sodium influx into astrocytes is via high-affinity sodium-dependent glutamate transporters. Astrocyte sodium signals differ in many respects from the well-described glial calcium signals both in terms of their temporal as well as spatial distribution. There are no known buffering systems for sodium ions, nor is there store-mediated release of sodium. Sodium signals thus seem to represent rather direct and unbiased indicators of the site and strength of neuronal inputs. As such they have an immediate influence on the activity of sodium-dependent transporters which may even reverse in response to sodium signaling, as has been shown for GABA transporters for example. Furthermore, recovery from sodium transients through Na^+/K^+-ATPase requires a measurable amount of ATP, resulting in an activation of glial metabolism. In this review, we present basic principles of sodium regulation and the current state of knowledge concerning the occurrence and properties of activity-related sodium transients in astrocytes. We then discuss different aspects of the relationship between sodium changes in astrocytes and neuro-metabolic coupling, putting forward the idea that indeed sodium might serve as a new type of intracellular ion signal playing an important role in neuron–glia interaction and neuro-metabolic coupling in the healthy and diseased brain.

*Corresponding author. Tel: +49-211-81-13416; fax: +49-211-81-13415.
E-mail address: rose@uni-duesseldorf.de (C. R. Rose).

Abbreviations: EAATs, excitatory amino acid transporters; GLAST, glutamate/aspartate-transporter; GLT-1, glutamate-transporter-1; NBC, sodium-bicarbonate cotransport; NCX, sodium/calcium exchange; NHE, sodium/proton exchange; NKCC, Na^+–K^+–$2Cl^-$-cotransport.

http://dx.doi.org/10.1016/j.neuroscience.2015.03.002

This article is part of a Special Issue entitled: Astrocyte-Neuron Interact. © **2015 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: astrocytes, Na^+/K^+-ATPase, glutamate transport, neuron–glia interaction, metabolism.

INTRODUCTION

Active neurons and glial cells dynamically interact in many ways. One of the most prominent and most widely known examples of such an interaction was described about 30 years ago, through studies demonstrating that transmitters released by active neurons result in the activation of transmitter receptors on astrocytes (Bowman and Kimelberg, 1984; Kettenmann et al., 1984). It took about another 10 years before the advent of imaging techniques enabled the detection of astrocyte calcium signals in response to neuronal transmitters (Nedergaard, 1994). Astrocyte calcium signaling has since taken center stage in research efforts and interests. This is mainly because such signaling can result in the release of gliotransmitters and vasoactive substances by astrocytes, which thereby feedback onto and modulate the neuronal network (see chapters by Panatier/Robitaille and Volterra; this issue).

In addition to calcium signals, neuronal activity is, however, accompanied by a second type of ion signal in astrocytes: these are sodium transients, detected upon neuronal release of glutamate and -to a lesser extent- GABA. The existence of such activity-dependent sodium signals is surprising at first glance (Rose and Karus, 2013). First of all, they occur against a relatively high background sodium concentration (10–15 mM), which is fundamentally different from other ion species involved in signaling (e.g., baseline intracellular calcium or proton concentrations are roughly around 100 nM). Also, as compared to calcium changes, which usually occur in the low μM range, sodium changes are a 1000-fold larger, occurring in the mM range. Furthermore, sodium signals not only differ in their magnitude, but also in their spatial and temporal profiles from classical calcium signaling in astrocytes. Sodium changes are quite long lasting, exhibiting decay times in the range of tens of seconds. Given the high diffusion coefficient for sodium ions measured in mammalian cytosol (0.6 $\mu m^2/s$; (Kushmerick and Podolsky, 1969), sodium transients should, however, dissipate within fractions of a second. Apparently, free

diffusion of sodium ions is considerably slowed because of increased tortuosity in the cytosol (Sykova and Nicholson, 2008), and/or binding to plasma membrane transporters such as the Na^+/K^+-ATPase. Moreover, a recent study has provided evidence for restricted molecular diffusion and the existence of subcellular compartments astrocytes (Nuriya and Yasui, 2013).

There are no known classical buffering mechanisms for sodium ions inside cells and, apart from the Na^+/K^+-ATPase (see below), there are no explicit sodium-binding proteins present that activate enzymes and enzyme cascades. Because sodium ions are central charge carriers, channel- or transporter-mediated influx of sodium resulting in changes in intracellular sodium concentration in the mM range, directly influences the cellular membrane potential. In contrast to the situation with calcium ions, there are no intracellular compartments or organelles which serve as storage compartments for sodium and thus there is no comparable release from stores.

When considering sodium signaling, it is also important to bear in mind that many secondary active transport systems depend on the sodium gradient and that sodium transients – that is, a decrease in the inwardly directed sodium gradient – have an immediate impact on the driving force and activity of these transporters. Among those are transporters for regulation of other ions (e.g., sodium/proton exchange (NHE) and sodium/calcium exchange (NCX)) as well as transporters for the re-uptake of transmitters (e.g., high-affinity, sodium-dependent transporters for glutamate or GABA). In fact, it is conceptually astonishing how many highly relevant transporters work close to their equilibrium potential and may reverse upon increases in intracellular sodium. This topic has been comprehensively discussed recently and the reader is kindly referred to these earlier reviews (Kirischuk et al., 2012; Rose and Karus, 2013). One might argue that this is an inherent ''weakness'' of the system, based on a somewhat faulty design. Instead of this rather unsatisfactory argument, we prefer the interpretation that sodium transients might serve as signals.

A critical aspect in this argumentation is the question of what kind of information content such sodium signals might represent and encode. This point has not been fully been clarified yet and many questions still remain open. An established finding, however, is that extrusion of sodium ions is metabolically relevant because recovery from sodium signals requires a measurable amount of ATP. Thus, sodium increases will cause activation of glial metabolism. Consequently, activity-induced sodium transients are ideally positioned to take an essential signaling role in neuro-metabolic coupling between neurons and astrocytes.

SODIUM HOMEOSTASIS AND REGULATION

Cellular sodium homeostasis is of the upmost functional importance for the brain and most of brain energy is in fact consumed by the Na^+/K^+-ATPases (Erecinska and Silver, 1994; Ames, 2000; Howarth et al., 2012). By transporting sodium ions out of the cell in exchange for potassium, the activity of the Na^+/K^+-ATPase establishes a low intracellular sodium concentration against a high sodium concentration in the extracellular space (~145 mM; cf. Fig. 2; (Skou and Esmann, 1992; Kaplan, 2002; Somjen, 2004)). In hippocampal neurons, baseline sodium concentrations of about 12 mM were reported, whereas data obtained from hippocampal astrocytes indicate a sodium concentration of about 11 mM (e.g., (Rose and Ransom, 1996a, 1997b; Chatton et al., 2001; Sheldon et al., 2004; Langer and Rose, 2009). This indicates that, at least in this preparation, there is no significant difference in intracellular sodium concentrations between neurons and astrocytes. The cellular uptake of potassium by the Na^+/K^+-ATPase results in a high intracellular potassium concentration (> 100 mM) as compared to that of the extracellular space (~2 mM; (Erecinska and Silver, 1994; Kofuji and Newman, 2004)). In light of the essential role of sodium homeostasis for cellular function, it is remarkable that the sodium pump is the *only* transport mechanism for efficient extrusion of sodium across the plasma membrane. Regulation of most other ions, in contrast, involves at least two mechanisms (e.g., plasma membrane Ca^{2+}-ATPase works together with NCX to extrude calcium ions and several other transporters in addition to the Na^+/K^+-ATPase mediate uptake of potassium).

Low intracellular sodium concentrations together with the about 10-fold higher extracellular sodium concentration and negative cellular membrane potentials result in inwardly directed electro-chemical gradients for sodium ions across the plasma membrane of both neurons and glial cells. Thus, most of the basic currency of cellular metabolism, ATP, is converted into -and stored as- a strong inward driving force for sodium ions. This enables sodium-dependent electrical signaling and serves to energize many secondary transport processes across the plasma membrane (Rose and Karus, 2013). Changes in intracellular sodium will ultimately feedback on the activity of such sodium-dependent transport processes. Among these are transporters for the re-uptake of glutamate as well as of GABA and glycine, and the latter two may even reverse in response to sodium elevations (Kirischuk et al., 2012; Rose and Karus, 2013). There is also increasing evidence that sodium transients directly modulate intracellular calcium signaling through reversal of NCX (Kirischuk et al., 2012).

The transport cycle of the Na^+/K^+-ATPase has been characterized in great detail in cell culture models and heterologous expression systems, and new crystal structures of defined binding states are continuously being published (Morth et al., 2011; Kanai et al., 2013; Nyblom et al., 2013). Despite its central importance, the pump's functional properties in astrocytes and neurons in the intact brain, including basic attributes such as ion-binding affinities or intracellular interaction partners, are poorly understood. One problem that arises in studies addressing these issues is that manipulation of sodium and the Na^+/K^+-ATPase in the intact tissue directly alters basic physiological cellular parameters and influences extracellular ion homeostasis. Moreover, ''the sodium pump'' is in fact a protein complex comprised of different

Please cite this article in press as: Rose CR, Chatton J-Y. Astrocyte sodium signaling and neuro-metabolic coupling in the brain. Neuroscience (2015), http://dx.doi.org/10.1016/j.neuroscience.2015.03.002