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Review

Diversity of astrocyte potassium channels: An update

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ABSTRACT

Astrocyte K^+ channels and the K^+ currents they mediate dwarf all other transmembrane conductances in these cells. This defining feature of astrocytes and its functional implications have been investigated intensely over the past decades. Nonetheless, many aspects of astrocyte K^+ handling and signaling remain incompletely understood. In this review, we provide an update on the diversity of K^+ channels expressed by astrocytes and new functional implications. We focus on inwardly-rectifying K^+ channels (particularly Kir4.1), two-pore K^+ channels and voltage and Ca^{2+}-dependent K^+ channels. We further discuss new insights into the involvement of these K^+ channels in K^+ buffering, control of synaptic transmission, regulation of the vasculature and in diseases of the central nervous system.

Contents

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1. Introduction

Astrocytes represent an abundant non-neuronal cell type that is found across species, nervous system architectures and brain regions. An early observation during study of this cell type was that these cells are electrically non-excitable in the sense that no action potentials could be elicited. In addition, their voltage responses to current injection were reminiscent of a 'passive' ohmic resistor, the nature of which was unclear and disputed for a long period (Walz, 2000; Bordey and Sontheimer, 1998). This controversy was partially due to the fact the initial developmental studies of glial cells in acute brain slices in the 1990s often mixed up astrocytes with another cell type that has later on been identified as NG2 glia (Bergles et al., 2010). Because of the predominating K^+ conductance the astrocytic the membrane potential of these cells is largely, and more than for instance that of neurons, determined by the transmembrane K^+ gradient (Kuffler and Nicholls, 1966). Therefore, one of the predominant functions attributed to astrocytes was to buffer excess extracellular K^+, i.e. to take up K^+ released into the extracellular space during neuronal activity and, according to the spatial buffering hypothesis, to distribute it to sites of lower relative extracellular K^+ concentration ($[K^+]_o$) (Orkand et al., 1966). As a consequence, astrocyte K^+ buffering is thought to contribute to the regulation of $[K^+]_o$ and, in turn, to be crucial for controlling the neuronal membrane potential and excitability. For these reasons, astrocyte K^+ channels, their properties, distributions and their functional contributions to neuronal information processing and cerebral blood flow regulation in the healthy brain but also in disease are of fundamental impact and have been intensely studied.

It is not our aim to comprehensively review the wealth of data available on astrocyte K^+ channels (see *e.g.* Nwaobi et al., 2016; Weller et al., 2016; Steinhäuser et al., 2013 for recent books and reviews on the subject). Instead, we will focus on more recent insights into astrocyte K^+ channel diversity and function in the grey matter of the mammalian brain. In the following we will provide an update on the K^+ channels expressed by astrocytes, novel functional insights regarding the role of astrocyte K^+ channels for synaptic transmission and newly emerging implications of astrocyte K^+ channels in diseases of the central nervous system (CNS).

2. K^+ channels expressed by astrocytes

2.1. Astrocytic expression of inwardly rectifying K^+ (Kir) channels

Electrophysiologically, astrocytes are characterized by a large time- and voltage-independent, K^+-selective membrane conductance (Fig. 1). The resulting very low input resistance (usually < 5MΩ) impairs significantly any biophysical analysis of the functional properties of these cells (Seifert et al., 2009; Zhou et al., 2009), and for a long time it remained unclear which ion channel(s) mediate this large K^+ conductance. Takumi and colleagues were the first to clone the Kir4.1 (formerly K_{AB}-2) subunit of inwardly rectifying K^+ (Kir) channels, and reveal its glia-specific expression in the CNS (Takumi et al., 1995). Subsequent immunohistochemical analyses confirmed that throughout the brain, spinal cord and retina, Kir4.1 is selectively expressed by glial cells (astrocytes, oligodendrocytes, NG2 glia) but not by neurons (reviewed by Steinhäuser et al., 2013). Ultrastructural inspection identified a polarized subcellular expression pattern, with high densities of Kir4.1 channels being present along the thin processes enwrapping synapses and on astrocytic endfeet facing blood vessels (Higashi et al., 2001; Nagelhus et al., 2004). This non-uniform distribution is thought to serve specific functions of astrocytes, including the rapid uptake and re-distribution of K^+, which is released into the extracellular space during neuronal activity, a mechanism called spatial buffering (see below). Genetic deletion of Kir4.1 entailed strong depolarization and increase in astrocytic membrane resistance, confirming that this subunit sets the resting potential of astrocytes and is responsible for the large inward currents recorded at negative membrane potentials (Djukic et al., 2007; Seifert et al., 2009).

Kir4.1 mRNA and protein is upregulated during the first three weeks of postnatal development, which is accompanied by an increase in Kir currents and a decline of the astrocyte input resistance (Fig. 1) (Seifert et al., 2009; Moroni et al., 2015; Zhong et al., 2016). Because the immature brain is particularly prone to the development of seizure activity (Swann et al., 1986; Moshe and Albala, 1983) these observations imply that astrocyte Kir currents could limit increases of neuronal firing and thus prevent pathophysiological rises of network activity. Together, the data demonstrate a key role of Kir4.1 channels in setting the physiological properties of astrocytes.

Besides Kir4.1, the subunits Kir5.1 and Kir6.1 have been detected. Astrocytes of the retrotrapezoid nucleus co-express Kir4.1 and Kir5.1 channels. The latter confer high pH sensitivity to the heteromeric channels, thereby contributing to chemoreception and the control of breathing (Mulkey and Wenker, 2011). Antibody staining found Kir6.1 almost ubiquitously expressed by astrocytes across many brain regions including the retina, preferentially in perisynaptic and peridendritic processes (Thomzig et al., 2001). Kir6-like membrane currents were also recorded from Bergmann glia (Brockhaus and Deitmer, 2000). However, the contribution of Kir6.1 channels to the overall astrocytic Kir conductance seems to be very limited, given that deletion of Kir4.1 leads to an almost complete loss of Kir currents in these cells (cf. above).

2.1.1. Interaction of Kir4.1 with AQP4 in extracellular K^+ and volume regulation

A close structural association and complexation of AQP4 water channels and Kir4.1K^+ channels was found in astrocytic endfeet (Nagelhus et al., 1999; Connors et al., 2004), which is probably mediated through a dystrophin complex (Amiry-Moghaddam et al., 2004). The glial-vascular interface including the protein complex of Kir4.1, dystrophin and AQP4 is established in the first postnatal week and it was suggested that the extracellular matrix plays a pivotal role in this process (Lunde et al., 2015). Macromolecular complexes of Kir4.1 were only formed with the M23-AQP4 isoform and confined to endfeet while these complexes were not found in parenchymal regions (Smith and Verkman, 2015). However, the view of a functional interaction between AQP4 and Kir4.1 (Nagelhus et al., 1999) was not supported by follow-up studies showing AQP4-independent Kir4.1 function (Ruiz-Ederra et al., 2007; Zhang and Verkman, 2008; Strohschein et al., 2011).

An alternative hypothesis would be that astrocytic K^+ uptake during neuronal activity is accompanied by AQP4-dependent osmotic water uptake and, therefore, a reduction of the ECS. ECS shrinkage by water movement, in turn, causes an increase of $[K^+]_o$ and consequently further K^+ uptake by astrocytes (Papadopoulos and Verkman, 2013). Recently, this hypothesis was supported by mathematical modeling (Jin et al., 2013). Interestingly, in heterologous expression systems co-expression of AQP4 and Kir4.1/Kir5.1 conferred volume-sensitivity to the Kir channels. This was demonstrated by recording of K^+ currents upon cell swelling/shrinkage in hypo/hyperosmolar solutions (Soe et al., 2009). The findings emphasize the impact of Kir4.1-AQP4 interaction in astrocytic endfeet for coordination of water and K^+ flux in the context of brain volume and ion homeostasis (reviewed by Nagelhus et al., 2004).

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