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Invited review

A role of TARPs in the expression and plasticity of calcium-permeable AMPARs: Evidence from cerebellar neurons and glia

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ABSTRACT

The inclusion of GluA2 subunits has a profound impact on the channel properties of AMPA receptors (AMPARs), in particular rendering them impermeable to calcium. While GluA2-containing AMPARs are the most abundant in the central nervous system, GluA2-lacking calcium-permeable AMPARs are also expressed in wide variety of neurons and glia. Accumulating evidence suggests that the dynamic control of the GluA2 content of AMPARs plays a critical role in development, synaptic plasticity, and diverse neurological conditions ranging from ischemia-induced brain damage to drug addiction. It is thus important to understand the molecular mechanisms involved in regulating the balance of AMPAR subtypes, particularly the role of their co-assembled auxiliary subunits. The discovery of transmembrane AMPAR regulatory proteins (TARPs), initially within the cerebellum, has transformed the field of AMPAR research. It is now clear that these auxiliary subunits play a key role in multiple aspects of AMPAR trafficking and function in the brain. Yet, their precise role in AMPAR subtype-specific regulation has only recently received particular attention. Here we review recent findings on the differential regulation of calcium-permeable (CP-) and -impermeable (CI-) AMPARs in cerebellar neurons and glial cells, and discuss the critical involvement of TARPs in this process.

This article is part of the Special Issue entitled 'Glutamate Receptor-Dependent Synaptic Plasticity'.

1. Introduction

Many properties of AMPARs are dictated by the edited GluA2 subunit (Geiger et al., 1995; Swanson et al., 1997). AMPARs without GluA2 are permeable to calcium and display an inwardly rectifying IV-relationship, as they are blocked by endogenous intracellular polyamines at positive potentials, (Bowie and Mayer, 1995; Kamboj et al., 1995; Koh et al., 1995). When compared with their GluA2-containing counterparts, CP-AMPARs display a greater channel conductance (Feldmeyer et al., 1999; Swanson et al., 1997) and faster kinetics (Geiger et al., 1995). Expression, assembly and trafficking of CP-AMPARs are essential to basal transmission at many central synapses, and play pivotal roles in several important forms of synaptic plasticity. At the same time, over activation of these receptors can be injurious, and is thought to be a major contributor to cell death following stroke and hypoxic–ischemic white matter damage in infants. In addition, the upregulation or dysfunction of CP-AMPARs appears to be a significant contributor in several neurological disease states including glioblastoma cell proliferation, chronic pain and drug addiction (Cull-Candy et al., 2006; Kwak and Weiss, 2006; Liu and Zukin, 2007). For these reasons there has been growing interest in the regulation and plasticity of CP-AMPARs.

It has become clear that the diversity of native AMPAR properties is determined not only by AMPAR subunit composition and posttranslational modifications (such as phosphorylation; Lu and Roche, 2012), but also by the presence of auxiliary AMPAR subunits. Following the recognition that stargazin (γ-2) is a key regulator of AMPAR behaviour (Chen et al., 2000; Hashimoto et al., 1999), a number of related transmembrane AMPAR regulatory proteins have been identified (TARPs γ-3, -4, -5, -7, and -8) (Kato et al., 2007; Soto et al., 2009; Tomita et al., 2003). These various TARPs differ in their influence on AMPAR properties and display distinct, although partially overlapping, patterns of expression in the cerebellum (see Fig. 1) and elsewhere in the CNS (Fukaya et al., 2005; Tomita et al., 2003). Native AMPARs are thought to contain from one to four TARPs in addition to their core pore-forming subunits (Hastie et al., 2013; Kim et al., 2010; Shi et al., 2009); however, it is generally thought that only one type of TARP is present within a given AMPAR complex (Kato et al., 2007; Tomita et al., 2003). TARP association modifies several important aspects

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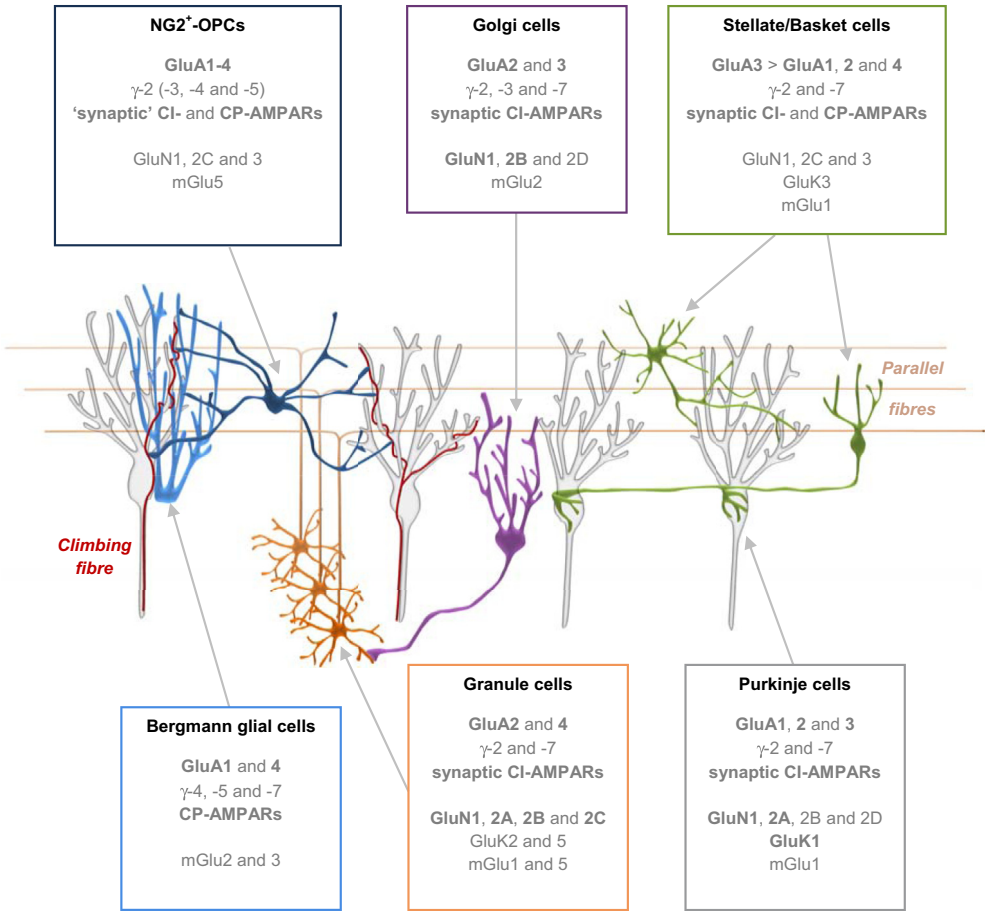

Fig. 1. Main cerebellar neurons and glial cells: location, connectivity, glutamate receptor and TARP content. Subunits indicated in bold form a majority of the AMPARs, NMDARs, and KARs involved in fast synaptic transmission. Other subunits listed are also expressed, but evidence of their contribution to synaptic currents is unclear. Note that extrasynaptic receptors can be activated by glutamate spillover, and that mGluRs are usually located perisynaptically.

of AMPAR function. It increases their single-channel conductance (Soto et al., 2007, 2009; Tomita et al., 2005a), slows their deactivation and desensitization (Bedoukian et al., 2006; Cho et al., 2007; Korber et al., 2007; Milstein et al., 2007; Priel et al., 2005; Tomita et al., 2005a; Turetsky et al., 2005), attenuates voltage-dependent block by endogenous intracellular polyamines and modifies their pharmacological properties (Korber et al., 2007; Soto et al., 2007, 2009; Turetsky et al., 2005).

TARPs also play a critical role in AMPAR trafficking, promoting AMPAR maturation (Vandenberghe et al., 2005), delivery to the cell surface and clustering at the synapse (Chen et al., 2000; Kato et al., 2007; Soto et al., 2009; Tomita et al., 2003; Vandenberghe et al., 2005). Recent evidence also suggests that TARPs are involved in the regulation of AMPAR number that occurs with long-term potentiation (LTP) or depression (LTD) of synaptic transmission in hippocampal pyramidal neurons (Tomita et al., 2005b) and in cerebellar Purkinje cells (Nomura et al., 2012). While the role of TARPs in the neuronal trafficking of GluA2-containing CI-AMPARs is relatively well characterized, their role in the regulation of CP-AMPAR expression is much less well understood.

The importance of TARPs for AMPAR expression and function was revealed initially in the cerebellum, where the lack of γ-2 in the mutant mice *waggler* and *stargazer* (*stg*/*stg*) was associated with a selective loss of AMPAR-mediated synaptic currents in cerebellar granule cells (Chen et al., 2000; Hashimoto et al., 1999; Tomita et al., 2003). Whereas granule cells contain only CI-AMPARs, a variety of other cerebellar neurons and glia express both CP- and CI-AMPARs (see Fig. 1). Recent studies conducted on the cerebellum of *stg*/*stg* mice indicate that the extent of the disruption to AMPAR-mediated currents caused by the absence of γ-2 varies from one cell type to another, and depends both on the other TARP isoforms normally expressed, as well as the subtypes of AMPARs present (Bats et al., 2012; Jackson and Nicoll, 2011; Menuz et al., 2008; Yamazaki et al., 2010). There is now growing evidence for a differential regulation of CI- and CP-AMPARs by TARPs (Bats et al., 2012; Soto et al., 2007, 2009; Yamazaki et al., 2010; Zonouzi et al., 2011). Below we present recent findings and discuss the specific roles of γ-2 and other TARPs in the regulation of CP-AMPAR expression and plasticity.

2. CP-AMPARs in the cerebellum

2.1. CP-AMPARs in molecular layer interneurons: stellate and basket cells

The cerebellar cortex plays an essential role in the learning and execution of coordinated movements. Stellate and basket cells — inhibitory molecular layer interneurons — influence the output of the cerebellar cortex by modulating the spatiotemporal activity of Purkinje cells (Dizon and Khodakhah, 2011; Häusser and Clark, 1997; Wulff et al., 2009). While stellate cells are found primarily in the outer region of the molecular layer (where they form synapses with Purkinje cell dendrites), basket cells are found in the inner molecular layer and make characteristic perisomatic synaptic