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Review

Extrasynaptic AMPA receptors in the dorsal horn: Evidence and functional significance

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ABSTRACT

Extrasynaptic AMPA receptors (AMPARs) are widely expressed in the brain, spinal cord and periphery. These receptors are critically involved in activity-dependent synaptic transmission and changes in their functioning are causally linked to multiple neuropathologies in the central nervous system (CNS). However, most studies in this field have been concentrated on elucidating synaptic AMPAR functioning, leaving a possible involvement of an extrasynaptic pool of AMPARs in normal and pathological signaling open for consideration.

Here, we review the present evidence for extrasynaptic AMPAR function in the dorsal horn neurons of the spinal cord, linking these receptors to neurotransmission and non-synaptic signaling in this part of the CNS. In addition, we summarize current knowledge about the role of extrasynaptic AMPARs in the development and maintenance of pain states during inflammation. This knowledge potentially suggests the development of alternative therapies to prevent and/or treat inflammatory pain.

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1. Introduction

During the last 100 years and until recently most attention in neuroscience was directed toward the study of synaptic connections in the central nervous system (CNS), being considered as the intrinsic and the most important component of neuronal network functioning. However, a number of experimental studies over the last decades have indicated that, in addition to synaptic transmission, there is another way to transmit information between the cells, based upon diffusion of neurotransmitters into the extracellular space and the activation of extrasynaptic receptors (Kullmann, 2000; Makani and Zagha, 2007). Such routes of intercellular communication have been termed non-synaptic (Vizi, 1980, 1984), parasynaptic (Schmitt, 1984), "volume" (Agnati et al., 1991) or extrasynaptic transmission (Kopanitsa, 1997).

Glutamate is the major excitatory neurotransmitter in the CNS, since over half of 100 billion neurons release glutamate (van der Zeyden et al., 2008; Vizi et al., 2010). Furthermore, almost all neurons express receptors sensitive to this neurotransmitter (van der Zeyden et al., 2008). Glutamate is not only involved in most normal aspects of brain function, including cognition, memory and learning, but also in multiple brain pathologies,

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such as epilepsy (Albrecht et al., 2010), cancer (de Groot and Sontheimer, 2011), schizophrenia (Rotaru et al., 2012), neurodegenerative disorders (Kwak and Weiss, 2006) excitotoxicity and ischemic damage (Kostandy, 2012). In the spinal cord, altered glutamatergic transmission is associated with central sensitization and pain (Latremoliere and Woolf, 2009). Enhanced glutamate release from primary afferents in the dorsal horn (DH) and upregulated glutamate receptor functioning in DH neurons result in increased pain sensation following tissue or nerve injury (Xu and Yaksh, 2011). In addition to synaptically localized receptors for glutamate, the extrasynaptic receptors provide an extra route for the local regulation of synaptic signals under physiological and pathological conditions (Camire et al., 2012).

Glutamate receptors of the AMPA type (AMPARs) are present in multiple locations throughout DH neurons, including the extrasynaptic plasma membrane, where they are apparently involved in physiological and pathological processing of sensory information (Triller and Choquet, 2005). Extrasynaptic AMPARs, identified within spines, dendrites, and somata, possess high mobility and rapidly move between the plasma membrane and intracellular compartments by exocytosis and endocytosis, and diffuse laterally to and from synaptic sites (Borgdorff and Choquet, 2002; Choquet and Triller, 2003; Cognet et al., 2006; Bredt and Nicoll, 2003; Malinow and Malenka, 2002). Such continuous AMPAR exchange between synapses and different cellular pools (AMPAR trafficking) ensures dynamic fitting of synaptic AMPAR number and participates in synaptic plasticity under different cell conditions (Bredt and Nicoll, 2003; Carroll et al., 2001). The induction of long-term potentiation (LTP) is mediated by an increase in the number of extrasynaptic AMPARs that can then be translocated to synapses (Nusser, 2000), and conversely, for long-term depression (LTD), a decrease in the number of extrasynaptic AMPARs has been reported (Carroll et al., 2001; Triller and Choquet, 2005). It has been shown in hippocampal neurons that lateral diffusion of extrasynaptic AMPARs allows fast exchange of desensitized receptors with fresh functional ones at synapses upon fast synaptic stimulation (Heine et al., 2008). Therefore, extrasynaptic AMPARs contributed to the precise and fine regulation of synaptic efficacy. Besides, extrasynaptic AMPARs also contribute to glutamate-induced signaling at nonsynaptic locations (Rossi et al., 2008) due to spillover of glutamate (Kullmann, 2000) or glutamate release from glia (Araque et al., 1999).

Here, we review recent key findings in molecular and cellular mechanisms of extrasynaptic AMPARs functioning in DH neurons and their role in peripheral hypersensitivity and inflammatory pain syndromes.

2. AMPAR structure, subunits expression and localization in the DH

AMPAR channel consists of four subunits, GluA1–GluA4 (or GluR1–GluR4), identified by molecular cloning in the late 1980s (Hollmann et al., 1989). Four different genes (GluR1, GluR2, GluR3, and GluR4) encode AMPAR subunits. Each subunit includes an N-terminal extracellular amino domain, a ligand-binding domain, a receptor-channel domain, and an intracellular C-terminal domain (Song and Huganir, 2002). GluR1, GluR4, and GluR2L (a long splice form of GluR2) have a long cytoplasmic carboxy-terminal tail (C-tail), whereas GluR2, GluR3, and GluR4c (a short splice form of GluR4) have short and structurally similar C-tails (Kessels and Malinow, 2009). The C-terminal domain contains multiple protein phosphorylation sites for various protein kinases, and several binding sites (motifs) for various membrane-related and intracellular proteins, such as scaffolding proteins. The receptor-channel domain consists of three transmembrane segments (M1, M3, and M4) crossing the membrane, and one re-entrant loop within the membrane (M2), which forms part of the ion-channel pore and controls the flow of calcium ions through the channel (Song and Huganir, 2002).

The functional properties of AMPAR are dependent on the subunit composition. Functional AMPARs are homomeric or heteromeric tetramers. Mutational analysis demonstrated that the Ca^{2+} permeability of the channel is strictly determined by the R/Q position in the pore-forming M2 segment: Ca^{2+} permeability of the channel assembled from GluR1, GluR3, and GluR4 subunits, in which the arginine is replaced by glutamine (R586Q), is high, whereas the Ca^{2+} permeability of the channel assembled from GluR2 subunits, in which the glutamine is replaced by arginine (Q587R), is low (Burnashev et al., 1992). Therefore, incorporation of GluR2 subunit into heteromeric AMPARs dramatically reduces their Ca^{2+} permeability and changes the current properties and channel conductance (Burnashev et al., 1992; Song and Huganir, 2002).

All four GluR subunits are expressed in the DH of the spinal cord. Among these subunits, GluR1 and GluR2 were found to be highly expressed in the superficial DH (laminae I–II), where primary afferents carrying nociceptive inputs make synapses to the spinal second-order nociceptive neurons. GluR3 and GluR4 are weakly expressed in the DH (Furuyama et al., 1993), although GluR4 was recently detected in large neurokinin-1 receptor-expressing projection neurons in lamina I (Polgar et al., 2010). Thus, GluR1 and GluR2 represent the two most abundant subunits forming the AMPAR channel in the DH.

Most GluR1 and GluR2 immunoreactivity in the superficial DH is restricted to the postsynaptic density (PSD) (Petralia et al., 1997). Nonetheless, a high level of extrasynaptic AMPAR expression has been also detected in the DH within neuronal dendrites and somata (Kopach et al., 2011). Electron microscopy of the spinal cord shows substantial staining for GluR1 and GluR2 in the extrasynaptic membranes of the superficial DH. Analysis of electrophysiological recordings and Ca^{2+} influx using Ca^{2+}-sensitive dyes further indicated that GluR2-containing, Ca^{2+}-impermeable AMPARs and GluR2-lacking, Ca^{2+}-permeable AMPARs are both expressed extrasynaptically in the soma and dendrites of lamina II DH neurons (Kopach et al., 2011; Kyrozis et al., 1995). In contrast to other parts of the CNS, in the adult rat DH, a majority of the neurons densely express Ca^{2+}-permeable homomeric GluR1 AMPARs (Albuquerque et al., 1999; Engelman et al., 1999; Hartmann et al., 2004). Interestingly, in laminae III–IV of the DH, synaptic AMPARs located on the dendrites of neurokinin 1 receptor-expressing projection neurons contain GluR2, GluR3 and GluR4 subunits, but not GluR1 (Todd et al., 2009). All these data suggest that extrasynaptic AMPAR channel composition differs from the channel assembly of the synaptic receptor. However, the precise subunit composition of synaptic and extrasynaptic AMPARs has not been determined in DH neurons as yet. To the best of our knowledge, the only region where the subunit composition for synaptic and extrasynaptic AMPA has been described is the hippocampus where synaptic receptors contain both GluR1R2 and GluR2R3 heteromers, whereas the extrasynaptic AMPARs mainly consist of only GluR1R2 heteromers (Beique and Huganir, 2009; Lu et al., 2009). Homomeric GluA1 AMPARs are found in the extrasynaptic membranes of adult rat nucleus accumbens (Ferrario et al., 2011). By using a gene knockout approach the GluR1 subunit has been revealed as an obligatory component of extrasynaptic AMPARs, because extrasynaptic AMPARs were almost totally absent in hippocampal neurons of the GluR1 knockout mice (Andrasfalvy et al., 2003).

The density of the extrasynaptic AMPARs detected in different parts of the CNS varies among the neuron types. A high AMPAR immunolabeling in the extrasynaptic sites of the plasma membrane ($\sim$100 particles μm^{-2}) was shown in the dentate gyrus of the hippocampus, whereas it was much lower ($\sim$10 particles μm^{-2}) in the