



Ca²⁺ permeable AMPA channels in diseases of the nervous system

John H. Weiss^{1,2} *

¹ Department of Neurology, University of California Irvine, Irvine, CA, USA

² Department of Anatomy and Neurobiology, University of California Irvine, Irvine, CA, USA

Edited by:

R. Suzanne Zukin, Albert Einstein College of Medicine, USA

Reviewed by:

KeWei Wang, Peking University, China
Frantisek Jursky, Slovak Academy of Sciences, Slovak Republic

*Correspondence:

John H. Weiss, Department of Neurology, University of California Irvine, Irvine, CA 92697, USA.
e-mail: jweiss@uci.edu

Since the discovery and molecular characterization of Ca²⁺-permeable AMPA channels just over two decades ago, a large body of evidence has accumulated implicating contributions of these unusual glutamate activated channels to selective neurodegeneration in certain conditions, including ischemia and amyotrophic lateral sclerosis. Factors likely involved in their contributions to disease include their distinct patterns of expression in certain neuronal populations, their upregulation via various mechanisms in response to disease associated stresses, and their high permeability to Zn²⁺ as well as to Ca²⁺. However, full characterization of their contributions to certain diseases as well as development of therapeutics has been limited by the lack of selective and bioavailable blockers of these channels that can be employed in animals or humans. This review summarizes some of the clues that have emerged over recent years to the contributions of these channels in disease.

Keywords: calcium, zinc, ALS, motor neuron, neurodegeneration, glutamate, excitotoxicity

INTRODUCTION

Glutamate is the main excitatory transmitter in the mammalian central nervous system. Overactivation of post-synaptic receptors for glutamate places a metabolic stress upon neurons which can contribute to neuronal injury in a wide range of conditions. The evidence for a contribution of glutamate receptor overactivation (termed “excitotoxicity”) is strongest in conditions like ischemia, prolonged seizures, and trauma, in which there is rapid release and extracellular accumulation of glutamate. However, there is also compelling evidence for important excitotoxic contributions to injury in neurodegenerative conditions including amyotrophic lateral sclerosis (ALS).

Glutamate acts at a number of receptors comprising both ligand-gated ion channels (ionotropic receptors) and G-protein linked (metabotropic) receptors. Three families of ionotropic glutamate receptors (NMDA, AMPA, and kainate receptors) have been characterized both pharmacologically and by the identification and cloning of their subunit genes. Early studies of excitotoxic mechanisms focused on possible contributions of NMDA receptors, which unlike most AMPA, and kainate receptors (collectively referred to as AMPA/kainate receptors), are highly permeable to Ca²⁺ ions, and brief activation of which could potentially trigger delayed injury to cultured neurons. However, despite clear contributions of these channels in some models of acute neurodegeneration, NMDA blockers have to date failed to show impressive efficacy in therapeutic trials. Furthermore, in some studies AMPA/kainate receptor blockade has shown greater efficacy against ischemic injury than NMDA receptor antagonism (Buchan et al., 1993).

Another early clue to contributions of AMPA/kainate in neurodegeneration derives from studies of syndromes in humans or primates linked to the consumption of environmental toxins, beta-N-methylamino-L-alanine (BMAA),

beta-N-oxalylamino-L-alanine (BOAA), and domoic acid (Spencer et al., 1986, 1987; Teitelbaum et al., 1990). BOAA and domoic acid, the respective causes of lathyrism and a form of shellfish poisoning, are both well established AMPA/kainate receptor agonists. BMAA, an unusual cyanobacterial toxin suspected of contributing to forms of human neurodegenerative disease, can induce selective injury to vulnerable subpopulations of neurons, including motor neurons (MN, which degenerate in ALS), via activation of AMPA/kainate receptors (Weiss et al., 1989; Weiss and Choi, 1991; Rao et al., 2006). Whereas most AMPA/kainate type glutamate channels are Ca²⁺ impermeable, subsets of these channels, which are expressed in characteristic temporal and spatial patterns on discrete populations of neurons, are Ca²⁺-permeable, and it is the activation of these channels that likely mediates most of the neurodegeneration attributable to AMPA/kainate receptor activation. This review focuses specifically on Ca²⁺-permeable AMPA (Ca-AMPA) channels and clues that have accumulated over the past two decades to their roles in both acute and chronic neurodegenerative conditions.

STRUCTURE AND REGULATION OF Ca-AMPA CHANNELS

AMPA channels are the most prevalent glutamate channels in the mammalian central nervous system, and mediate most routine excitatory neurotransmission. They are tetramers comprised of combinations of four subunits – GluA (previously referred to as GluR) 1, 2, 3, or 4. The presence of one or more GluA2 subunits in a heteromeric channel prevents Ca²⁺ permeability. The ability of GluA2 subunits to block Ca²⁺ permeability is dependent upon the presence of a positively charged arginine residue at a critical site in the channel lining region of the peptide (the “Q/R site”); the other AMPA subunits (GluR1, 3, and 4) all have a neutral glutamine at the homologous site. Interestingly, the genomic DNA encodes a neutral glutamine residue at this site in all four

subunits, and the arginine codon is post-transcriptionally inserted into the GluA2 mRNA transcript via RNA editing by the enzyme ADAR2 (Higuchi et al., 2000). After translation, the subunits are assembled in the ER. Likely indicative of the critical importance of these channels to normal physiological function, channel assembly, and membrane insertion are both sensitive to the editing state of GluA2 (Greger et al., 2002, 2003; Araki et al., 2010). It has further become apparent that pathological upregulation of these channels in disease states can occur via several mechanisms, including downregulation of GluA2 mRNA transcription, defective editing of the GluA2 pre-mRNA, and aberrant internalization of GluA2 containing (and Ca^{2+} impermeable) channels and insertion of GluA2 lacking channels.

The presence of Ca-AMPA channels is neither uniform nor constant, but varies with cell type and developmental stage. Whereas most adult neurons possess relatively few of these channels, discrete populations of neurons, most prominently many GABAergic inhibitory interneurons, possess large numbers of Ca-AMPA channels (Jonas et al., 1994; Yin et al., 1994a; Leranth et al., 1996). In contrast most adult excitatory pyramidal neurons possess few of these channels. However, numbers of Ca-AMPA channels on pyramidal neurons change with developmental stage, and are present in markedly increased numbers in both rats and humans in early postnatal periods (Kumar et al., 2002; Talos et al., 2006a,b; Brill and Huguenard, 2008).

MECHANISMS OF INJURY CAUSED BY Ca-AMPA CHANNELS

As mentioned above, relatively brief but strong activation of highly Ca^{2+} permeable NMDA channels is sufficient to trigger degeneration of cultured neurons. A large number of studies have highlighted mechanisms through which such neuronal Ca^{2+} loading can induce injury, which may vary depending upon the intensity of the Ca^{2+} load. With strong loading, Ca^{2+} is taken up into mitochondria and can disrupt their function, causing release of damaging reactive oxygen species (ROS; Dugan et al., 1995; Reynolds and Hastings, 1995). In addition, Ca^{2+} loading can induce ROS generation through other mechanisms, including the activation of nitric oxide synthetase (NOS), with resultant nitric oxide production, and the activation of NADPH-oxidase, with resultant superoxide production (Dawson et al., 1991; Brennan et al., 2009). These ROS may induce DNA damage, causing activation of the enzyme, PARP, which can injure neurons via NAD^+ depletion, resulting in glycolytic block, depletion of ATP, and induction of apoptotic signaling via release of AIF from mitochondria (Hong et al., 2004; Alano et al., 2010).

It appears likely that many of these same downstream mechanisms may apply to injury caused by strong activation of Ca-AMPA channels (Carriedo et al., 1998). A key question thus concerns differences between NMDA and Ca-AMPA dependent injury, possibly accounting for the apparent greater contributions of Ca-AMPA channels in some conditions. One difference is that NMDA channels are subject to a voltage dependent block of their pores by extracellular Mg^{2+} ions, such that there is relatively little ion flux through these channels in the absence of significant post-synaptic depolarization. This voltage dependence allows NMDA channels to detect temporally and spatially convergent post-synaptic inputs and is thus important to their roles in activity dependent synaptic

plasticity. In contrast, Ca-AMPA channels are not blocked by extracellular cations (but are subject to voltage dependent block by intracellular polyamines, resulting in inwardly rectifying currents), and thus freely permit Ca^{2+} entry with any level of receptor activation. Secondly, whereas the expression of NMDA channels is relatively static, AMPA channels are strongly regulated in response to physiological and pathological signals, and numbers of Ca-AMPA channels may increase sharply in certain stress conditions and disease states (as discussed further below). Thus, the increase in numbers of these channels in already stressed neurons adds an additional metabolic burden that may impair their ability to restore homeostasis and survive.

A likely third factor in their propensity to contribute to injury concerns their permeability to other divalent cations. Zn^{2+} is present in pre-synaptic vesicles of many (but not all) forebrain excitatory pathways, and appears to be co-released with glutamate upon pre-synaptic activation (Assaf and Chung, 1984; Howell et al., 1984; Qian and Noebels, 2005). Although the physiological significance of pre-synaptic Zn^{2+} release is uncertain, it can effectively block NMDA channels, limiting their ion flux in response to intense pre-synaptic activation (Paoletti et al., 2009). In contrast, Zn^{2+} readily permeates Ca-AMPA channels (Jia et al., 2002), and its entry through these channels can clearly injure cultured neurons and likely contributes to injury in conditions like ischemia (Yin and Weiss, 1995; Sensi et al., 1999; Yin et al., 2002; Calderone et al., 2004; Noh et al., 2005). Intracellular Zn^{2+} can trigger neurodegeneration via a number of mechanisms, including some previously attributed to Ca^{2+} , including the induction of mitochondrial dysfunction, which it appears to do with considerably greater potency than Ca^{2+} (Sensi et al., 2009; Shuttleworth and Weiss, 2011).

Ca-AMPA CHANNELS IN ISCHEMIC NEURODEGENERATION

As mentioned above, some early studies found AMPA/kainate blockers to provide greater protection than NMDA blockers against ischemic neurodegeneration, and it is likely that much of this protection reflects blockade of Ca-AMPA channels. Studies to date have suggested that Ca-AMPA channels may contribute to different forms of ischemic injury in a number of ways.

The immature brain is particularly susceptible to ischemia, and pre-term, or perinatal hypoxia ischemia of both white and gray matter is a major cause of early life morbidity, for instance as an antecedent of cerebral palsy. A number of studies have indicated that periods of high ischemic susceptibility correspond to developmental periods of increased Ca-AMPA channel numbers, suggesting that the presence of these channels contributes to the ischemic susceptibility (Talos et al., 2006a,b).

Transient global ischemia (TGI), as occurs in cardiac arrest, causes a variable degree of neuronal damage and loss, depending upon the duration of the ischemia. In hippocampus, pyramidal neurons (HPNs) in the CA1 subfield are particularly susceptible. Although adult HPNs were previously felt to lack Ca-AMPA channels, especially in contrast to strongly Ca-AMPA channel expressing GABAergic interneurons, a number of studies have suggested that they may often be present under basal conditions in relatively low numbers, and preferentially on dendrites at a distance from the soma where they are not readily detected electrophysiologically

(Lerma et al., 1994; Ikonovic et al., 1995; Yin et al., 1999; Ogoshi and Weiss, 2003).

In specific support of a role for Ca-AMPA channels in ischemic injury, maneuvers to increase numbers of these channels increased susceptibility of CA1 pyramidal neurons to ischemic injury, whereas decreasing channel numbers decreased injury (Anzai et al., 2003; Liu et al., 2004). A very intriguing clue to contributions of Ca-AMPA was provided by the observation that transient ischemia could induce a selective downregulation of GluA2 mRNA in CA1 pyramidal neurons, resulting in a delayed (after 2–3 days) incorporation of increased numbers Ca-AMPA channels into synapses (Gorter et al., 1997; Pellegrini-Giampietro et al., 1997; Grooms et al., 2000; Opitz et al., 2000). Furthermore, indicating a direct role of these channels in the delayed neurodegeneration of CA1 neurons, the injury was attenuated by the delayed administration of a Ca-AMPA channel blocker (Noh et al., 2005).

Further studies point toward intriguing roles of Zn^{2+} in this form of injury. First, highlighting contributions of Zn^{2+} to ischemic neurodegeneration, Zn^{2+} accumulates in degenerating neurons and injury was attenuated by an extracellular Zn^{2+} chelator (Tønder et al., 1990; Koh et al., 1996). Supporting a contribution of Zn^{2+} entry through Ca-AMPA channels, either an extracellular Zn^{2+} chelator or a Ca-AMPA channel blocker attenuated neuronal Zn^{2+} accumulation and subsequent degeneration in a hippocampal slice model of ischemia (Yin et al., 2002). Interestingly, Zn^{2+} may act in distinct ways during different temporal phases of the ischemic process. Addition of an extracellular Zn^{2+} chelator before the ischemic episode attenuated the GluA2 downregulation, preventing the delayed increase in Ca-AMPA channels (Calderone et al., 2004). A number of recent studies suggest that mitochondria might be an important target of these early Zn^{2+} rises (Calderone et al., 2004; Bonanni et al., 2006; Medvedeva et al., 2009). These acute events appear to result in upregulation of the gene silencing transcription factor neuronal repressor element-1 silencing transcription factor (REST)/neuron-restrictive silencer factor (NRSF), which has been linked to the delayed downregulation of GluA2 (Calderone et al., 2003). In contrast, late addition of either the chelator or of a Ca-AMPA channel blocker, after the channel upregulation was already underway, attenuated the occurrence of a delayed intracellular Zn^{2+} rise and associated cell death (Calderone et al., 2004; Noh et al., 2005), consistent with the idea that Zn^{2+} entry through the newly inserted channels might contribute to the delayed injury. Of note, however, it is clear that not all ischemic Zn^{2+} accumulation reflects entry through Ca-AMPA or other channels, and that there are stores of Zn^{2+} already present in the CA1 neurons which can be mobilized in response to acidosis and oxidative stress associated with ischemia, contributing to the rises (Aizenman et al., 2000; Lee et al., 2000).

Whereas downregulation of GluA2 results in the incorporation of new Ca-AMPA channels after a significant delay, other recent studies have suggested that ischemia can also induce a more rapid endocytosis of Ca^{2+} impermeable AMPA channels and exocytosis of Ca-AMPA channels into synapses via mechanisms involving receptor trafficking events that may be involved in synaptic plasticity (Liu et al., 2006; Dixon et al., 2009). Another study suggested that defects in GluA2 editing may occur after ischemia, resulting

in the incorporation of unedited GluA2 into channels, rendering them Ca^{2+} permeable (Peng et al., 2006). Interestingly, AMPA receptors containing unedited GluA2 may be particularly toxic to neurons, in part because of their constitutive trafficking to the plasma membrane (Mahajan and Ziff, 2007).

Ca-AMPA CHANNELS IN ALS

Amyotrophic lateral sclerosis is a neurodegenerative disease characterized by progressive weakness due to the relatively selective degeneration of upper and lower MNs, usually leading to death within 2–5 years of diagnosis. Whereas most cases are sporadic, ~10% are familial, and of those a fraction are linked to dominant mutations in the gene superoxide dismutase 1 (SOD1). Observations of loss of the ability of astrocytes to take up extracellular glutamate provided an early clue that excitotoxicity might contribute to the MN injury. Consistent with this idea, glutamate uptake blockers caused preferential loss of MNs both in organotypic slice and dissociated culture models (Rothstein et al., 1993; Carriedo et al., 1996). Furthermore, supporting a role of AMPA/kainate receptors in the disease, this MN degeneration was prevented by AMPA/kainate blockers, but not by NMDA blockers.

We and others have investigated mechanisms underlying the excitotoxic vulnerability of MNs. First, they possess substantial numbers of Ca-AMPA channels (Carriedo et al., 1996; Van Den Bosch et al., 2000; Vandenberghe et al., 2000). In addition, populations of MNs that degenerate in ALS are characterized by having low levels of cytosolic Ca^{2+} buffering proteins (Alexianu et al., 1994; Elliott and Snider, 1995), and buffer cytosolic Ca^{2+} loads poorly (Vanselow and Keller, 2000), such that excitotoxicity induced Ca^{2+} loads are rapidly taken up into the mitochondria, with consequent strong mitochondrial ROS release (Carriedo et al., 2000). In further studies, we have found evidence that this mitochondrial ROS might not only damage the MNs, but also exit the MNs and contribute to the loss or dysfunction of glutamate transporters on surrounding astrocytes (Rao et al., 2003). Such a mechanism might contribute to the propagation of a feed forward cascade, with loss of glutamate transport resulting in increased extracellular glutamate levels, more activation of Ca-AMPA channels, and more mitochondrial Ca^{2+} loading resulting in more ROS generation (Rao and Weiss, 2004; Yin et al., 2007).

Transgenic mice overexpressing familial ALS associated SOD1 mutations have provided by far the most studied animal models of the disease. Providing strong evidence that Ca-AMPA channels play a role in this form of the disease, generation of SOD1 mutant mice with increased numbers of Ca-AMPA channels in their MNs accelerates disease progression, while decreasing numbers of the channels in these mice slows the disease (Tateno et al., 2004; Kuner et al., 2005; Van Damme et al., 2005).

In addition to the presence of some Ca-AMPA channels on MNs under basal conditions, an intriguing series of studies suggests that there may be a loss of GluA2 editing in ALS MNs, such that numbers of Ca-AMPA channels may increase, further predisposing them to injury (Kawahara et al., 2004; Kwak et al., 2010). As mentioned above, AMPA receptors containing unedited GluA2 may be particularly effective at inducing neurotoxicity (Mahajan and Ziff, 2007). Another recent study suggests that the loss of GluA2 editing may be triggered as a consequence of excitotoxic exposures,

via proteolytic cleavage of the editing enzyme, RNA-dependent adenosine deaminase, ADAR2 (Mahajan et al., 2011).

Ca-AMPA CHANNELS IN OTHER CONDITIONS

Although roles of Ca-AMPA channels have been most studied in the cases of ischemia and ALS, there are compelling clues to contributions in other conditions as well. First, Ca-AMPA channels may well contribute to neurodegeneration in conditions of prolonged seizures, or brain, or spinal cord trauma, both of which, like ischemia are associated with prolonged elevations of extracellular glutamate. Much as in ischemia, GluA2 mRNA, and protein levels have been observed to decrease following prolonged seizures in CA1 and CA3 hippocampal pyramidal neurons prior to the death of these cells (Friedman et al., 1994; Grooms et al., 2000). In the case of traumatic injury, ventral root avulsion induced loss of GluA2 in spinal MNs (Nagano et al., 2003) and spinal cord contusion caused preferential loss of GluA2 in MNs that persisted for at least a month (Grossman et al., 1999). In addition, recent studies in models of cerebral trauma provide evidence for endocytosis of GluA2 containing receptors and insertion of Ca-AMPA receptors that contributed to the induction of injury (Spaethling et al., 2008; Bell et al., 2009).

Other studies suggest possible contributions of Ca-AMPA channels to neurodegeneration in Alzheimer's disease. Cholinergic neurons of the basal forebrain conspicuously degenerate in Alzheimer's disease (Whitehouse et al., 1982), and there is evidence for loss of other subpopulations of interneurons including those containing parvalbumin or somatostatin (Davies et al., 1980; Rossor et al., 1980; Arai et al., 1987). Interestingly, *in vitro* studies indicate that these populations are all selectively sensitive to AMPA/kainate receptor mediated excitotoxicity, probably in large part due to their possession of substantial numbers of Ca-AMPA channels (Weiss et al., 1990, 1994; Yin et al., 1994b). Other studies have found GluA2 on basal forebrain cholinergic neurons to be markedly decreased in aged humans (Ikonomovic et al., 2000), and that levels of GluA2 on pyramidal neurons in the entorhinal cortex and hippocampus of Alzheimer brains decrease prior to neurofibrillary tangle formation (Ikonomovic et al., 1997), suggesting that increased numbers of Ca-AMPA channels may predispose to the degeneration of these neuronal populations.

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Further intriguing studies suggest a link between inflammation and increases in Ca-AMPA channel numbers. The inflammatory cytokine, tissue necrosis factor- α (TNF- α) can lead to rapid exocytosis of Ca-AMPA channels on pyramidal neurons (Beattie et al., 2002; Ogoshi et al., 2005; Stellwagen et al., 2005), and recent studies strongly suggest that TNF- α dependent trafficking of Ca-AMPA channels contributes to neurodegeneration after spinal cord trauma (Ferguson et al., 2008). This mechanism could prove relevant to neurodegeneration in other immune or neurodegenerative conditions in which acute or chronic inflammation occurs.

CONCLUSIONS

The past two decades have seen the accumulation of a host of clues to contributions of Ca-AMPA channels in a wide range of diseases of the nervous system. The presence of Ca-AMPA channels is not felt to be causative of the diseases. But the preferential expression of Ca-AMPA channels on subpopulations of neurons may be a factor in the selective patterns of neurodegeneration seen in certain conditions. In addition, the propensity for the upregulation of Ca-AMPA channel numbers, likely via a range of mechanisms, in response to disease associated signals may well subject affected neurons to new stresses that may tip the balance toward degeneration. Despite the accumulation of numerous clues to roles of Ca-AMPA channels in disease, many questions, and obstacles exist. There are as yet no proven therapeutics based on the modulation or block of these channels. This likely reflects the absence to date of any highly effective, selective, and bioavailable drugs for blocking Ca-AMPA channels in whole animals, as would be necessary to fully test their contributions to disease. Such blockers, if available, might be remarkably useful neuroprotectants in a wide range of conditions, as they may effectively antagonize toxic Ca²⁺ and Zn²⁺ entry through these channels without overly suppressing overall glutamatergic neurotransmission.

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