AMPA receptors mediate fast synaptic transmission at excitatory synapses in the CNS and are crucial during neuronal development, synaptic plasticity and structural remodeling. AMPA receptors lacking GluR2 subunits are permeable to Ca\(^{2+}\) and Zn\(^{2+}\). Ca\(^{2+}\) permeation through AMPA receptors is crucial in several forms of synaptic plasticity and cell death associated with neurological diseases and disorders. The subunit composition and Ca\(^{2+}\) permeability of AMPA receptors are not static, but they are dynamically remodeled in a cell- and synapse-specific manner during development and in response to neuronal activity, sensory experience and neuronal insults. Exciting new research shows that these changes arise not only because of regulated expression of the AMPA receptor subunit GluR2, but also as a consequence of RNA editing, receptor trafficking and dendritic protein synthesis. This article reviews new insights into the role of Ca\(^{2+}\)-permeable AMPA receptors in neuronal function and survival.

Introduction

AMPA receptors mediate fast synaptic transmission at excitatory synapses in the CNS and are crucial during neuronal development, synaptic plasticity and structural remodeling. AMPA receptors are tetrameric assemblies of subunits GluR1–4 (or subunits GluRA–D), which are encoded by separate genes and differentially expressed throughout the CNS (reviewed in [1]). Additional molecular diversity arises through RNA editing (Box 1) and alternative splicing. Each AMPA receptor subunit contains a large extracellular N-terminal domain, three membrane-spanning domains, a re-entry or hairpin loop that forms the pore-lining region (membrane domain 2) and an intracellular C-terminal domain. AMPA receptors lacking GluR2 are permeable to Ca\(^{2+}\) and Zn\(^{2+}\) [2–5] and exhibit distinctly fast kinetics [4] and a characteristic inwardly rectifying current–voltage (I–V) relation, owing to voltage-dependent block by intracellular polyamines [6–9] (Figure 1). Owing largely to a crucial arginine (R) residue in its pore-lining membrane domain 2, the presence of GluR2 in heteromeric AMPA receptors renders the channel impermeable to Ca\(^{2+}\) and Zn\(^{2+}\) and electrically linear (Figure 1). The presence of GluR2 also influences channel kinetics [4], conductance [10], AMPA receptor assembly, forward trafficking from the endoplasmic reticulum (ER) and targeting to and from synaptic sites [11–14] (Box 2). Thus, even a modest alteration in the level of expression of GluR2 is expected to have profound implications for synaptic efficacy and neuronal survival.

Most principal neurons of the neocortex, hippocampus, amygdala and cerebellum express GluR2-containing, Ca\(^{2+}\)-impermeable AMPA receptors [4,15–17]. In these cells, the acute loss of GluR2 confers selective vulnerability to neuronal insults (see below). By contrast, aspy neurons throughout the CNS, including neocortical, hippocampal and amygdaloid fast-sampling interneurons, cerebellar stellate cells, dorsal horn interneurons, large striatal cholinergic interneurons, bushy and stellate cells of the cochlear nucleus, spinohalamic projection neurons and retinal AII amacrine cells, in addition to Bergmann glia and oligodendrocyte precursor cells of the cerebellum, express GluR2-lacking, Ca\(^{2+}\)-permeable AMPA receptors [18]. In these cells, AMPA receptor-mediated Ca\(^{2+}\) signaling is rapid and compartmentalized, owing mainly to fast, local Ca\(^{2+}\)-extrusion pumps, and crucial for synaptic plasticity. The rapid response kinetics of GluR2-lacking AMPA receptors is also thought to be instrumental in synchronous firing of neocortical layer 2 and 3 interneurons during fast brain waves or gamma oscillations involved in transmission of information to distant regions of the brain [19]. The subunit composition and electrical properties of AMPA receptors also vary in a synapse-specific manner within individual neurons [20,21]. This feature enables individual neurons to produce different responses to distinct afferent inputs and might be important to information processing and integration within neural circuits. The subunit composition and Ca\(^{2+}\) permeability of AMPA receptors are not static, but they are dynamically remodeled in a cell- and synapse-specific manner during development and in response to neuronal activity. Recent studies show that these changes arise not only as a consequence of redistribution or trafficking of AMPA receptor subunits, but also owing to activity-dependent local protein synthesis of AMPA receptors in dendrites [22,23]. The subunit composition and Ca\(^{2+}\) permeability of AMPA receptors are also remodeled by neuronal insults (e.g. seizures) [24–26], ischemic insults [27–31], excitotoxicity [32,33], spinal cord injury [34], antipsychotics [35], drugs of abuse [36], corticosteroids [37] and neurological diseases (e.g. Alzheimer’s disease [38] and amyotrophic lateral sclerosis (ALS) [39,40]). These changes arise not only owing to dysregulation of the expression of GluR2, but also because of RNA editing [41,42] and...
This article reviews new insights into the molecular mechanisms underlying activity-dependent remodeling of the subunit composition and permeability of synaptic AMPA receptors and highlights the importance of Ca\(^{2+}\)-permeable AMPA receptors in synaptic plasticity and neuronal death.

**Ca\(^{2+}\)**-permeable AMPA receptors in synaptic plasticity

AMPA receptor-mediated Ca\(^{2+}\) influx can influence synaptic efficacy in at least two ways. First, Ca\(^{2+}\) influx can activate intracellular signaling cascades, which regulate AMPA receptor trafficking, local translation and/or gene transcription, and thereby effect long-term changes in synapse performance. Second, Ca\(^{2+}\) influx can induce a switch in synaptic AMPA receptor subtype, thereby altering the qualitative properties (permeability, kinetics and electrical rectification) of the synapse. A striking feature of Ca\(^{2+}\)-permeable AMPA receptor-dependent synaptic plasticity is a self-regulating mechanism, whereby repetitive activation of these receptors limits the number of synaptic Ca\(^{2+}\)-permeable AMPA receptors [44] (see below).

**Induction of long-term plasticity by activation of Ca\(^{2+}\)**-permeable AMPA receptors

Permeation of Ca\(^{2+}\) through AMPA receptors can trigger multiple forms of synaptic plasticity on aspiny interneurons. This was first demonstrated at dorsal horn onto spinal cord synapses, which densely express Ca\(^{2+}\)-permeable AMPA receptors [45]. At these synapses, AMPA receptor-mediated Ca\(^{2+}\) influx serves as the trigger for induction of long-term potentiation (LTP) or enhanced synaptic efficacy. Although little is known about the molecular mechanisms underlying this form of synaptic plasticity, the functional consequences of LTP have been revealed. For example, LTP at these synapses is implicated in the nociceptive plasticity associated with chronic pain. Targeted deletion of GluR1 generates mice with a reduced complement of Ca\(^{2+}\)-permeable AMPA receptors in the dorsal horn and loss of nociceptive plasticity [46]. By contrast, targeted deletion of GluR2 generates mice with an enhanced complement of Ca\(^{2+}\)-permeable AMPA receptors and facilitates spinal nociceptive plasticity [46]. Ca\(^{2+}\)-permeable AMPA receptor-dependent synaptic plasticity also occurs at the inputs of excitatory synapses onto interneurons of the amygdala and area CA3 of the hippocampus. Repetitive activation of synaptic inputs onto interneurons of the amygdala produces LTP of the excitatory postsynaptic current (EPSC) [47], a form of synaptic plasticity which depends on the subunit composition. Rectification of GluR2-lacking AMPA receptors arises as a consequence of use- and voltage-dependent channel blockade by endogenous intracellular polyamines. Ca\(^{2+}\)-permeable AMPA receptors are highly permeable to Ca\(^{2+}\) and exhibit doubly rectifying I–V relationships. Ca\(^{2+}\)-impermeable AMPA receptors are impermeable to Ca\(^{2+}\) and exhibit electrically linear I–V relationships. The presence of the GluR2 in heteromeric AMPA receptor channels limits Ca\(^{2+}\) and Zn\(^{2+}\) influx and markedly reduces single-channel conductance [10], owing largely to the presence of a positively charged R instead of a Q residue at the Q/R RNA editing site. Assuming the channel number is unaltered, current amplitudes will be smaller for GluR2-containing AMPA receptors (b). Reproduced, with permission, from Ref. [69]. I–V relationships reproduced, with permission, from Ref. [4,15–17].
Box 2. GluR2 in AMPA receptor trafficking

Activity-dependent AMPA receptor trafficking is a mechanism crucial for many forms of synaptic plasticity and remodeling [74,75]. AMPA receptors move rapidly between the plasma membrane and intracellular compartments through regulated receptor endocytosis and exocytosis. In addition, AMPA receptors are laterally translocated within the membrane between synaptic and extrasynaptic sites [76]. Synaptic plasticity is thought to involve alterations in the number and phosphorylation state of postsynaptic AMPA receptor channels [74,75], but might also involve alterations to the subunit composition of AMPA receptors [44,52,53,77]. In addition to the role of the AMPA receptor in synaptic plasticity, AMPA receptor trafficking also contributes to ischemia-induced neuronal death [43].

AMPA receptors interact with intracellular (cytosolic) receptor trafficking and anchoring proteins, which regulate their recycling and synaptic targeting in response to neuronal activity [13,74,75,78]. GluR2 has a dominant role in interacting with proteins strategic to AMPA receptor trafficking and synaptic plasticity. GluR2 binds to the receptor-trafficking proteins NSF and adaptor protein 2 (AP2) through a recognition motif in the membrane-proximal portion of the C-terminal. GluR2 and 3 bind to the postsynaptic density 95/discs large/zona occludens-1 (PDZ) domains of anchoring proteins PICK1 and ABP/GRIP through PDZ recognition motifs at the distal end of their C-terminals [79,80]. Whereas the function of ABP/GRIP is primarily in anchoring GluR2 to synapses, activation by PKC, PICK1 has a function in endocytosis and insertion by bringing the receptor in close proximity to GRIP [74,79]. Dissociation of AMPA receptors from ABP/GRIP and association with PICK1 are crucial for receptor endocytosis and exchange of GluR2-lacking AMPA receptors for GluR2-containing AMPA receptors at synaptic sites [52,73]. AMPA receptor trafficking is governed by subunit-specific rules [13,78]. Whereas receptors containing GluR2 and GluR3 undergo rapid constitutive recycling at synapses and require interaction of GluR2 with NSF and other PDZ domain proteins, receptors containing GluR1 and GluR2 are internalized and inserted in an activity-dependent manner and require interaction between GluR1 and group I PDZ domain proteins (regulated trafficking). Whereas exocytosis of GluR2 is rapid and constitutive, insertion of GluR1 is primarily activity-dependent. Regulated AMPA receptor trafficking establishes and stabilizes the surface-receptor number, which is a mechanism crucial to long-term changes in synaptic efficacy.

In addition to receptor trafficking proteins, the state of QR editing in the pore-lining region also controls AMPA receptor number by influencing AMPA receptor assembly, ER exit and forward trafficking to the membrane surface [11,12]. Whereas edited GluR2 is present as a dimer and retained in the ER, unedited subunits readily form tetramers and exit the ER, appearing relatively rapidly at nascent or pre-existing synapses [11,12]. This intrinsic property limits edited GluR2 numbers in AMPA receptors delivered to synaptic and extrasynaptic sites.

Activity-dependent switch in AMPA receptor subtypes produces a qualitative change in synaptic transmission

Long-lasting Ca2+-permeable AMPA receptor-dependent synaptic plasticity is not only limited to changes in synaptic efficacy or membrane excitability, but it can also involve activity-dependent changes in the subunit composition of AMPA receptors. This form of synaptic plasticity is compelling because it provides a self-regulating mechanism. Whereas repetitive activity or sensory experience favors synaptic incorporation of Ca2+-impermeable AMPA receptors and scaling down of synaptic activity, activity blockade favors incorporation of Ca2+-permeable AMPA receptors and scaling up of synaptic strength.

Perhaps the best-characterized example of this form of synaptic plasticity is at the parallel fiber–stellate cell synapse, which expresses GluR2-lacking AMPA receptors. Repetitive activity at these synapses produces a long-lasting switch in the subunit composition of synaptic AMPA receptors, from GluR2-lacking to GluR2-containing receptors. During HFS, Glu released from parallel fibers activates synaptic AMPA receptors and promotes AMPA receptor-mediated Ca2+ influx [44]. Protein kinase C (PKC) activates protein interacting with PKC (PICK1), which facilitates delivery of GluR2-containing AMPA receptors to synaptic sites; PKC could phosphorylate GluR3, promoting dissociation of glutamate-receptor-interacting protein (GRIP) from GluR2-lacking AMPA receptors and retrieval of receptors from synaptic sites [52,53] (Figure 2). Binding of N-ethylmaleimide-sensitive fusion protein (NSF) to GluR2 disrupts interactions between PICK1 and GluR2-containing AMPA receptors, enabling newly inserted GluR2-containing AMPA receptors to associate with GRIP and anchor at synapses. Because GluR2-containing AMPA receptors exhibit reduced Ca2+ permeability and characteristically slow channel kinetics, the switch in AMPA receptor phenotype could alter the shape of the waveform of stellate cells. These changes are thought to modify the efficacy of inhibitory synaptic transmission at stellate cell onto Purkinje cell synapses [44].

Activity-dependent alterations in the composition of AMPA receptor also occur at synapses onto principal neurons. An elegant study by Isaac and co-workers showed that HFS of the Schaffer collateral–CA1 synapse, which expresses primarily Ca2+-impermeable AMPA receptors, causes transient synaptic incorporation of GluR2-lacking receptors during induction of LTP; this is followed by a switch to GluR2-containing AMPA receptors [54]. By contrast, using a different paradigm to induce LTP, Thompson and co-workers observed a different result [55]. These authors evoked synaptic responses by photo-releasing the resting membrane potential of basket cells (a type of inhibitory interneuron) and enhanced efficacy of excitatory synaptic potential (EPSP)–action potential coupling (interneuronal long-term depolarization, iLTDep) [51]. Long-term maintenance of depolarization (iLTDep) requires activation of Ca2+-permeable AMPA receptors. Thus, Ca2+-permeable AMPA receptors can set the level of excitability of hippocampal interneurons in response to neuronal activity.
caged Glu over individual dendritic spines in hippocampal slice cultures and induced LTP by a single pairing of Glu uncaging with postsynaptic depolarization. At rest, some spines exhibited postsynaptic paired-pulse facilitation, a hallmark feature of GluR2-lacking AMPA receptors. Potentiation at these synapses produced a rapid, long-lasting decrease in paired-pulse facilitation, suggesting a switch from GluR2-lacking to GluR2-containing AMPA receptors. Further experiments are warranted to resolve these differences.

The subunit composition of synaptic AMPA receptors can also be modified by activity blockade. In cultured hippocampal neurons, chronic AMPA receptor blockade induces a switch from GluR2-containing to GluR1-dominated synaptic AMPA receptors [56]. Recent findings indicate that not only receptor trafficking, but also local protein synthesis at synaptic sites underlies alterations in the number and phenotype of AMPA receptors and synaptic efficacy. NMDA receptor signaling during miniature synaptic events stabilizes synaptic function by suppressing local protein synthesis. Brief activity blockade promotes dendritic protein synthesis, incorporation of newly synthesized GluR2-lacking AMPA receptors and scaling-up of synaptic strength [22]. Local translation endows the postsynaptic cell with the ability to alter the composition of AMPA receptors, channel kinetics and permeability properties in response to distinct stimuli in a synapse-specific manner.

Not only activity blockade, but also sensory deprivation alters the number and/or subunit composition of AMPA receptors. For example, sensory experience promotes an increase in GluR2-lacking AMPA receptors at neocortical excitatory synapses [57]. Visual deprivation, caused by dark rearing rats, potentiates the complement of GluR2-lacking Ca2+-permeable AMPA receptors in the visual cortex but reduces their number in the somatosensory cortex [58].

Whereas activity or sensory blockade favors incorporation of Ca2+-permeable AMPA receptors and scaling up of synaptic strength, chronic activity or sensory experience favors Ca2+-impermeable AMPA receptors and scaling down of synaptic activity. Synaptic scaling is thought to be a mechanism crucial for long-term stability of neuronal function [59]. An increase in the number GluR2-lacking AMPA receptors not only enhances the amplitude, but also reduces the duration of the postsynaptic response, thereby altering EPSP–action potential coupling [19]. This form of homeostasis, unlike classic synaptic scaling, produces qualitative, in addition to quantitative, changes in synaptic responses and plasticity.

**Figure 2.** Activity-dependent switch in AMPA receptor subtypes at parallel fiber–stellate cell synapses. (a) Synaptic currents in stellate cells exhibit an inwardly rectifying I–V relationship, a characteristic feature of GluR2-lacking AMPA receptors. HFS induces a subunit switch in AMPA receptors, from GluR2-lacking to GluR2-containing receptors at synaptic sites, as indicated by increased linearity of the AMPA EPSC. (b) GluR2-containing and GluR2-lacking AMPA receptors (but not NMDA receptors) are present in the postsynaptic membrane [70]. (c) During HFS, Glu released from parallel fibers activates synaptic AMPA receptors and promotes AMPA receptor-mediated Ca2+ influx. (d) PKC activates PICK1, which facilitates delivery of GluR2-containing AMPA receptors to synaptic sites. PKC could phosphorylate GluR3, promoting dissociation of GRIP from GluR2-lacking AMPA receptors and retrieval of receptors from synaptic sites. (e) Binding of NSF to GluR2 disrupts the interaction between PICK1 and GluR2-containing AMPA receptors. (f) Newly inserted GluR2-containing AMPA receptors associate with GRIP and are stabilized at synapses. Panel (a) was reproduced, with permission, from Ref. [44]; (b–f). Adapted, with permission, from Ref. [52].

**Short-term plasticity at synapses that express Ca2+-permeable AMPA receptors**

Activity-dependent short-term plasticity, defined as alterations in synaptic responses that last tens of
milliseconds during a train of presynaptic activity, can dynamically regulate synaptic transmission and the pattern of activity generated by neural networks [60]. Although short-term plasticity is typically presynaptic, this type of plasticity can also arise in response to postsynaptic alterations. A hallmark property of Ca$^{2+}$-permeable GluR2-lacking AMPA receptors is their voltage-dependent blockade by endogenous intracellular polyamines. As a consequence, HFS at synapses onto interneurons, for example layer 2 or 3 neocortical pyramidal cell onto multipolar interneuron synapses, promotes polyamine unblocking of GluR2-lacking AMPA receptors [61]. Relief from polyamine block overcomes paired-pulse, presynaptic depression and facilitates postsynaptic AMPA currents in a frequency-dependent manner. This form of activity-dependent, short-term postsynaptic plasticity is also observed in the principal cells of the medial septum, which express Ca$^{2+}$-permeable AMPA receptors [62], and at Schaffer collateral–CA1 synapses [55]. Polyamine-dependent facilitation provides a means to selectively enhance synaptic gain at only those synapses that express Ca$^{2+}$-permeable AMPA receptors. Furthermore, a lasting change in AMPA receptor subtypes probably alters short-term plasticity at these synapses.

Ca$^{2+}$ signaling through Ca$^{2+}$-permeable AMPA receptors occurs in microdomains within aspiny neurons

Whereas Ca$^{2+}$ signaling in spines is mediated primarily through NMDA receptors and is relatively slow, Ca$^{2+}$ signaling in aspiny neurons throughout the CNS is mediated by fast, Ca$^{2+}$-permeable AMPA receptor synapses [18]. In an elegant study involving two-photon Ca$^{2+}$ imaging, Goldberg and Yuste demonstrated that activation of single synapses onto aspiny dendrites of neocortical fast-spiking interneurons creates highly localized Ca$^{2+}$ microdomains (<1 μm of dendritic space) owing to the fast kinetics of Ca$^{2+}$-permeable AMPA receptors, fast local extrusion through the Na$^{+}$/Ca$^{2+}$ exchanger and buffering by Ca$^{2+}$-binding proteins, such as parvalbumin [18]. Repetitive stimulation of the parallel fiber–cerebellar stellate cell synapse also evokes a spatially restricted Ca$^{2+}$ rise through GluR2-lacking AMPA receptors, which promotes endocannabinoid production and triggers input-specific LTD [63]. Thus, expression of Ca$^{2+}$-permeable AMPA receptors on aspiny neurons might represent a unique solution to compartmentalization of Ca$^{2+}$ signals within aspiny dendritic shafts, with important implications for synaptic plasticity and neural processing [18].

**Glur2-lacking AMPA receptors in neuronal death**

**Glur2-lacking AMPA receptors in ischemia**

Ca$^{2+}$-permeable AMPA receptors have a crucial role not only in synaptic plasticity, but also in the excitotoxicity associated with several neurological disorders and diseases. Transient global or forebrain ischemia arising as a consequence of cardiac arrest or induced experimentally in animals causes selective, delayed neuronal death, primarily of hippocampal CA1 pyramidal neurons, and marked cognitive deficits. A striking feature is an early rise in intracellular Ca$^{2+}$ during the ischemic episode and a delayed rise in intracellular free Zn$^{2+}$ in CA1 neurons 24–48 h after ischemia and just before onset of cell death.

Under physiological conditions, the principal neurons of the hippocampus abundantly express GluR2-containing Ca$^{2+}$-impermeable AMPA receptors (see above). Because these cells do not express high levels of Ca$^{2+}$-binding proteins or fast, local Ca$^{2+}$-extrusion pumps, acute loss of GluR2 would be expected to confer enhanced pathogenicity of endogenous Glu and vulnerability to neuronal insults. Accordingly, ischemic insults trigger downregulation of GluR2 mRNA expression and protein abundance in selectively vulnerable CA1 neurons and induce a long-lasting switch in AMPA receptor phenotype, from GluR2-containing to GluR2-lacking receptors [27–31,64]. By 42 h after ischemia, AMPA EPSCs exhibit properties of Ca$^{2+}$- and Zn$^{2+}$-permeable GluR2-lacking AMPA receptors, including enhanced rectification of AMPA EPSCs, sensitivity to polyamines and AMPA receptor-mediated Ca$^{2+}$ influx [28,31,43,64]. In addition to their role in mediating Ca$^{2+}$ entry, GluR2-lacking AMPA receptors are thought to mediate the late rise in toxic Zn$^{2+}$ [42].

Considerable evidence indicates that Ca$^{2+}$-permeable GluR2-lacking AMPA receptors are causally related to ischemic cell death. Acute knockdown of GluR2 by antisense oligonucleotides, even in the absence of an ischemic insult, causes death of pyramidal neurons [65]. Overexpression of Ca$^{2+}$-permeable GluR2 (Q) channels in vivo promotes ischemia-induced death of normally resistant CA3 pyramidal cells and dentate gyrus granule cells; overexpression of Ca$^{2+}$-impermeable GluR2 (R) channels protects CA1 neurons against ischemic death [64]. The subunit-specific channel blockers N-naphthylspermine and philanthotoxin, which selectively inhibit GluR2-lacking AMPA receptors, afford neuroprotection in models of global ischemia [31,32,66].

Recent studies document a role for the gene-silencing transcription factor repressor element-1 silencing transcription factor (REST) in the switch of AMPA receptor

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**Box 3. REST-dependent silencing of GluR2 expression**

A great deal of interest has focused on the regulation of GluR2 expression in response to neuronal activity and insult. In progenitor cells and non-neuronal cells, the gene-silencing factor REST (also known as neuron-restrictive silencer factor, NRSF) actively represses neural-specific genes important to synaptic plasticity and remodeling, including synaptic vesicle proteins, structural proteins, voltage-gated ion channels and neuroreceptors [81,82]. As neural progenitors differentiate, downregulation by REST is essential for induction and maintenance of the neural phenotype. Consistent with this model, ectopic expression of REST in differentiating neurons disrupts gene expression, promotes axon-guidance errors and produces cellular apoptosis [83]. Neuronal insults, such as ischemia and seizures, activate REST in vulnerable hippocampal neurons [26,27,68].

REST functions, using epigenetic modifications, to silence target genes in neurons destined to die (Figure 3). REST binds to the repressor element 1 (RE1) element in the promoter of GluR2 [84] and recruits co-repressors (mSin3A and CoREST) and histone deacetylases [85,86]. CoREST recruits the site-specific histone methyltransferase G9a. The co-repressor complex promotes histone deacetylation and methylation. Whereas histone deacylation mediates dynamic, short-term gene silencing, histone and DNA methylation mediate long-term, irreversible silencing [81].
phenotype and highly selective neuronal death produced by global ischemia. Ischemic insults trigger activation of the transcriptional repressor REST (Box 3 and Figure 3) in selectively vulnerable CA1 neurons [27]. REST binds the GluR2 promoter and functions through chromatin remodeling to suppress gene expression in neurons destined to die. Acute knockdown of REST prevents GluR2 suppression and rescues CA1 neurons. These findings are consistent with a model in which REST orchestrates epigenetic reprogramming of postischemic neurons and implicate REST in ischemic cell death. Emerging evidence indicates that not only GluR2 expression, but also receptor trafficking and GluR2 RNA editing (Box 1) can be dysregulated in response to neuronal insults. For example, ischemia promotes internalization of GluR2-containing AMPA receptors through clathrin-dependent endocytosis and synaptic targeting of GluR2-lacking AMPA receptors to synapses of insulted hippocampal neurons by exocytosis, leading to a switch in AMPA receptor phenotype [43] (Figure 4). The switch in phenotype is PKC-dependent and involves dissociation of GluR2 from AMPA receptor binding protein (ABP) and its association with PICK1. Global ischemia also inhibits the activity of the RNA-editing enzyme adenosine deaminase acting on RNA 2 (ADAR2) and disrupts Q/R editing of GluR2 [67]. Direct delivery of ADAR2 or constitutively active CAMP response element binding protein (CREB), which induces ADAR2 expression, restores Q/R editing and protects vulnerable neurons from cell death. Thus, reduced Q/R editing further contributes to neuronal vulnerability in brain ischemia.

GluR2-lacking AMPA receptors in seizures

In addition to their role in global ischemia, Ca\(^{2+}\)-permeable AMPA receptors are implicated in the cell death associated

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**Figure 3.** Ischemia activates the transcriptional repressor REST and silences GluR2 expression in CA1. (a) Representative gel of reverse transcription polymerase chain reaction products amplified for REST, GluR2 and actin RNAs. (b, c) AMPA receptors at Schaffer collateral–CA1 synapses in postischemic hippocampus exhibit properties of Ca\(^{2+}\)- and Zn\(^{2+}\)-permeable GluR2-lacking AMPA receptors. Representative AMPA EPSCs and I–V relations of the peak responses at the Schaffer collateral synapses on CA1 pyramidal cells recorded in acute hippocampal slices. (b) AMPA EPSCs recorded from control slices exhibit a linear I–V relation; AMPA EPSCs recorded from slices of animals at 42 h after ischemia exhibit inwardly rectifying currents when spermine (1 mM) is included in patch pipette. (c) The rectification index (EPSC at +40 mV versus −60 mV × 1.5) is reduced in ischemic versus control slices. (d) AMPA EPSCs in ischemic slices were inhibited by 1-naphthyl acetyl spermine (Naspm) (250 μM), a subunit-specific antagonist of GluR2-lacking AMPA receptors, and the selective AMPA antagonist GYKI-53655 (50 μM). (e) Summary of data in (d). (f) Scheme showing REST-dependent silencing of GluR2 gene expression in insulted neurons. Ischemia triggers activation of the repressor REST. REST binds to the RE1 element in the GluR2 promoter and silences GluR2 transcription. REST recruits co-repressors (mSin3A and CoREST) and histone deacetylases, which silence gene expression through chromatin remodeling. CoREST recruits methyl-CpG binding protein 2 (MeCP2) and site-specific histone methyltransferase G9a, which promotes DNA and histone methylation [79]. Silencing of GluR2 expression reduces the total GluR2 number, leading to assembly and insertion of functional, GluR2-lacking AMPA receptors at CA1 synapses of the postischemic hippocampus. Panels (a–f) were reproduced, with permission, from Ref.[27–31,64].
with other neurological insults and disorders, including seizures, excitotoxicity, spinal cord injury, ALS and Alzheimer’s disease. Seizures markedly downregulate GluR2 mRNA and subunit expression in vulnerable CA1 and CA3 pyramidal neurons before the onset of neuronal death [24,25]. Moreover, seizures markedly upregulate REST messenger RNA [26] and suppress GluR2 promoter activity in vulnerable hippocampal neurons [26,68]. Together, these findings indicate that REST-dependent silencing of the AMPA receptor GluR2 gene might be a broad mechanism of insult-induced neuronal death.

Concluding remarks

The past few years have witnessed an explosion of new information concerning the role of Ca²⁺-permeable AMPA receptors in synaptic plasticity and neuronal death. Exciting new research has revealed novel mechanisms by which the subunit composition and Ca²⁺ permeability of AMPA receptors are modified in response to neuronal activity, sensory experience and neuronal insults. Unlike activity-dependent modifications in the number of synaptic AMPA receptors, activity-dependent modifications in the composition of AMPA receptors give rise to alterations in Ca²⁺ signaling, channel conductance and kinetics, producing qualitative, in addition to quantitative, changes in synaptic transmission. Several important questions remain unanswered. What accounts for the low abundance of GluR2 in inhibitory interneurons and other aspiny neurons? What mechanisms subserve expression of afferent-specific AMPA receptors? What mechanisms underlie activity-dependent, cell-specific (and even synapse-specific) changes in the subunit composition of AMPA receptors? Whereas regulated AMPA receptor trafficking has an important role in cerebellar stellate cell synapses, the presence and significance of such mechanisms at other synapses are as yet unknown. In addition to regulated receptor trafficking, unexplored mechanisms include regulated targeting of GluR2, trafficking of dendritic mRNAs and activity-dependent, local protein synthesis in response to neuronal activity and/or external stimuli.

Another unsolved problem concerns the functional consequences of AMPA receptor-mediated Ca²⁺ signaling. Whereas strong evidence indicates that AMPA receptor-mediated Ca²⁺ influx can trigger LTP, relatively little is known about the postsynaptic target of Ca²⁺. As reviewed in this article, at cerebellar stellate cell synapses, AMPA receptor-mediated Ca²⁺ influx can drive AMPA receptor trafficking and endocannabinoid synthesis and signaling. The target(s) of AMPA receptor-mediated Ca²⁺ signaling at other synapses are, however, unclear. The next few years should provide answers to some of these questions.

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