SYMPOSIUM REVIEW

Redefining the classification of AMPA-selective ionotropic glutamate receptors

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Abstract AMPA-type ionotropic glutamate receptors (iGluRs) represent the major excitatory neurotransmitter receptor in the developing and adult vertebrate CNS. They are crucial for the normal hardwiring of glutamatergic circuits but also fine tune synaptic strength by cycling into and out of synapses during periods of sustained patterned activity or altered homeostasis. AMPARs are grouped into two functionally distinct tetrameric assemblies based on the inclusion or exclusion of the GluA2 receptor subunit. GluA2-containing receptors are thought to be the most abundant AMPAR in the CNS, typified by their small unitary events, Ca$^{2+}$ impermeability and insensitivity to polyamine block. In contrast, GluA2-lacking AMPARs exhibit large unitary conductance, marked divalent permeability and nano- to micromolar polyamine affinity. Here, I review evidence for the existence of a third class of AMPAR which, though similarly Ca$^{2+}$ permeable, is characterized by its near-insensitivity to internal and external channel block by polyamines. This novel class of AMPAR is most notably found at multivesicular release synapses found in the avian auditory brainstem and mammalian retina. Curiously, these synapses lack NMDA-type iGluRs, which are conventionally associated with controlling AMPAR insertion. The lack of NMDARs suggests that a different set of rules may govern AMPAR cycling at these synapses. AMPARs with similar functional profiles are also found on some glial cells suggesting they may have a more widespread distribution in the mammalian CNS. I conclude by noting that modest changes to the ion-permeation pathway might be sufficient to retain divalent permeability whilst eliminating polyamine sensitivity. Consequently, this emerging AMPAR subclass need not be assembled from novel subunits, yet to be cloned, but could simply occur by varying the stoichiometry of existing proteins.

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Derek Bowie (McGill University, Montreal, Canada) earned his PhD from the University of London with Trevor G. Smart in 1992 after completing an undergraduate degree in Biochemistry and Pharmacology at Strathclyde University in Scotland. He then spent the next 2 years as an Eli-Lilly postdoctoral fellow in Paul Feltz’s lab at the Université Louis Pasteur in Strasbourg, France with a short stay in the lab of Jean-Marc Fritschy at the University of Zurich, Switzerland before moving to the National Institutes of Health in the USA in 1994 where he worked with Mark L. Mayer on the biophysics of glutamate receptor ion-channel block. After taking up a faculty position at Emory University in 1998, he turned his attention to gating mechanisms, identifying ion-dependent gating of kainate-type glutamate receptors, before moving to McGill in 2002. He is currently an Associate Professor in the Department of Pharmacology and Therapeutics and recipient of the Canada Research Chair award in Receptor Pharmacology. His research theme has since broadened to also look at the role of glutamate and GABA receptors in neurodevelopment.

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**Introduction**

The vast majority of excitatory synaptic transmission in the CNS is mediated by ionotropic glutamate receptors (iGluRs) which are grouped into kainate-, AMPA- and NMDA-selective receptor subclasses (Hollmann et al. 1989; Dingledine et al. 1999). In addition to their traditional roles in synaptic transmission and plasticity (Kullmann & Siegelbaum, 1995; Isaac et al. 2007; Kerchner & Nicoll, 2008), iGluRs have also been implicated in numerous disease states associated with postnatal development (e.g. autism, schizophrenia) (Lisman et al. 1999; Krueger & Bear, 2011), cerebral insult (e.g. stroke, epilepsy) (Liu & Cull-Candy, 2000; Thiagarajan et al. 2005; Ge et al. 2006; Plant et al. 2006). This approach is based on the observation that recombinant AMPAR heteromers are rendered 

In this review, I consider the evidence for a third class of AMPAR-type iGluR. This receptor is distinguished by its divalent permeability and weak sensitivity to block by internal and external polyamines. As discussed below, evidence supporting the existence of another functionally distinct AMPAR has been in the literature for more than two decades but its significance has been largely overlooked. With the value of hindsight, however, it is now possible to piece together a common pattern of receptor behaviour amongst these otherwise disparate group of studies that point to the existence of a third type of AMPAR subfamily.

**The emergence of AMPARs with distinct functional and molecular properties**

In the 1990s, it became clear that AMPARs have several distinct response characteristics based on a comparison of native and recombinant receptors. In one

![Figure 1. The inter-relationship between the GluA2 subunit, ion permeation and channel block](image-url)
of the first of these investigations, Iino and colleagues reported that most AMPARs expressed by cultured hippocampal neurons were weakly permeable to external Ca²⁺ \((P_{Ca/Na} < 0.18)\) with near-linear current–voltage \((I–V)\) relationships (Iino et al. 1990). However, in some cases, AMPAR-mediated membrane currents exhibited appreciable divalent permeability \((P_{Ca/Na} = 2.3)\) and profound inward rectification (Iino et al. 1990). The occurrence of an inwardly rectifying, Ca²⁺-permeable AMPAR surprised most investigators at the time since it had been assumed that the prime source of Ca²⁺ entry into glutamatergic synapses was via the NMDA-type iGluR (Mayer & Westbrook, 1987; Debski et al. 1990). However, the occurrence of inward–rectification was consistent with even earlier, and often overlooked, reports describing AMPARs expressed in Xenopus laevis oocytes from bovine retina (Parker et al. 1985) or rat striatum/cerebellum (Randle et al. 1988) polyA⁺ mRNA. The molecular identity of the two AMPAR response types was revealed soon afterwards with the cloning and characterization of the GluA1, GluA3 and GluA4 receptor subunits that formed homomeric receptors with inward rectification behaviour which became linear when co-expressed with the GluA2 subunit (Boulter et al. 1990; Verdoorn et al. 1991).

Over the next years, it was then appreciated that AMPARs with different \(I–V\) characteristics and divalent permeability were preferentially expressed by certain cell types in the CNS. In general terms, excitatory principal cells of neuronal circuits were thought to possess AMPARs with low divalent permeability and linear \(I–V\) characteristics whereas AMPARs of inhibitory interneurons and glial cells exhibited appreciable divalent permeability and inwardly rectifying behaviour (McBain & Dingledine, 1993; Geiger et al. 1995; Tempia et al. 1996). The situation was nuanced further by data later on showing that different synapses on the same neuron may express different AMPAR types based on their afferent input (Toth & McBain, 1998). It was also understood that recombinant AMPARs could be distinguished by their sensitivity to externally applied polyamines such as argiotoxin and joro spider toxin (Blaschke et al. 1993; Herlitze et al. 1993; Bowie et al. 1999).

The molecular basis of inward rectification of AMPARs vexed the glutamate receptor field for several additional years until it was shown that similar behaviour in K⁺ channels was due to voltage-dependent block by cytoplasmic polyamines (Ficker et al. 1994; Lopatin et al. 1994; Fakler et al. 1995). With this information at hand, several labs went on to show that inward rectification of AMPARs (and kainate-type iGluRs) was also caused by channel block via endogenous polyamines, namely spermine, spermidine and putrescine (Bowie & Mayer, 1995; Donevan & Rogawski, 1995; Isa et al. 1995; Kamboj et al. 1995; Koh et al. 1995). In retrospect, it is surprising that the link between inward rectification and endogenous polyamines was not appreciated sooner given the sensitivity of CP-AMPARs to external polyamine toxin block (Bowie et al. 1999). The final piece of the puzzle was the observation that the inclusion of GluA2 into AMPAR heteromers significantly reduced the amplitude of single channel conductance (Swanson et al. 1997).

When taken together, the tacit agreement amongst investigators was the existence of two molecularly distinct AMPARs (i.e. GluR2-containing or lacking) distinguished by their functional properties (i.e. \(I–V\) and divalent permeability), pharmacology (i.e. polyamine toxin block) and unitary conductance (Cull-Candy et al. 2006; Isaac et al. 2007) (Fig. 1). However, not all data reported in the literature during this time conformed to this dual identity for AMPARs. As explained below, the most contentious issue was, and still is, whether the occurrence of polyamine block really goes hand-in-hand with divalent permeability.

### Ion flow through Ca²⁺-permeable AMPA receptors is not always inwardly rectifying

Over the last decades, several studies have emerged reporting receptor behaviour that is inconsistent with the current classification of AMPARs. Two of the studies were published early on as information from cloning studies was beginning to appear and in advance of the work establishing a link between cytoplasmic polyamine block and inward rectification (Gilbertson et al. 1991; Otis et al. 1995). By studying acutely isolated bipolar cells from the salamander retina, Gilbertson and colleagues reported the existence of calcium-permeable AMPARs \((P_{Ca/Na} \approx 3.2)\) at about the same time that Iino and colleagues (1990) reported similar findings on cultured hippocampal neurons. An important distinction of these studies is that visual inspection of recordings from retinal cells reveals that the AMPAR \(I–V\) relationships were linear and not inwardly rectifying as reported on hippocampal cells.

From our present understanding of polyamine block, it might be argued that washout of endogenous polyamines occurred during the experiments performed by Gilbertson and colleagues. In keeping with this, washout in other cell types, such as cerebellar granule cells, shows a fairly rapid depletion of channel block over the first 10 min of whole-cell recording (Kamboj et al. 1995) (Fig. 2A). However, this is not always the case. For example, in HEK 293 cells, depletion of cytoplasmic polyamines is slower (Bowie & Mayer, 1995) (Fig. 2B), which is more in keeping with the biochemical estimates of unbound polyamines in bovine lymphocytes and rat liver cells (Watanabe et al. 1991). Furthermore, most endogenous polyamines appear to be bound within cells to protein and DNA at millimolar concentrations (Watanabe et al. 1991) representing a substantial reserve that, in principle, would
be able to maintain the freely diffusible pool at the upper micromolar levels (e.g. \( \sim 60 \mu M \) for spermine) needed to bring about channel block (Bowie & Mayer, 1995). When fairly rapid washout has been achieved in HEK 293 cells, it required as much as 20 mM ATP in the patch pipette solution for effective chelation to occur (Bowie & Mayer, 1995) (Fig. 2B). Consequently, the range of washout rates reported in different studies most probably suggests that free endogenous polyamine levels vary between different cell types (Aizenman et al. 2002).

Given this, it is not possible to predict the rate at which endogenous polyamines would have been cleared with the 1 mM ATP used by Gilbertson and colleagues in their study. The conundrum, of course, still remains, as Lino and colleagues undoubtedly faced exactly the same problem, but yet observed inward rectification of AMPAR responses in cultured hippocampal neurons (Lino et al. 1990). However, if the study by Gilbertson and colleagues uncovered novel properties of extrasynaptic AMPARs, it raises the question of whether their findings could be extended to synaptic receptors.

With this in mind, data described by Otis and colleagues (1995) advances this idea by placing calcium-permeable, polyamine-insensitive AMPARs at glutamatergic synapses. The authors used an ion-substitution approach to study the divalent permeability of AMPARs expressed at synapses of the avian nucleus magnocellularis (nMAG), a homologue of the mammalian ventral cochlear nucleus (Otis et al. 1995). The advantage of this preparation is that divalent permeability can be estimated from reversal potentials with some accuracy due to the large and robust membrane currents elicited by AMPARs at nMAG synapses. Like Gilbertson et al., the authors also noted high divalent permeability of AMPARs (\( P_{Ca}/P_{Cs} \approx 3.3 \)) in the absence of any noticeable inward rectification (Fig. 3A). Here again, it could be argued that polyamine washout accounts for the absence of inward rectification. However, the Trussell lab was able to address this issue in a later study (Lawrence & Trussell, 2000). Although the authors subsequently observed channel block with high concentrations (1 mM) of spermine, they did not observe inward rectification with much lower and more physiologically relevant concentrations of spermine (i.e. 60 \( \mu M \), L. Trussell, personal communication). Since then, similar observations have been made from studies of AII amacrine cells in the rat retina where synaptic AMPARs show outward rectification (Fig. 3B and C) (Veruki et al. 2003) and appreciable divalent permeability (\( P_{Ca}/P_{Na} \approx 2 \)) (Morkve et al. 2002). Together, these studies suggest that, in some cases, CP-AMPARs are insensitive or weakly sensitive to block by cytoplasmic polyamines. As discussed below, this conclusion raises the possibility that some CP-AMPARs are similarly insensitive to block by externally applied polyamines.

**External polyamine block can be uncoupled from divalent permeability**

Two studies from the laboratory of Richard Miller were the first to document inconsistencies in the proposed
relationship between AMPAR divalent permeability and block by externally applied polyamine toxins (Meucci et al. 1996; Meucci & Miller, 1998). In the earlier study, Meucci and colleagues (1996) combined Ca\(^{2+}\) imaging and electrophysiology to compare divalent permeability and toxin sensitivity of native AMPARs expressed by O-2A progenitor cells. Since the inclusion of serum to O-2A cell cultures promotes differentiation into oligodendrocytes or type II astrocytes (Louis et al. 1992; Holzwarth et al. 1994) as well as GluA2 expression (Holzwarth et al. 1994; Patneau et al. 1994; Puchalski et al. 1994), the authors examined how this process may affect CP-AMPAR pharmacology. In undifferentiated cells, Ca\(^{2+}\) elevations and membrane currents elicited by AMPAR stimulation were blocked by joro spider toxin (JsTX) and argiotoxin 636, consistent with the conventional properties of GluA2-lacking CP-AMPARs expressed by Bergmann glia, for example (Burnashev et al. 1992). However, following the addition of serum, neither toxin was able to block the Ca\(^{2+}\) elevations that arise from ion flow through activated receptors (Meucci et al. 1996), suggesting that polyamine block and divalent permeability can be uncoupled in some AMPARs. Consistent with this, Meucci and Miller (1998) were able to recapitulate the same observation, but this time studying the functional properties of recombinant AMPARs assembled from GluA1 and GluA2 subunits. To explain their findings, the authors argued that, in some cases, AMPARs containing the GluA2 subunit are permeable to external divalent ions, suggesting that differentiating progenitor cells express a mosaic of GluA2-containing AMPARs, some of which are Ca\(^{2+}\) permeable (Meucci & Miller, 1998).

A similar switch in external polyamine sensitivity of CP-AMPARs has also been observed in the neurons of the developing rat retina (Diamond, 2007; Osswald et al. 2007). In this case, divalent permeability of AMPARs was assessed using the cobalt (Co\(^{2+}\)) staining technique (Pruss et al. 1991) in combination with electrophysiological recordings from acutely isolated retinal slices (Fig. 4). During the first two postnatal weeks after birth, the authors observed Co\(^{2+}\) labelling primarily of horizontal and AII amacrine cell interneurons that was blocked by the polyamine toxin philanthotoxin (PhTX) (Osswald et al. 2007). However, around postnatal day 14 when eye opening occurs, Co\(^{2+}\) staining elicited by AMPAR stimulation was unexpectedly insensitive to a range of known channel blockers (i.e. PhTX, JsTX and IEM-1460) even at concentrations well above those needed to block conventional CP-AMPARs (Fig. 4B). In support of this, Oswald and colleagues observed a similar insensitivity to PhTX in electrophysiological recordings of synaptic AMPARs (Fig. 4A). The most compelling aspect of this work is that sensitivity of AMPARs to external polyamine block was recovered by rearing developing rat pups in the dark, suggesting that light entering the eye during development triggers the surface expression of polyamine-insensitive CP-AMPARs (Osswald et al. 2007; Diamond, 2011). Intriguingly, more recent work reveals that overexpression of polyamine-insensitive CP-AMPARs in the adult may be a key factor in the neurotoxic effects of excessive levels of extracellular L-glutamate in models of retinal injury (Lebrun-Julien et al. 2009). Here, the surface expression of these novel CP-AMPARs was driven by the release of tumour necrosis factor α (TNFα) through a NF-κB-dependent pathway in Müller glia (Lebrun-Julien et al. 2009). Since glial-derived TNFα is more notably associated with regulating CP-AMPARs during homeostatic synaptic scaling (Beattie et al. 2002; Stellwagen et al. 2005), the observations by Lebrun-Julien and colleagues suggest that an imbalance in AMPAR synaptic scaling may lie at the heart of some chronic retinal diseases such as glaucoma (Almasieh et al. 2011).
How might polyamine insensitivity arise?

There are two general ways in which AMPARs may lose polyamine sensitivity whilst retaining the ability to transport calcium ions. The first of these is to directly change the physical properties of the ion conductance pathway, for example, by changing the cross-sectional diameter of its narrowest region. The unedited (Q-form) GluA1 AMPAR pore has been estimated to be about 0.78 nm (or 7.8 Å) at its narrowest point (Burnashev et al. 1996), which is remarkably similar to the 0.75 nm cross-sectional diameter of the polyamine toxin PhTX (Bahring et al. 1997). Since the dimensions of a single calcium ion in the absence of its hydration shells is about 2 Å, it would only take modest changes in the architecture of the pore region to impact polyamine block whilst allowing divalent permeability. On that note, the cross-sectional diameter of the pore of heteromeric AMPARs composed of GluA1 and GluA2 has been estimated to be about 0.70–0.74 nm (Burnashev et al. 1996), which may be sufficient to prevent polyamines from entering the pore to bring about block. This possibility is in keeping with the conclusion of the Meucci and Miller (1998) study that, in some cases, GluA2-containing AMPARs may be divalent permeable but insensitive to block by externally applied polyamines. The authors did not examine whether internal polyamine block was similarly affected. In fact, it is not possible to predict the outcome since biophysical work on homomeric kainate receptors suggests that internal and external polyamine block is non-equivalent (Bahring et al. 1997), a finding which is in line with more recent analysis of TARP-bound AMPARs (Jackson et al. 2011). Therefore, it remains to be established how GluA2 might affect internal polyamine block. For GluA2-containing AMPARs, the transport of large cations through a narrower pore region would be further complicated by unfavourable changes to the pore’s electrostatic environment. The edited GluA2 subunit contains a positively charged arginine residue at the Q/R site which is thought to form the apex of the pore loop region of both AMPA and kainate receptors (Panchenko et al. 1999; Sobolevsky et al. 2009). In contrast,
unedited GluA1, 3 and 4 subunits contain a neutral glutamine residue at the Q/R site. Given this, it would be possible to exert substantial changes to the pore’s ability to transport large cations by changing the number of GluA2 subunits per AMPAR tetramer, a process that might be constrained by the emerging set of rules that govern AMPAR heteromerization (Rossmann et al. 2011).

The other way in which to retain divalent permeability but lose polyamine sensitivity is through an indirect or allosteric mechanism that affects the pore’s permeation properties. This possibility is particularly relevant for AMPARs given the numerous subconductance states that are accessed during activation (Swanson et al. 1997; Rosenmund et al. 1998; Banke et al. 2000; Smith et al. 2000). By definition, each conductance state must have different ion permeation properties but, as yet, it is not known if this extends to differences in their divalent permeability or polyamine block. If it were the case, it may be possible to differentially affect channel block characteristics whilst maintaining similar divalent permeability by simply varying the relative contribution of each subconductance state. For example, this could be achieved by AMPAR phosphorylation (by CAM kinase II) (Derkach et al. 1999; Kristensen et al. 2011) or by varying the concentration of the neurotransmitter, L-glutamate (Smith & Howe, 2000). Another possibility is that allosteric modulation of the pore is achieved through auxiliary protein binding, for example, by the effect of the trans-membrane AMPAR regulatory protein, stargazin (Soto et al. 2007). In fact, co-expression of GluA1 or A4 AMPARs with stargazin lowers the blocking ability of cytoplasmic spermine whilst having no apparent effect on divalent permeability (Soto et al. 2007).

So could stargazin’s effect on AMPARs account for the polyamine-insensitive CP-AMPARs described here? Probably not and for several reasons. First, stargazin does not eliminate inward rectification of AMPARs but only reduces it (Soto et al. 2007) making it distinct from the near-linear I–V properties of native AMPAR responses recorded from nMAG neurons (Otis et al. 1995), retinal AII amacrine or bipolar cells (Gilbertson et al. 1991; Veruki et al. 2003) and O2-A progenitor cells (Meucci et al. 1996). Second, stargazin’s impact on polyamine block would be most effective on neurons that completely lack the GluA2 subunit which, to my understanding, has only ever been described for Bergmann glia (Burnashev et al. 1992). Almost all other neurons in the mammalian CNS are thought to express the GluA2 subunit to some degree which would diminish the role of stargazin (Lambolez et al. 1992; Jonas et al. 1994; Geiger et al. 1995). This issue is, of course, more complicated by the fact that individual synapses of the same neuron may express a mosaic of AMPARs with varying proportions of GluA2 (Toth & McBain, 1998). Third and finally, stargazin does not seem to affect external polyamine block (Jackson et al. 2011), making it distinct from the properties of AMPARs expressed by AII amacrine cells and O2-A progenitors (Meucci et al. 1996; Osswald et al. 2007). It is possible that the molecular basis of polyamine insensitivity in CP-AMPARs is multifactorial in nature, which may allow TARPs or other auxiliary proteins, such as CKAMP44 (von et al. 2010) and cornichon proteins (Schwenk et al. 2009; Kato et al. 2010), to play a role but the details of such a potentially complex mechanism will have to wait for further investigation.

**Diminished role for NMDA receptors at polyamine-insensitive Ca²⁺-permeable AMPA receptor synapses**

Given the predominant role assigned to NMDARs at glutamatergic synapses (Mayer & Westbrook, 1987; Dingledine et al. 1999), it is curious that...
Table 1. Summary table highlighting neuronal and glial cell studies where Ca^{2+}-permeable AMPA receptor expression has been found in the apparent absence of synaptic NMDA receptors

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Cell type</th>
<th>Synaptic NMDA receptor</th>
<th>I–V relationship</th>
<th>Calcium permeability</th>
<th>External polyamine block</th>
<th>References</th>
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<tbody>
<tr>
<td>Cerebellum</td>
<td>Stellate cell (rat)</td>
<td>a Absent (rat)</td>
<td>b Linear</td>
<td>c Variable (P_{Ca/Na}, 0.25 or 1.64)</td>
<td>d1 Strong (synaptic)</td>
<td>a1 (Clark &amp; Cull-Candy, 2002)</td>
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<td></td>
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<td>a2 Present (mouse)</td>
<td>b2 Rectifying</td>
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<td>d2 Weak (extrasynaptic)</td>
<td>a2 (Jackson &amp; Nicoll, 2011)</td>
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<td>c (Liu &amp; Cull-Candy, 2002)</td>
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<td>Amygdala</td>
<td>Basolateral interneuron (rat)</td>
<td>a Absent</td>
<td>b Rectifying</td>
<td>Not determined</td>
<td>d Strong</td>
<td>a (Mahanty &amp; Sah, 1998)</td>
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<td>b (Mahanty &amp; Sah, 1998; Polepalli et al. 2010)</td>
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<td>d (Mahanty &amp; Sah, 1998; Polepalli et al. 2010)</td>
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<td>Retina</td>
<td>Bipolar cell (salamander &amp; cat)</td>
<td>a Absent</td>
<td>b Linear</td>
<td>c Variable (P_{Ca/Na}, 0.5–3.2)</td>
<td>Not determined</td>
<td>a1 (Gilbertson et al. 1991)</td>
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<td>b2 (Gilbertson et al. 1991; Sasaki &amp; Kaneko, 1996; Pourcho et al. 2002)</td>
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<td>d (Osswald et al. 2007)</td>
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<td>Horizontal cell</td>
<td>(rat &amp; perch)</td>
<td>a Absent</td>
<td>b Linear</td>
<td>c Yes (Co^{2+} staining)</td>
<td>d Weak</td>
<td>a (Osswald et al. 2007)</td>
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<td>d (Osswald et al. 2007)</td>
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<tr>
<td>Aii amacrine cell</td>
<td>(rat)</td>
<td>a Absent</td>
<td>b1 Linear</td>
<td>c Yes (P_{Ca/Na}, 1.9–2.1)</td>
<td>d Weak</td>
<td>a1 (Morkve et al. 2002; Veruki et al. 2003)</td>
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<td>b2 Rectifying</td>
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<td>Brainstem</td>
<td>Nucleus magnocellularis neuron (avian)</td>
<td>a Absent</td>
<td>b Linear</td>
<td>c Yes (P_{Ca/X}, 3.3–5.0)</td>
<td>d Weak</td>
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<td>d (Lawrence &amp; Trussell, 2000)</td>
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<td>Glia</td>
<td>Progenitor cells (rat)</td>
<td>a Absent</td>
<td>b1 Linear</td>
<td>c Yes (Ca^{2+} imaging)</td>
<td>d1 Weak</td>
<td>a (Patneau et al. 1994)</td>
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<td>b2 Rectifying</td>
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<td>d1 (Meucci et al. 1996)</td>
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<td>d2 (Zonouzi et al. 2011)</td>
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all of the neurons expressing polyamine-insensitive Ca\(^{2+}\)-permeable AMPARs seem to entirely lack or have a diminished presence of synaptic NMDARs. The absence of NMDARs was first noted by Gilbertson and colleagues (1991) in their study of cultured retinal bipolar cells (Fig. 5) but has since been an unexpected finding from electrophysiological recordings of a range of neurons and glial cells from diverse brain regions (Table 1). Interestingly, the absence of synaptic NMDARs need not imply that the cell in question fails to express them at all. For example, although retinal AII amacrine cells seem to lack synaptic NMDARs (Osswald et al. 2007), they do respond (if somewhat weakly) to bath-applied agonist (Hartveit & Veruki, 1997) suggesting that they do respond (if somewhat weakly) to bath-applied agonist. A similar activated during synaptic transmission only when the level extrasynaptic NMDARs expressed by stellate cells are found in extrasynaptic locales. In the cerebellum, agonist (Hartveit & Veruki, 1997) suggesting that they do respond (if somewhat weakly) to bath-applied agonist (Hartveit & Veruki, 1997) suggesting that they do respond (if somewhat weakly) to bath-applied agonist (Hartveit & Veruki, 1997) suggesting that they do respond (if somewhat weakly) to bath-applied agonist (Hartveit & Veruki, 1997) suggesting that they do respond (if somewhat weakly) to bath-applied agonist (Hartveit & Veruki, 1997) suggesting that they do respond (if somewhat weakly) to bath-applied agonist (Hartveit & Veruki, 1997) suggesting that they do respond (if somewhat weakly) to bath-applied agonist (Hartveit & Veruki, 1997) suggesting that they do respond (if somewhat weakly) to bath-applied agonist (Hartveit & Veruki, 1997) suggesting that they do respond (if somewhat weakly) to bath-applied agonist (Hartveit & Veruki, 1997) suggesting that they do respond (if somewhat weakly) to bath-applied agonist (Hartveit & Veruki, 1997) suggesting that they do respond (if somewhat weakly) to bath-applied agonist (Hartveit & Veruki, 1997) suggesting that they do respond (if somewhat weakly) to bath-applied agonist (Hartveit & Veruki, 1997) suggesting that they do respond (if somewhat weakly) to bath-applied agonist. In contrast, the absence of synaptic NMDARs need not imply that the AMPAR under study is Ca\(^{2+}\) impermeable or, for that matter, GluA2 containing. These characteristics of the AMPAR should only be assigned following empirical determination. It is only then will we be able to appreciate how widespread this putative class of AMPAR-type iGlur is expressed throughout the mammalian CNS.

References


Meucci O & Miller RJ (1998). Dissociation between the Joro spider toxin sensitivity of recombinant a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors and their ability to increase intracellular calcium. Neuropharmacology 37, 1431–1443.


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