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EDITORIAL

Ionotropic glutamate receptors: structure, function and dysfunction

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Little could two young Scots, each with a keen interest in the study of ionotropic glutamate receptors, imagine when they started their PhDs at University College London (D.J.A.W.) and the London School of Pharmacy (D.B.) in the late 1980s just how much a field could advance in 30 years. Ionotropic glutamate receptors (not that the epithet 'ionotropic' was used back then) were still the relatively 'new kids on the block', as much more was known about ligand-gated ion channels (LGICs) activated by acetylcholine and GABA. Indeed glutamate-gated LGICs were simply referred to a NMDA receptors and non-NMDA receptors. However, research in glutamate LGICs was growing, and while much research was conducted using extracellular or micro-electrode recording from CNS tissue preparations, primary cultures of neurons and glia or in expression systems such as *Xenopus laevis* oocytes injected with whole-brain mRNA, the advent of whole-cell patch-clamp recording from acutely prepared *ex vivo* thin brain slices (Edwards *et al.* 1989) was probably the trigger that initiated the exponential rise in investigations of ionotropic glutamate physiology and pharmacology.

Recalling just where our knowledge stood as we commenced our PhD studies really does bring perspective to just how much we know now. For example, quisqualate, not AMPA, was still used as an agonist despite its action at metabotropic glutamate receptors. The requirement of glycine as a co-agonist for the activation of NMDA receptors had only recently been recognized (Johnson & Ascher, 1987). The first ionotropic glutamate receptor subunit was cloned in 1989 (Hollmann *et al.* 1989), and while sequence information was available, there was considerable debate as to the membrane topology of these subunits with many researchers pondering just how the sequence could fit into the four transmembrane structure of the nicotinic receptor superfamily. Indeed further analogies with pentameric receptors continued until it was recognized that ionotropic glutamate receptors did not belong in the nicotinic superfamily at all but defined their own class of three transmembrane–one re-entrant loop subunits that came together in a tetrameric assembly (for a review see Hansen *et al.* 2021). It was still to be several years until the importance of auxiliary subunits that modified the pharmacological and biophysical properties of AMPA receptors were to be elucidated (for reviews see Howe, 2015; Greger *et al.* 2017; Kamalova & Nakagawa, 2021). Furthermore, there was no indication that additional glycine-binding subunits existed which could be incorporated into NMDA receptor assemblies and modify their properties (Ciabarra *et al.* 1995; Sucher *et al.* 1995). Despite the pivotal roles played by ionotropic glutamate receptors, we were still unaware of the consequences for dysfunction and disease when they harboured deleterious mutations or when they were either over- or under-expressed (for a review see Myers *et al.* 2019).

Given the huge advances in our knowledge of many aspects regarding ionotropic glutamate receptor physiology and function mentioned above, we felt it appropriate that we/The Physiological Society host a mini-symposium on this topic. The symposium was scheduled as part of the Europhysiology Meeting planned to be held in Berlin in the summer of 2020, but the Covid-19 pandemic put paid to that meeting as well as many others. However, undaunted but disappointed not to meet in person and sample the beer halls of Berlin for post-meeting discussions, we held the symposium 'Ionotropic Glutamate Receptors: Structure, Function and Dysfunction' virtually on 6 October 2021 with the great assistance of The Physiological Society's Events' Team and the willing participation of the speakers. Reviews from this event appear in this issue of *The Journal of Physiology*. The five review articles (Crawley *et al.* 2022; Frydenvang *et al.* 2022; Geoffroy *et al.* 2022; Pampaloni & Plested, 2022; von Engelhardt, 2022) and one Techniques for Physiology paper (Obergrussberger *et al.* 2022) in this issue are a lasting legacy of the day's presentations and provide us with an excellent overview of aspects of contemporary ionotropic glutamate receptor research.

Frydenvang and colleagues provide a timely review of the latest breakthroughs in the structural pharmacology of allosteric modulators of AMPA and kainate-type ionotropic glutamate receptors (iGluRs) (Frydenvang *et al.* 2022). Aniracetam and cyclothiazide were some of the earliest allosteric modulators identified, noted for their apparent enhancement of cognition (Cumin *et al.* 1982) and antihypertensive effects (Julius *et al.* 1962), respectively, only to be later shown to be selective positive allosteric modulators (PAMs) of AMPA receptors (Ito *et al.* 1990; Bertolino *et al.* 1993). Subsequent, fast agonist concentration-clamp experiments linked their effects to a slowing in the onset of AMPA receptor deactivation and/or desensitization that was surprisingly differentially modulated by alternate splicing of the flip/flop cassette (Sommer *et al.* 1990). Cyclothiazide was more potent at flip variants whereas aniracetam was more effective at flop versions of AMPA receptors (Partin *et al.* 1994; Johansen *et al.* 1995). These observations paved the way for later structural studies showing that both PAMs exert their unique effects on channel gating by adopting different binding orientations within the back-to-back interface formed by two ligand binding domains (Sun *et al.* 2002; Jin *et al.* 2005). Now, with more than 80 PAM-AMPA receptor structures available, Frydenvang and colleagues propose to group them into five classes according to their binding modes. Class 1 comprises the classical thiazide PAMs, including cyclothiazide, whereas Class 2 is made up of the 'shifted' thiazide PAMs including two recently identified

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PAMs at GluK1 kainate receptors (Larsen *et al*. 2017). Two PAM molecules can bind to the LBD dimer interface within Classes 1 and 2 whereas Class 3 contains the 'full spanning' PAMs. Class 4, which includes aniracetam, are specially characterized by their binding to subsite A. Whereas only one PAM molecule binds to the LBD dimer interface of Classes 3 and 4, Class 5 comprises PAMs that bind at multiple sites. This detailed pharmacological understanding of PAMs certainly provides the impetus to explore them as potential therapeutics for the many CNS disorders now being linked to glutamatergic synapse dysfunction (Bowie, 2008; Hansen *et al*. 2021).

von Engelhardt (2022) discusses the mechanisms that give rise to short-term plasticity and in particular short-term depression of glutamatergic synapses. Focusing on retinogeniculate synapses of relay neurons in the dorsal lateral geniculate nucleus (dLGN), the review highlights the roles of high vesicle release probability, glutamate spillover and, most importantly, the effect of the auxiliary protein, cystine-knot AMPA receptor modulating protein 44 (CKAMP44) that together contribute to short-term depression of these synapses. First identified in a proteomic screen, CKAMP44's make-up suggested that it may act as an auxiliary subunit to AMPA receptors having a large extracellular N-terminal region, a single pass transmembrane domain and a cytoplasmic tail that contains a PDZ type II ligand motif (von Engelhardt *et al*. 2010). In keeping with this, overexpression or knockout of *CKAMP44* was shown to primarily affect recovery from desensitization of native hippocampal AMPA receptors strongly affecting short-term plasticity in granule cells of the dentate gyrus (DG), where it is abundantly expressed (von Engelhardt *et al*. 2010). Subsequent work in the hippocampus suggested that CKAMP44 may form AMPA receptor signalling complexes with another auxiliary subunit, transmembrane AMPA receptor regulatory protein 8 (or TARP γ8), at least in DG granule cells (Khodosevich *et al*. 2014). It is more challenging to determine the precise make-up of AMPA receptors in the dLGN, although the data favour the dominance of GluA1-containing AMPA receptors that co-assemble with CKAMP44 and possibly, TARP γ2 and/or γ4 (Jacobi & von Engelhardt, 2021). The exact contribution of TARP γ2 and/or γ4 is difficult to ascertain as they can have opposite effects on channel gating depending on the subunit composition of AMPA receptors. However, recent *in vivo* recordings of ON- and OFF-responses of dLGN neurons in knockout mice establishes that CKAMP44 not only modulates short-term depression at individual glutamatergic synapses but plays a critical role in integrating and relaying visual information from the retina to the cortex (Chen *et al*. 2018). Whether CKAMP44 or other AMPA receptor auxiliary proteins, such as CKAMP39 (Farrow *et al*. 2015) or GSG1L (Shanks *et al*. 2012; Kamalova *et al*. 2021), which also slow recovery from AMPA receptor desensitization, provide excitatory synapses throughout the CNS with similar signalling capacity will certainly be a topic for future enquiry.

Some of the most frequently stated facts about iGluRs are contained in statements worded something along the lines of 'The fast component of a glutamatergic excitatory postsynaptic current (EPSC) is mediated by AMPA receptors, while the slow component is mediated by NMDA receptors'. This is demonstrably true and the very brief open/burst times of AMPA receptors directly correlates, as would be expected, with the rapid exponential decay component of glutamatergic EPSCs (for example see Silver *et al*. 1992; Wyllie *et al*. 1993). Nevertheless, there have been many reports both historically and more recently of 'slow' currents mediated by AMPA receptors – this topic is the focus of the review by Pampaloni & Plested (2022). As mentioned above, auxiliary proteins modulate AMPA receptor single-channel conductance and kinetic behaviour (reviewed in Howe, 2015; Kamalova & Nakagawa, 2021) and while one school of thought has suggested that this modulatory action was restricted to heterologous expression of AMPA receptors and partner auxiliary proteins, Pampaloni and Plested discuss many studies of native AMPA receptors that describe slow (long-lasting) activity. The complex interplay between various auxiliary protein and their cell-type expression pattern with AMPA receptors provides for a diversity in long-lasting glutamate-mediated signalling that is generally considered the realm of NMDA (or kainate) receptor activation. In their review, Pampaloni and Plested consider the roles that such long-lasting AMPA receptor-mediated currents may fulfil. They note that the duration of these events, in the hundreds of milliseconds time scale, would be ideally suited to generating a plateau potential which could contribute to an alpha or theta oscillation, which are required for certain forms of learning and memory. However, as they also point out, slow AMPA receptor-mediated currents may also be detrimental, leading to the loss of precision of input/output function and, as such, there is likely to be tight regulation of the expression of AMPA receptors and their partner auxiliary subunits where these slow currents are present.

It has long been recognized that glutamate can induce neurotoxic lesions (Olney, 1969) and, furthermore, that block of NMDA receptors protects against ischaemia *in vivo* (Simon *et al*. 1984). Consequently, there have been considerable efforts devoted to the potential of therapeutic targeting of NMDA receptors to prevent glutamate-mediated excitotoxic cell death as might occur during ischaemic stroke. The indiscriminate targeting of NMDA receptors in a subtype-independent manner, however, has proved unsuccessful, in part because both hyper- and hypo-activation of NMDA receptors is deleterious (Hardingham & Bading, 2003). Thus in recent years there has been major interest in developing subtype-specific NMDA receptors that allosterically modulate receptor function both positively and negatively. Subtype-selective negative allosteric modulators (NAMs) may afford the potential to antagonize selectively excess NMDA receptor activation. In contrast, and the subject of the review by Geoffroy and colleagues, is the potential role of PAMs that could be of therapeutic use in conditions where hypofunction of NMDA receptors is thought to be present (Geoffroy *et al*. 2022). Such conditions include schizophrenia, age-dependent cognitive decline, Alzheimer's disease and anti-NMDA receptor encephalitis. The conditions also include genetic mutations that result in NMDA receptor loss of function or haploinsufficiency. The review provides a detailed and extensive account of our current understanding of the mechanisms and sites of action of the large number of PAMs that have been developed in recent years. A wealth of functional and quantitative data are summarized in the article in which the authors highlight the NMDA receptor subtype selectivity of these

compounds and their (or similarly acting compounds) potential as therapeutic agents in ameliorating deficits or preventing the emergence of pathophysiology in a variety of disease models. In the final parts of their review, Geoffroy and colleagues highlight the challenges that need to be overcome, noting that studies of the effects of PAMs on recombinantly expressed receptors do not necessarily predict their physiological effects. Additional considerations such as the fine balance between physiological levels of activation and over-activation need careful assessment to avoid the potential of excitoxicity. It remains to be seen whether subtype-selective targeting of NMDA receptors with PAMs is going to be a fruitful approach in the development of new therapeutics.

While 'conventional' NMDA receptors are considered to be tetrameric assemblies of two GluN1 and two GluN2 (reviewed in Hansen *et al*. 2021), the existence of 'non-conventional' NMDA receptors where GluN3 subunits are expressed either with GluN1 subunits or with a combination of GluN1 and GluN2 subunits (Ciabarra *et al*. 1995; Sucher *et al*. 1995; Das *et al*. 1998; Chatterton *et al*. 2002) adds to the richness of the physiological roles subserved by iGluRs. It is fair to say that GluN3-containing NMDA receptors are the least well-understood of the NMDA receptor family. Indeed given that GluN1–GluN3A–GluN3B receptor assemblies are in effect 'excitatory' glycine-gated receptors with no requirement of a conventional GluN2-acting orthosteric agonist for their activation, it can be debated whether they should be referred to as NMDA receptors at all. However, given the modulatory effects of the incorporation of a GluN3 subunit into assemblies of GluN1 and GluN2 NMDA receptor subunits, it seems appropriate to consider all GluN3-containing receptors as welcome members of the family. In their review, Crawley and colleagues assess the temporal and spatial expression pattern of GluN3A subunits, the location of their expression at the synapse and the physiological roles they have in normal brain development (Crawley *et al*. 2022). Like each of the GluN2 NMDA receptor subunits, GluN3A subunits display a unique fingerprint in their expression pattern, and their potential critical role in the early developing brain is underpinned by the fact that their peak expression occurs in the first two postnatal weeks and would appear to be regulated by activity. Additional diversity in their functional roles is hinted at by layer-specific and cell-type-specific expression patterns together with the fact that GluN3A subunits are expressed peri- or extra-synaptically with additional expression at presynaptic sites. The incorporation of GluN3A subunits into 'conventional' NMDA receptors resulting in decreased single-channel conductance and calcium permeability and reduced voltage-dependent magnesium block further adds to their repertoire of actions. The emerging role played by GluN3A subunits in synaptic plasticity and, through studies of *Grin3a*-null mice, in cognition emphasizes that, while less-well-studied, these NMDA receptors cannot be ignored if we are to have a full appreciation of their physiological functions. Indeed the review concludes by highlighting neuropsychiatric disorders and neurodevelopmental and neurodegenerative diseases where *GRIN3A* mutations may contribute to disease aetiology or progression.

The final article to appear in this issue and associated with the iGluR online symposium is a Techniques for Physiology paper by Obergrussberger and colleagues highlighting the advances and applications of high throughput methods for automated electrophysiological studies and specifically patch-clamp recording (Obergrussberger *et al*. 2022). As both of us can testify, conventional patch-clamp recording methods are labour-intensive, often repetitive and frequently frustrating – that being said, the child-like enthusiasm and delight with which a near-perfect recording is met is the reward for many unproductive hours sitting at an electrophysiological recording set-up. For many routine applications automation of the recording and data gathering process would be hugely beneficial, not only because of the repetitive nature of such tasks, but also because of the fact that it can remove operator-sampling bias and increase reproducibility. Nevertheless, the sceptics among us will always question the quality, appropriateness and rigour of such approaches. In their paper Obergrussberger and colleagues outline the 'quality control' measures than can and should be adopted in such automated recording methods and initially compare automated patch-clamp methodologies to other high throughput screens such as fluorescent imaging plate reader (FLIPR) assays and highlight the benefits of automated patch-clamp in identifying positive hits in assay development. Rapid solution exchange to mimic the fast activation experienced by ligand-gated ion channels physiologically is a technical challenge even for the most experienced patch-clamper. While automated systems are not capable of the most rapid exchange that can be achieved, they can perform to a level that allows quantitative comparisons to be made across receptor subtypes to identify changes in macroscopic activation and desensitization rates, for example allowing for the benchmarking of the actions of a variety of allosteric modulators. Automated systems come to the fore where there is a need for a rapid assessment of a novel compound's action in a toxicity screen, the classic example being screening compounds for cardiotoxicity, specifically deleterious actions at hERG channels. Their paper does not shy away from pointing out the disadvantages of automated systems, but equally the many applications and increasing affordability of such systems means that they will increasingly become workhorses within relatively small research labs/centres and not just be commonplace in the pharmaceutical industry.

We hope you enjoy reading the reviews from the iGluR online symposium and hope it is not too long until we host a follow-up symposium, though this time, in person!

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Additional Information

Competing interests

None declared.

Author contributions

Both authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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