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EDITORIAL

# Neurotransmitter-gated ion channels, still front and centre stage

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Neurotransmitter-gated ion channels are critical for the normal hardwiring of neuronal circuits but also fine tune synaptic strength during periods of sustained patterned activity and altered homeostasis. Ionotropic glutamate receptors (iGluRs) and nicotinic acetylcholine receptors transmit the vast majority of fast excitatory signalling in the developing and adult CNS whereas almost all inhibitory neurotransmission is mediated by $GABA_A$ and glycine receptors. The study of neurotransmitter-gated ion channels has undergone unprecedented advances in recent years with the convergence of several scientific disciplines on this important research topic. Structural biology has emerged as a leading approach to understanding ion channel function and drug action, and recent advances in genetics have permitted different families of neurotransmitter-gated ion channels to be assigned to distinct roles in neuronal health and disease.

To explore this advanced area of physiology, *The Journal of Physiology* sponsored back-to-back 2-day conferences on the downtown campus of McGill University in Montréal during the summer of 2019. The 2019 Ionotropic Glutamate Receptor Retreat or iGluRetreat was organized by Dr David Stellwagen (McGill) and myself and follows on a tradition since 2013 of holding the conference at a different university campus in North America (https://www.ion-channelconferences.org/). The iGluRetreat brought together 25 speakers whose work is at the forefront of this rapidly developing field of study (Fig. 1). The 2-day International Society of Neurochemistry (ISN) satellite conference on 'Neurotransmitter-gated ion-channels in health and disease' was organized by Dr Katherine Roche (NIH) and myself and brought together a unique group of leading researchers from across the globe to showcase the most recent advances in the study of excitatory and inhibitory receptor synapses (Fig. 2). The first day of the satellite conference focused on the complexity of the ion channel signalling complex and how structural studies have brought new advances in drug design and therapy. The conference's second day examined the emerging roles of neurotransmitter-gated ion channels in plasticity mechanisms and their involvement in neuronal circuits and CNS disease. This issue of *The Journal of Physiology* brings together eight timely review articles that capture some of the ideas and discussions that arose during these 4 days of exciting and intense scientific discourse.

Dr Lonnie Wollmuth and colleagues from Stony Brook University discussed their recent work on disease-causing mutations that disrupt the functional properties of NMDA-type ionotropic glutamate receptors (iGluRs) (Amin *et al.* 2021). The Wollmuth lab has spent the past two decades mapping out the structure–function properties of wild-type NMDA- and AMPA-type iGluRs. In particular, they have pinpointed the unique roles fulfilled by different subunits and evolutionarily conserved domains, such as DRPEER (Watanabe *et al.* 2002) and SYTANLAAF (Jatzke *et al.* 2003), in channel gating and ion permeation as well as identifying the role of the transmembrane region in channel tetramerization (Gan *et al.* 2015). This work has provided a useful framework in which to understand the impact of disease-causing mutations on NMDARs which, in some cases, are able to curtail the time course of channel activation whilst diminishing $Ca^{2+}$ transport through the pore (Amin *et al.* 2018). Given the key role of NMDARs in neurodevelopment and plasticity (Constantine-Paton *et al.* 1990;

Correction made on 12 January 2021, after first online publication: The article has been updated to include the Kamalova, A & Nakagawa T. (2021) reference.

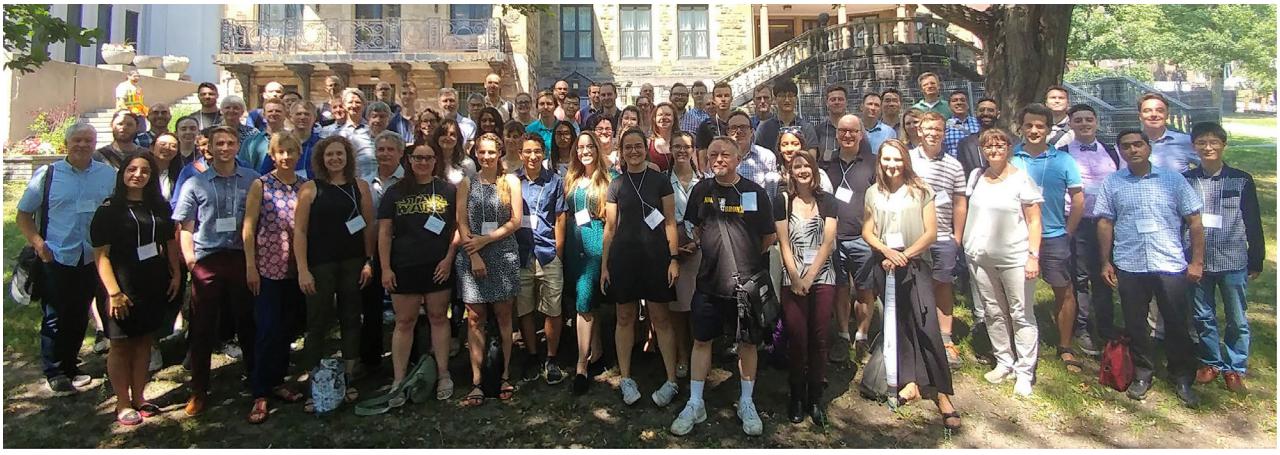

**Figure 1. Photograph of the speakers and attendees at the 2019 iGluRetreat conference that was organized by Drs David Stellwagen (McGill) and Derek Bowie (McGill) on the downtown campus of McGill University**



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Nicoll, 2017), the negative impact of these mutations can be readily appreciated. In their review, Amin and colleagues argue that the study of disease-causing mutations not only provides insight into how defects in NMDAR function and assembly contribute to neurological disease, but also expands our understanding of the inner workings of NMDARs. The authors also acknowledge that many disease mutations are found at sites in the NMDAR that have yet to be tied to a particular functional role. An ongoing challenge is to understand how both gain- and loss-of-function mutations in the NMDAR (Myers *et al*. 2019) can lead to neurological disease with many of the same cardinal features.

Dr David MacLean, his graduate student Matthew Rook from Rochester University, USA and Dr Maria Musgaard from the University of Ottawa, Canada presented work on a collaborative project of acid-sensing ion channels (ASICs), which have been the focus of intense research activity in recent years (Rook *et al*. 2021). ASICs are distinguished from most other ligand-gated ion channels by their trimeric subunit stoichiometry which differs from the more conventional tetrameric or pentameric stoichiometry associated with iGluRs and $GABA_A$ receptors, respectively, at central synapses. First identified through early forays into using the concentration clamp technique, ASICs respond to rapid millisecond changes in extracellular pH by evoking a rapidly decaying, cationic membrane conductance in freshly isolated sensory neurons (Krishtal, 2015). Since then, ASICs have been shown to be expressed throughout the body in the central and peripheral nervous systems where they have been linked to learning and memory, pain sensation, fear and anxiety, substance abuse, and cell death. Perhaps most surprisingly, ASICs are able to respond to rapid and brief changes in extracellular acidification (MacLean & Jayaraman, 2016) much like the rapid gating properties of AMPARs in response to L-Glu at auditory synapses (Joshi & Wang, 2002). Their importance to cell physiology and implication in numerous disease states has placed the spotlight on ASICs and a need to better understand their structure–function characteristics, which is the focus of the review. An immediate challenge is trying to understand how proton binding elicits conformational changes in the ASIC channel structure to access the open and desensitized states. Structural studies have shown that each ASIC subunit consists of a large extracellular domain, two transmembrane helices, and short intracellular N and C termini (Baconguis *et al*. 2014). The extracellular domain has been proposed to contain the proton binding site, although, as noted by the authors, its role in the process of channel activation and desensitization is still debated. Aided by recent full-length structures of ASIC channels (e.g. Yoder *et al*. 2018), Rook and colleagues have recently developed a working model of how ASIC1 channels enter into and out of the desensitized state(s) using a combination of fast perfusion electrophysiology, molecular dynamic simulations and crosslinking experiments (Rook *et al*. 2020). Their work unexpectedly highlights the importance of the $\beta$11-12 linker connecting the proposed extracellular proton binding pocket with transmembrane helices as being a key regulator of channel desensitization. Despite all these advances, the authors reflect on the challenges in studying gating events promoted by proton binding but offer some insights for the way forward for this important area of ion channel biology.

Dr Anthony Koleske and graduate student Juliana Shaw from Yale University also discussed the role of NMDARs and questioned exactly how they couple to the cell's cytoskeleton (Shaw & Koleske, 2021). The idea that NMDARs are linked to the cytoskeleton was first appreciated from experiments showing that the inactivation of NMDARs, which occurs due to the transport of $Ca^{2+}$ through the channel pore, could be blocked by agents that prevent actin depolymerization (Rosenmund & Westbrook, 1993). This finding linking channel activity to the cell's architectural proteins was further supported by work showing that NMDARs were, in fact, mechanosensitive (Paoletti & Ascher, 1994). Direct biochemical evidence was established by using latrunculin-A to induce actin depolymerization, which dispersed NMDARs from synaptic sites

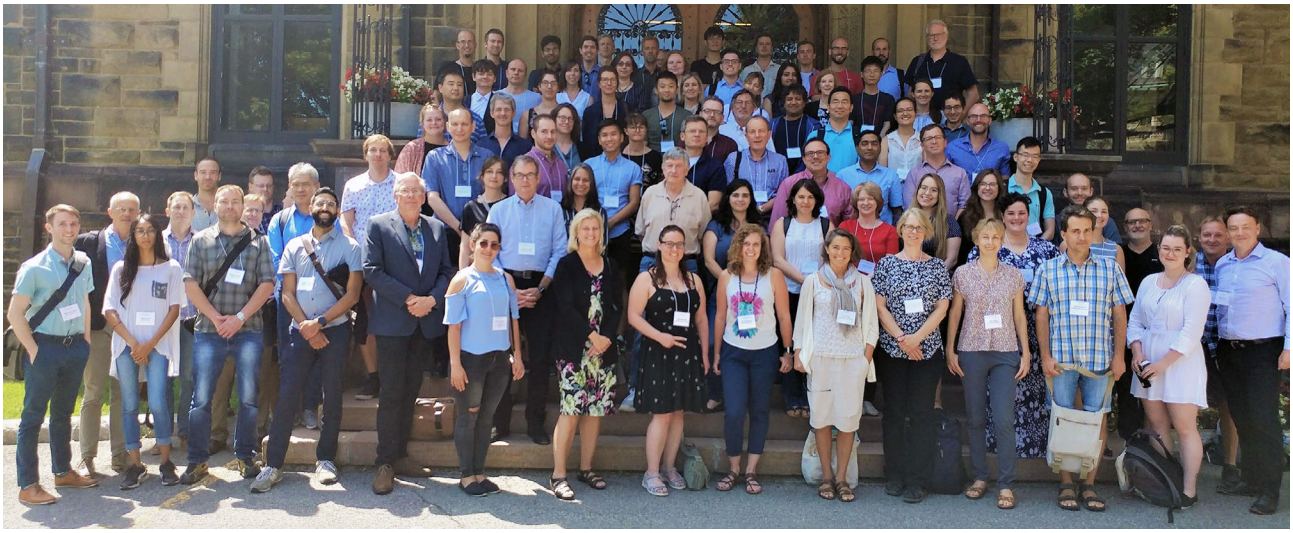

**Figure 2. The speakers and attendees at the 2019 ISN satellite conference on 'Neurotransmitter-gated ion-channels in health and disease' that was organized by Drs Katherine Roche (NIH) and Derek Bowie (McGill) on the downtown campus of McGill University**

(Allison *et al.* 1998) through its interaction with $\alpha$-actinin-2, which binds to the cytoplasmic tails of GluN1 and GluN2B NMDAR subunits (Wyszynski *et al.* 1997). In their review article, Shaw and Koleske describe the mechanisms by which actin regulates the functional properties of different voltage- and ligand-gated channel families with an emphasis on the regulation of NMDARs (Shaw & Koleske, 2021). Previous work from the Koleske lab has established the importance of dynamic actin networks in regulating NMDAR function at central synapses in Noonan syndrome (Levy *et al.* 2018), a multi-system disorder characterized by developmental delay and learning difficulties (Roberts *et al.* 2013). Noonan syndrome is caused by hyperactivating mutations in the SHP2 tyrosine phosphatase which disrupt the phosphorylated tyrosine binding site on the GluN2B cytoplasmic tail for the Nck2 adaptor protein. This phosphorylation event is detrimental in Noonan syndrome since it disrupts the partnership of Nck2 with N-WASp, which activate actin branch nucleation via the Arp2/3 complex (Levy *et al.* 2018). The untethering of Nck2 selectively impairs GluN2B NMDAR functionality at Schaffer collateral–CA1 neuron excitatory synapses inducing deficits in long-term potentiation (Levy *et al.* 2018). The authors conclude by speculating on why NMDARs may couple to the cytoskeleton via actin, suggesting that the interaction may be important in the gating properties of NMDARs. Since alterations in the intrinsic disorder of the cytoplasmic tail of NMDARs, by phosphorylation for example, impact channel functionality (Choi *et al.* 2011, 2013), it is clear that more work is needed to better understand how these molecular events impact neuronal communication and ultimately contribute to CNS disease.

The review article by Drs Katherine Roche and Sehoon Won from the National Institutes of Neurological Disorders and Stroke in Bethesda, MD highlights the important balancing role of striatal-enriched tyrosine phosphatase 61 ($STEP_{61}$) at glutamatergic synapses (Won & Roche, 2021). The strength of signalling at glutamatergic synapses is strongly regulated by phosphorylation events driven by the actions of a number of serine and tyrosine kinases (Chen & Roche, 2007). The NMDAR, in particular, is targeted by a family of src tyrosine kinases, which includes Src and Fyn, which upregulate channel activity and contribute to long-term potentiation in the CA1 region of the hippocampus (Salter & Kalia, 2004). Tyrosine phosphatases, such as STEP, are thus important in regulating the balance at central synapses. The most abundant isoform in the brain is $STEP_{61}$, which has garnered a lot of attention due to its implicated roles in neurological disease (Goebel-Goody *et al.* 2012). $STEP_{61}$ has a number of synaptic targets including tyrosine kinase Fyn and NMDA- and AMPA-type ionotropic glutamate receptors (Won *et al.* 2016, 2019). Fyn and Src kinases phosphorylate NMDARs on several tyrosine residues in the cytoplasmic tail of the GluN2A and GluN2B subunits. Among these tyrosine residues, Y1472 is adjacent to the PSD-95 binding site, which when phosphorylated inhibits clathrin-mediated endocytosis of GluN2B-containing NMDARs. $STEP_{61}$ targets GluN2B Y1472 for dephosphorylation and internalization. Although AMPARs have shorter cytoplasmic tails, phosphorylation and dephosphorylation events by numerous kinases and phosphatases similarly regulate receptor trafficking, endocytosis and synaptic plasticity. For example, phosphorylation of Y876 in the cytoplasmic tail of the GluA2 subunit disrupts GRIP1/2 binding leaving PICK1 bound, which promotes internalization of AMPARs (Hayashi & Huganir, 2004). $STEP_{61}$ was recently shown by mass spectrometry to bind directly to the cytoplasmic tails of the GluA2 and A3 subunits but not the GluA1 subunit. Accordingly, expression of GluA2 and GluA3 subunits at synapses is increased in STEP-KO mouse brain whereas $STEP_{61}$ overexpression reduces the synaptic expression and responsiveness of AMPARs (Won *et al.* 2019). The authors conclude by reviewing the evidence linking an upregulation in the expression of $STEP_{61}$ in cognitive impairment associated with ageing reported in several rodent, rhesus monkey and human studies suggesting that $STEP_{61}$ inhibitors, such as TC-2153 (Xu *et al.* 2014), may be a valuable form of treatment.

The article by Dr Teru Nakagawa and graduate student Aichurok Kamalova from Vanderbilt University provides a timely review of the multifaceted nature of the AMPA receptor–auxiliary subunit complex (Kamalova & Nakagawa, 2021). An early cryo-EM study gave us our first glimpse of the complex nature by which transmembrane AMPA receptor auxiliary proteins (TARPs) affect receptor function by bracing the transmembrane domains of the ion channel pore region (Nakagawa *et al.* 2005). Since then, several labs have provided an even greater picture of these interactions by studying full-length homo- and heteromeric structures of the AMPAR in complex with $\gamma$2 and $\gamma$8 TARPs, germ cell-specific gene 1-like protein (GSG1L; Greger *et al.* 2017; Chen & Gouaux, 2019; Twomey *et al.* 2019) and more recently, in association with cornichon-3 (CNIH3; Nakagawa, 2019). It is becoming clear that native AMPARs co-assemble with a number of different auxiliary subunit families, which has made it imperative to better understand how these associations affect brain function. The review focuses on the emerging evidence suggesting that different families of auxiliary subunits interact with AMPARs in different ways, explaining their distinct effects on ion channel gating and ion-permeation. The slower gating behaviour of the AMPAR–TARP complex can be explained by TARP interactions with the KGK site (Dawe *et al.* 2016) of the ligand-binding domain of AMPARs as well as residues located in the transmembrane regions (Ben-Yaacov *et al.* 2017; Hawken *et al.* 2017). GSG1L has a similar overall architecture to TARPs and it is thought to interact with AMPARs in a similar manner (Twomey *et al.* 2017), yet it lacks an extracellular helix found in TARPs and possesses a larger $\beta$1–$\beta$2 loop. The authors argue that these distinctions explain why TARPs preferentially slow entry into desensitization whereas GSG1L slows recovery, although the exact details remain to be resolved. The recent structure of the AMPAR–CNIH3 complex reveals that cornichons contain four transmembrane regions, not three as originally proposed, and lack the extensive extracellular domains that are so critical for TARP and GSG1L function (Nakagawa, 2019). Consequently, the modulatory effects of CNIHs that slow AMPAR channel gating and relieve polyamine channel block are presumably mediated by residues in the transmembrane domain. Details are still emerging, but it may suggest that the structural events that regulate channel gating and ion permeation are perhaps functionally coupled. What is clear is that the coming years will provide a fuller understanding of the structural and functional nature of the AMPAR–auxiliary subunit complex and how it shapes the physiology of neuronal circuits and disrupts them in neurological disease.

Drs Jakob von Engelhardt and Eric Jacobi from the Johannes Gutenberg University Mainz, Germany also discuss the importance of the AMPAR–auxiliary subunit complex but focus on its critical role in shaping the strength and fidelity of synaptic communication as well as its impact on the signalling capacity of neuronal circuits (Jacobi & von Engelhardt, 2021). AMPARs co-assemble with three major auxiliary subunit families, including members of the claudin family (TARPs $\gamma$2-5 and $\gamma$7-8 as well as GSG1L), the CKAMP family (CKAMP39, -44, -52 and -59) and the cornichons (CNIH2 and -3), most of which facilitate the trafficking and synaptic localization of AMPARs in neurons. Knockout mice or overexpression studies reveal that auxiliary proteins also impact the gating and permeation properties of native AMPARs. The TARP, CKAMP and CNIH families are, however, differentially expressed in the mammalian brain (Schwenk *et al*. 2014) suggesting that signalling in different brain regions may be finely tuned by their expression pattern. For example, TARP $\gamma$8 and CNIH2 are predominantly expressed in the hippocampus, cortex and striatum (Schwenk *et al*. 2014), with CKAMP44 and GSG1L primarily expressed in glutamatergic neurons of the cortex (Zeisel *et al*. 2018). The authors discuss how most auxiliary subunits increase the strength of glutamatergic synapses through a number of mechanisms that include increasing channel density and augmenting open channel probability and/or its unitary conductance. The exception to this is GSG1L, which has been shown to decrease channel density and unitary conductance in the cerebellum and hippocampus (McGee *et al*. 2015; Gu *et al*. 2016). The von Engelhardt lab has provided compelling evidence to support the important role of CKAMP44 in governing short-term plasticity of granule cells in the dentate gyrus (von Engelhardt *et al*. 2010; Khodosevich *et al*. 2014) and relay neurons in the dorsal lateral geniculate nucleus (Chen *et al*. 2018), with other groups similarly establishing the importance of CKAMP52 in CA1 neurons of the hippocampus and Purkinje cells of the cerebellum (Klaassen *et al*. 2016; Peter *et al*. 2020). The review concludes by discussing the extensive literature on the important role fulfilled by TARP $\gamma$2 and $\gamma$8 in long-term potentiation in the hippocampus and the paucity of information on how AMPAR auxiliary subunits affect homeostatic plasticity. The greater understanding of the AMPAR–auxiliary subunit complex and the role it plays in neuronal circuits and ultimately in human behaviour and disease may lead to breakthrough strategies of drug design that target the complex and not simply the channel pore forming subunits (Rosenbaum *et al*. 2020).

Drs Melanie Woodin and Jessica Pressey from the University of Toronto review the unexpectedly diverse mechanisms by which native kainate-type (KARs) ionotropic glutamate receptors signal at different synapses in the hippocampus (Pressey & Woodin, 2021). Unlike the canonical view of AMPARs and NMDARs, it has been much more difficult to assign general guiding principles to how KARs signal at central synapses. A major breakthrough was the appreciation that the selective, non-competitive block by several GYKI compounds of the much larger AMPAR response revealed the smaller amplitude, slower decaying responses of synaptic KARs (Paternain *et al*. 1995). With this research tool at hand and with genetic knockout strategies, it has been possible to pinpoint KARs to both the pre- and postsynaptic sides of excitatory glutamatergic and inhibitory GABAergic synapses (Contractor *et al*. 2011). As outlined by the authors, a significant surprise has been the understanding that KARs not only signal via an ionotropic pathway but also regulate the activity of voltage-gated potassium (Melyan *et al*. 2002) and calcium (Rodriguez-Moreno & Lerma, 1998) channels via a metabotropic G-protein coupled pathway. The Woodin lab has added further complexity to the KAR signalling profile by linking their activity to that of the neuron-specific $K^+$–$Cl^-$ co-transporter, KCC2 (Pressey *et al*. 2017). Since KCC2 sets the chloride equilibrium potential in mature neurons (Kaila *et al*. 2014), it ultimately determines the strength of GABAergic neurotransmission. The indirect regulatory effect of KARs on KCC2 is mediated by the KAR auxiliary protein, Neto2, which not only binds and regulates the gating and permeation properties of KARs but also binds directly to KCC2 (Ivakine *et al*. 2013; Mahadevan *et al*. 2014). The importance of this interaction can be appreciated from the behavioural analysis of Neto2 KO mice, which have a reduced threshold for seizures through the loss of KCC2 and diminished GABAergic neurotransmission (Mahadevan *et al*. 2015). Whether dysfunction of the newly discovered KAR–Neto2–KCC2 complex plays a role in CNS disease awaits to be uncovered.

Last but certainly not least, Drs Stephen Glasgow, Ed Ruthazer and Tim Kennedy from the Montreal Neurological Institute of McGill University provide a comprehensive review of their work highlighting the significant role of netrin-1 in synaptic plasticity and memory consolidation in the adult brain (Glasgow *et al*. 2021). Netrins were originally identified as chemoattractant guidance cues during embryogenesis that direct cell and axon migration (Kennedy & Tessier-Lavigne, 1995). However, netrins continue to be expressed by neurons into adulthood opening the question of whether they adopt different roles in mature neuronal circuits. The authors open their review by noting that many of the signalling cascades that are activated during changes in synaptic plasticity in the adult brain are similar to the cascade of signalling events triggered by chemotropic axon guidance cues during development. The first clue to understanding this puzzle was the observation that genetic deletion of the canonical receptor for netrin-1, the single-pass transmembrane protein called deleted in colorectal cancer (DCC) results in the loss of hippocampal long-term potentiation and impairment of spatial and recognition memory (Horn *et al*. 2013). Their next findings revealed that the ligand, Netrin-1, promotes excitatory synaptogenesis between cortical neurons by initiating synapse assembly and contact points, which increases the efficacy of excitatory synaptic transmission (Goldman *et al*. 2013). More details of this mechanism emerged with the finding that membrane depolarization and NMDAR activation at central synapses promotes the secretion of netrin-1 from dendrites (Glasgow *et al*. 2018). In agreement with their earlier findings with DCC deletion, the authors show that netrin-1 expression by hippocampal CA1 pyramidal neurons is required for NMDAR-dependent long-term potentiation (Glasgow *et al*. 2018). In fact, the exogenous application of netrin-1 is enough to trigger the potentiation of CA1 neuron glutamatergic synapses with the insertion of GluA1-containing AMPARs mediated through a rise in cytosolic $Ca^{2+}$ (Glasgow *et al*. 2018). This surprising yet rational alignment between molecular events in embryogenesis and the signalling

and structural processes that give rise to long-term potentiation in the adult brain reveals a remarkable economy in how the neurons are able to find different uses for processes with quite distinct purposes. Much is still to be uncovered about the role of netrin-1 in the adult brain though more recent work highlighting its role in spatial memory formation (Wong *et al*. 2019) and the specific pre- and postsynaptic role of its receptor, DCC (Glasgow *et al*. 2020), suggest that a fuller understanding may be forthcoming.

It has been more than three decades since the first cloning studies began to reveal the molecular identity of the neurotransmitter receptors that populate glutamatergic and GABAergic synapses in the mammalian brain (Schofield *et al*. 1987; Hollmann *et al*. 1989). Since then, genetic knockout and knockin studies have helped pinpoint the distribution and synaptic roles of iGluRs and $GABA_A$ receptors and refine an understanding of their roles in synaptic transmission and plasticity mechanisms. With many full-length homomeric and heteromeric structures of pore-forming subunits iGluRs and $GABA_A$ receptors reported in the last decade (Sobolevsky *et al*. 2009; Miller & Aricescu, 2014), our next steps will be to understand the structural biology of the synapse in its entirety. This is needed if we are to appreciate how auxiliary subunits and signalling proteins, such as kinases and phosphatases, couple to ion channels and regulate excitatory and inhibitory neurotransmission in the brain. The cell- and region-specific expression pattern of auxiliary subunits in the developing and adult brain (Zeisel *et al*. 2018) also offers an opportunity for more targeted neuropharmacology that exploits their unique protein–protein interactions to develop drugs with more specificity and fewer side effects (Rosenbaum *et al*. 2020). Together with the strident advances in systems biology, the next decade looks set to provide for the first time a comprehensive understanding of how molecular events at the synapse and within neuronal circuits give rise to complex animal and human behaviour and go awry in neurological disease.

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