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EDITORIAL

Shared and unique aspects of ligand- and voltage-gated ion-channel gating

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Ligand- and voltage-gated ion channels form a large superfamily of membrane-bound signalling proteins that fulfil many important roles in health and disease (Hille, 2001). Voltage-gated ion channels are primarily responsible for the generation and propagation of action potentials in excitable tissue (Stuart *et al.* 1997; Catterall *et al.* 2005; Jan & Jan, 2012) whereas ligand-gated ion channels constitute the hardwiring of chemical synapses – though they also fine tune synaptic strength during periods of sustained patterned activity and altered homeostasis (Turrigiano, 2008; Nicoll, 2017). Together, the combined activity of ligand- and voltage-gated ion channels gives rise to many complex physiological processes from cardiac and skeletal muscle contraction to the more enigmatic behaviours of the CNS such as cognition and memory.

The study of 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 understand ion channel function as well as drug action (Gouaux & Mackinnon, 2005). Furthermore, recent advances in genetic manipulations, particularly in rodents, have permitted ion channel families to be assigned distinct roles in health and disease. To explore this emerging area of physiology, *The Journal of Physiology* sponsored a symposium at the 2017 International Union of Physiological Sciences meeting in Rio de Janeiro, Brazil entitled 'Shared and unique aspects of the gating mechanisms of ligand- and voltage-gated ion-channels'. Chaired by *Journal* editors Drs Yoshihiro Kubo and Derek Bowie, it brought together five researchers (see Fig. 1) whose work is at the forefront of this rapidly developing field of study. This issue of *The Journal of Physiology* brings together three timely review articles and an original paper that capture some of the ideas, discussions and debates that arose during the symposium.

Dr Yoshihiro Kubo from Japan's National Institute for Physiological Sciences opened the symposium by presenting recent data from his lab where they looked at the unexpected effect of the broad-spectrum antiparasitic agent ivermectin on the G-protein-gated inwardly rectifying K^+ (or GIRK) channel (Chen *et al.* 2017). Since its discovery in soil samples of bacteria taken near a Japanese golf course in the 1970s (Laing *et al.* 2017), ivermectin has proven to be one of the most effective drugs used by veterinarians and health professionals to combat parasite infection. Although its anthelmintic action is primarily mediated by targeting the activity of nematode glutamate-gated chloride channels to curtail motility, feeding and reproductive behaviour (Yates *et al.* 2003), ivermectin has also been shown to affect other ion channel families such as $GABA_A$, glycine and nicotinic acetylcholine receptors (Wolstenholme & Rogers, 2005). This multifaceted nature of ivermectin pharmacology is the main topic of the comprehensive review by Chen and Kubo where they explore shared and unique modulatory properties of ivermectin on a variety of ligand-gated ion channels (Chen & Kubo, 2018). Insight into ivermectin's action on each ion channel target is beautifully illustrated by the authors' effective use of X-ray crystallographic data to compare and contrast the structural determinants of each binding pocket. Given its hydrophobicity, ivermectin binds to residues lining the transmembrane (TM) regions of Cys-loop ligand-gated ion channels, such as the nematode glutamate-gated chloride channels and mammalian glycine receptors. The binding of ivermectin near the extracellular surface of the plasma membrane is critical as it induces the rotation of TM regions to facilitate channel opening. Surprisingly, however, ivermectin binds to GIRK channels on a different site, which lies at the interface of the TM region and intracellular domains (Chen *et al.* 2017). The authors conclude that although ivermectin binds to many ion channel targets, its clinical value as a drug with few side effects is afforded by its preferred high-affinity binding to nematode glutamate-gated chloride channels.

Dr Cecilia Bouzat from the National University of the South (UNS), Bahìa Blanca, Argentina, presented recent work from her lab on the functional and pharmacological properties of α7 subunit-containing nicotinic acetylcholine receptors (nAChRs) (daCosta *et al.* 2011; Andersen *et al.* 2013, 2016; Nielsen *et al.* 2018). Although nAChRs are expressed throughout the body, α7 receptors are especially concentrated in the mammalian brain where they exhibit both ionotropic and metabotropic functions (Wu *et al.* 2016; Kabbani & Nichols, 2018). They are also implicated in several CNS disorders (Dineley *et al.* 2015) and consequently there has been a need to develop selective drugs. The review article by Bouzat and colleagues (Bouzat *et al.* 2018) highlights these recent advances in our understanding of the α7 nAChR. Potentiation of the α7 receptor has been identified as a novel therapeutic strategy to treat several neurodegenerative disorders, including Alzheimer's and Parkinson's diseases, and inflammatory disorders, whereas drugs which reduce receptor activity may be beneficial in the treatment of cancer cell proliferation (Bouzat *et al.* 2018).

Dr Frank Bosmans from Johns Hopkins University in Baltimore, MD, USA talked about the pioneering work that he and his colleagues have performed using animal toxins to probe the functional behaviour of voltage-gated ion channels, particularly voltage-gated Na^+ channels (Nav) (Bosmans & Swartz, 2010; Kalia *et al.* 2015). Voltage-gated Nav channels are primarily responsible for the rapid upstroke of the action potential in cardiac and skeletal muscle as well as being integral to the complex firing properties of central neurons. Not surprisingly, therefore, Nav channels are involved in many physiological processes and have also been implicated in numerous pathologies including cardiac dysfunction, neuropathic pain and genetic forms of epilepsy, such as Dravet syndrome (Abriel, 2010; Catterall, 2012; Waxman, 2013; Chen-Izu *et al.* 2015). Given all of this, the Nav channel community has been developing a comprehensive understanding of how the structural architecture

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of Nav channels relates to their functional behaviour (Ahern *et al.* 2016). In the current issue of *The Journal*, Gilchrist and Bosmans present an original research article detailing how animal toxins can be used to understand the slow gating kinetics of Nav1.8 (Gilchrist & Bosmans, 2018), a Nav channel implicated in pain mechanisms (Han *et al.* 2016). To do this, the authors introduced toxin sensitivity into each of the four voltage sensor domains of Nav1.8 by exchanging their sequences with those of Nav1.2 to probe their role in channel gating and inactivation. Using this chimera approach, Gilchrist and Bosmans conclude that the voltage sensor domains I–III participate in channel opening, whereas voltage sensor domain IV regulates channel opening as well as the onset of fast inactivation (Gilchrist & Bosmans, 2018).

Dr Marc Gielen presented a compelling account of his postdoctoral work with Dr Trevor Smart at University College London where he performed a comprehensive analysis of Cys-loop $GABA_A$ and glycine receptor desensitization (Gielen *et al.* 2015). The review article co-authored with his colleague, Dr Pierre-Jean Corringer, from the Institut Pasteur in Paris, is a *tour de force* treatise of the structural biology of Cys-loop receptors (Gielen & Corringer, 2018). The authors argue that although the mechanism of Cys-loop receptor activation has been studied extensively at both the functional (Lape *et al.* 2008; Mukhtasimova *et al.* 2009; Purohit *et al.* 2013) and structural (Corringer *et al.* 2010; Althoff *et al.* 2014; Sauguet *et al.* 2014) level, an understanding of the structural basis of desensitization is only beginning to emerge (Miller & Aricescu, 2014). Functional work had already argued that desensitization of Cys-loop nicotinic acetylcholine receptors involves two distinct, but inter-related gates (Auerbach & Akk, 1998), though their location within the ion channel pore remained to be established. The authors propose that the activation and desensitization gates are structurally distinct and located at each end of the ion channel pore. This proposal is consistent with the 'foot in the door' mechanism assigned to the channel blocker picrotoxin (Gielen *et al.* 2015) and Markov modelling of channel activation (Gielen & Corringer, 2018). Gielen and Corringer conclude by emphasizing the importance of the dual gate mechanism of activation and desensitization as a common explanation for the behaviour of several structurally unrelated ion channels.

Dr Derek Bowie from McGill University in Montréal, Canada closed the symposium with a presentation focusing on the structural and functional mechanisms that define the distinct families of the ionotropic glutamate receptor (iGluR). iGluRs are widely expressed in the vertebrate brain where they mediate the vast majority of fast excitatory transmission at central synapses (Dingledine *et al.* 1999; Traynelis *et al.* 2010). Not surprisingly, iGluRs are also implicated in many debilitating CNS disorders (Bowie, 2008). Despite their similar and overlapping tetrameric architecture (Sobolevsky, 2015), Bowie argued that the distinct gating behaviour of different iGluR subfamilies can be linked to differences in residues that line the interface between two subunit binding pockets that are arranged in a back-to-back formation (Dawe *et al.* 2015). This region of the protein is often referred to as the ligand-binding domain (LBD) dimer interface and was recognized from early structural studies as an important determinant of channel gating (Horning & Mayer, 2004; Bowie, 2010). Recent work from the Bowie lab has shown that the apex of the LBD dimer interface is critically important in defining the rapid millisecond gating behaviour of AMPA- and kainate-type iGluRs as well as their regulation by auxiliary proteins (Daniels *et al.* 2013; Dawe *et al.* 2013, 2016). He concluded that ongoing work from his lab suggested that the tardier gating of NMDA-type iGluRs was also determined by residues in the LBD dimer interface but from a different site. Taken together, this work

Figure 1. The speakers and colleagues who attended the symposium on 'Shared and unique aspects of the gating mechanisms of ligand- and voltage-gated ion-channels' at the 2017 International Union of Physiological Sciences meeting in Rio de Janeiro, Brazil
Top row, left to right: Drs Marc Gielen, Filip Van Petegem and Frank Bosmans; bottom, left to right: Drs Yoshihiro Kubo, Cecilia Bouzat and Derek Bowie.

highlights how subtle yet critical changes to the amino-acid sequence that encodes the LBD dimer interface may have contributed to the emergence of different iGluR classes during evolution.

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Additional information

Competing interests

None declared.