Targeting the cell's gatekeepers for novel drug discovery

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EDITORIAL

Targeting the cell's gatekeepers for novel drug discovery

Integral membrane proteins embedded in the plasma membrane are the gatekeepers of cell activity because they precisely regulate the transfer of information in a cellular context. The three major classes of integral membrane proteins (namely receptors, transporters and ion channels) are critically involved in diverse cellular and physiological processes in any given organism. Membrane proteins constitute one of the more prominent classes of targets for existing drugs, and they continue to be attractive targets for novel drug discovery for a broad spectrum of human disorders and pathological conditions. Therefore, understanding the mechanistic basis of activation and regulatory paradigms of these molecules represents an important frontier in modern biology. Against this backdrop, a focused symposium was organized at the Pharmacology 2019 conference in Edinburgh and that meeting sparked the idea for a thematic issue in the British Journal of Pharmacology focussing on Structure Guided Pharmacology of Membrane Proteins. This thematic issue includes a set of review and research articles covering diverse aspects of the structure and function of distinct types of membrane proteins (including GPCRs, ion channels and catalytic receptors).

Rosenbaum and co-authors present an up-to-date review on the structural insights into ligand-recognition and activation of the cannabinoid CB_1 receptor, a GPCR that critically mediates the functional response to endocannabinoids (e.g. anandamide) as well as other important exogenous ligands, and thus represents a prominent drug target for neurological disorders (Ramesh & Rosenbaum, 2021). They discuss how the recent crystal structures of CB_1 receptor in different conformations provide a previously lacking structural framework to rationalize activation and modulation of subtype selectivity at this receptor. Carlsson and co-authors synthesize a summary of structural observations on the caffeine-activated adenosine A_{2A} receptor which, in the recent past, has been one of the most extensively characterized GPCRs using X-ray crystallography and cryo-EM (Jacobson et al., 2020). In particular, their review underscores the power of structural snapshots in facilitating the visualization of ligand-receptor interaction and how this information can be utilized to drive rational ligand discovery with an emphasis on drug selectivity and efficacy. Klein-Seetharaman and co-authors summarize recent advances on the insulin receptor, which is critically involved in the physiology of nutrient balance and represents an important therapeutic target in diabetes mellitus and metabolic disorders(Kumar & Klein-Seetharaman, 2021). In particular, these authors present a comprehensive analysis of the emerging structural data to draw mechanistic insights into ligand binding, activation and pharmacology of the insulin receptor, and also discuss how these insights may facilitate the design of potential therapeutics targeting this receptor. Milligan and co-authors discuss the emerging insights into the activation and signalling of GPR84, a GPCR that is up-regulated in many immune cells under pro-inflammatory conditions and is being pursued as a target for therapeutic intervention in idiopathic pulmonary fibrosis (Marsango et al., 2020). They discuss the recent developments in terms of ligands for GPR84 and the existing pharmacological data in the context of how this receptor may be involved in pathological conditions and how this information hints at additional therapeutic opportunities. Ahring and co-authors systematically design and evaluate various concatemeric constructs of the α4β2-containing nicotinic ACh receptor (nAChR), a member of the cys-loop receptor subfamily, critically involved in synaptic excitation and in nicotine addiction (Liao et al., 2020). Using a combination of functional assays and molecular dynamics simulations, they observed that dimeric subunit constructs designed through concatenation were not effective in promoting functional expression of the nACh receptor. On the other hand, the tetrameric and pentameric subunit constructs which included linker sequences expressed efficiently in functional forms and therefore offer future strategies to facilitate structure-function studies of these important nACh receptors.

In the next section, there are two research articles and a review on TRP channels. Lejla Zubcevic writes a comprehensive review on vanilloid TRP channels (e.g. TRPV1) that are critically involved in temperature sensing and body temperature regulation, in addition to their roles in inflammation, pain and osmotic regulation (Zubcevic, 2020). In particular, this author presents an up-to-date summary of how structural snapshots have guided our understanding of ligand interaction and channel gating with a focus on the pharmacological and physiological aspects of these channels. Vriens and colleagues describe the pharmacological properties of TRPM3 splice variants, in particular those in the pore-forming region, and how they provide important insights into channel activation and gating (Held et al., 2020). They have utilized a combination of calcium imaging, patch-clamp recordings and site-directed mutagenesis to discover that alternative splicing in the pore-forming region of TRPM3 leading to different lengths of the pore-forming loop significantly determines the ligand-binding and activation of this channel. Valverde and colleagues combine computational and experimental approaches to characterize the binding sites of the known inhibitors of TRPV4 channels (Doñate-Macian et al., 2020). They also identify and characterize a set of additional compounds as potential modulators of TRV4 and demonstrate that one of these compounds harbours antiviral activity against the Zika virus.

Two review articles in the final section cover the structure, function and pharmacology of the sodium channel $Na_V1.7$ and ionotropic glutamate receptors (GluD), whereas a research article presents the structural basis of AMPA receptor inhibition by a potential anti-epileptic drug, 4-BCCA. King and co-authors present the contribution to nociception of $Na_V1.7$ sodium channel blockers, and how this sodium channel has emerged as a promising alternative target for designing effective analgesics (Eagle s et al., 2020). They also discuss the potential caveats and limitations associated with targeting $Na_V1.7$ for therapeutic intervention, despite rather successful preclinical efforts on the development of potent and specific blockers. Kumar and co-authors present a synthesis of the current understanding of activation and regulation of the GluD1 and GluD2 receptors, which play a crucial role in synapse formation and maturation (Burada et al., 2020). These receptors also are implicated in multiple neuronal diseases such as schizophrenia, autism and depression, and they have emerged as an drug target. The authors discuss the domain organization and architecture of GluD receptors, how they differ from other ionotropic glutamate receptors, and what are the potential implications for functional mechanisms. Sobolevsky and co-authors describe the structural mechanism of how the anti-epileptic drug 4-BCCA interacts with AMPA receptors, by using a combination of crystallography, site-directed mutagenesis, electrophysiology and molecular dynamics approaches (Yelshanskaya et al., 2020). They report that 4-BCCA binds primarily to the transmembrane domain of the AMPA receptor, which is distinct from non-competitive inhibitors, although it can take several poses in the same binding pocket.

We would like to take this opportunity to thank all the authors for taking the time to contribute to this thematic issue and for making it successful. We also thank the reviewers for providing timely feedback on the articles included in this issue, which has helped improve the articles in a comprehensive and complete manner. Finally, our sincere thanks to the editorial and production staff at the British Journal of Pharmacology for providing excellent support throughout the process and for making this issue possible. We very much hope that our readers enjoy this thematic issue and we look forward to your feedback.

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