Potassium Channels: A Big Family, Many Different Targets, Great Pharmacological Opportunities

The potassium channels family represents the most widely distributed among ion channels families. Thanks to this feature and to their ability of inducing hyperpolarization, potassium channels are involved in many physiologic processes such as regulation of smooth musculature tone, release of neurotransmitters, regulation of diuresis or glycaemia and so on, and these properties make potassium channels suitable targets for many pharmacological approaches to different pathologies in several districts. Among them, in the last decades the classes of ATP-sensitive (K<sub>ATP</sub>) potassium channels and large conductance Ca<sup>2+</sup>-activated (BK<sub>Ca</sub>) potassium channels were widely investigated both for the patho-physiological impact in many districts and for the design, synthesis and pharmacological characterization of novel chemical entities able to act as blocker or activators. Currently, more categories of potassium channels, hitherto little exploited, could represent a new exciting horizon to be explored. Among these less investigated classes, a special interest was certainly evoked by the Renal Outer Medullary (ROMK) potassium channels, the Voltage-gated (Kv) potassium channels and the peculiar sub-class of mitochondrial potassium (Mito-K<sup>+</sup>) channels.

The purpose of this issue is to offer a broad overview the most important pharmacological tools, such as novel and well-known molecules, having these classes of potassium channels as therapeutic target, in order to highlight promising drugs with exciting perspectives for the treatment of cardiovascular, neurological and metabolic diseases.

The first review, by Calderone et al. addresses the most unexplored class, that is the Renal Outer Medullary (ROMK) potassium channels. The ROMK or Kir 1.1, channels belong to the family of inwardly rectifying potassium channels and play a key role in K<sup>+</sup> recycling in the thick ascending limb of Henle’s loop, across the luminal membrane, and in K<sup>+</sup> secretion in the cortical collecting duct. From their discovery, a great interest in the possibility to inhibit these channels was aroused. Indeed, although the several diuretic classes are drugs with a general favorable risk/benefit balance, however they are not devoid of some adverse effects like hypokalemia or hyperkalemia. On the other hand, ROMK inhibitors, seem to give a diuretic/natriuretic effect, even higher than that evoked by loop diuretics, without inducing hypokalemic and hyperkalemic side effects. In light of this, many molecules were synthesized and a great number of patents were proposed, and among them some compounds seem to have better features to be applied in further clinical studies.

The contribution of Miceli et al. focuses on the Kv7 (KCNQ) subfamily of voltage-gated potassium channels and in particular on the pharmacological role and therapeutic applications of molecules able to modulate the neuronally-expressed Kv7 channels. A special interest was evoked by neuronal Kv7.2 and Kv7.3 channels because of their involvement in epilepsy. Starting from the reference drug retigabine, currently approved for clinical use against seizures, the authors describe the extreme heterogeneity in the molecular scaffolds studied to develop Kv7 modulators, as an evidence of a vibrant and growing field of research which could act as an incubator for future improvements in the treatment of hyperexcitability diseases.

Finally, in the review of Citi et al. a peculiar sub-class of potassium channels, Mito-K<sup>+</sup> channels, was described as a key target in many pathologies, related with cell metabolism, in several districts. Indeed, the recent literature confirms that mitochondria play a pivotal role in apoptosis, cardio- and neuro-protection, and in neurodegenerative disorders, ranging from Parkinson’s to Alzheimer’s disease. So targeting mitochondria with new chemical entities, represents a challenging goal for many researchers because drugs able to target and modulate Mito-K<sup>+</sup> channels, have a critical impact on mitochondrial function, and therefore they could represent a therapeutic chance in cardiovascular diseases, such as myocardial infarct, or neurodegenerative diseases and, as recent finding, in oncological diseases.

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