Tentative Outline

Special Issue for Current Medicinal Chemistry

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Purinergic P2X Receptors: Physiological and Pathological Roles and Potential as Therapeutic Targets

Aims & Scope:

Since the publication of the early studies ('50s-'60s) suggesting a role played by purine nucleotides in the extracellular environment, an increased interest was devoted to the investigation and clarification of the targets of these molecules and their mechanism of action. These studies led to the identification of specific receptors as mediators of the so-called purinergic transmission and Burnstock in late '70s suggested a first subdivision for two types of purinergic receptors, one selectively activated by adenosine (obtained by degradation of ATP; these proteins are called P1 receptors) and the other targeted by ATP/ADP (called P2). Further studies provided firstly a pharmacological basis for distinguishing two types of P2-purinceptors, defined as P2X and P2Y, secondly the evidence that the P1 and P2Y receptors are G Protein-Coupled Receptors while P2X are Ion Channels.

Currently, 7 subtypes of P2X receptors are known and several experiments based on different approaches showed that the combination of three P2X receptor subunits are required to form the channel, with evidence that they may assemble either as homomultimers and heteromultimers. In the last years, X-ray crystallography finally provided the 3D architecture of zebrafish P2X4 receptor in both apo and ATP-bound forms. P2X receptors are selectively activated by ATP and much less by ADP, but not by AMP or adenosine and once activated they allow the passage of small cations (Na⁺, K⁺, Ca²⁺). Some subtypes after a prolonged activation allow permeation also of larger cations and molecules.

P2X receptors are widely distributed in excitable and non-excitable cells and mediate several processes like neurotransmission and neuromodulation, cell secretion, acute inflammation, cell proliferation and differentiation. An increasing interest is due in particular to the possible targeting of P2X receptors by modulators with a variety of possible therapeutic applications like the treatment of cancer, inflammation, pain, neurological and neurodegenerative diseases, cardiovascular, renal and endocrine disorders.

This Issue is aimed at providing a wide description of P2X receptors considering a variety of aspects. In particular, two reviews will be focused on structural and functional features of these membrane proteins, taking in account the structural studies (i.e. crystallography and molecular modelling) and site direct mutagenesis data. Further reviews will provide introductions on the physiopathological roles of P2X receptors in cardiovascular and central nervous systems and in bones, with a special focus on the roles played by these membrane proteins in cancer, inflammation, and pain. Finally, two further reviews will describe the medicinal chemistry efforts to develop orthosteric agonists and antagonists and allosteric modulators and their therapeutic potential.

Keywords: Purinergic P2X receptors, Mutagenesis, Inflammation, Purine nucleotides, Membrane proteins
Subtopics:

- Purinergic P2X receptors: structural and functional features depicted by X-ray and molecular modeling studies
- Key sites for P2X receptor function and multimerization: overview on mutagenesis studies
- Physiopathological roles of P2X receptors in the central nervous system
- P2X receptor roles in the cardiovascular system
- P2X receptor roles in the bone biology
- P2X receptors and inflammation
- P2X receptors and cancer
- P2X receptors, sensory neurons, and pain
- P2X receptors and diabetes
- Medicinal chemistry of P2X receptors: orthosteric agonists and antagonists
- Medicinal chemistry of P2X receptors: allosteric modulators

Schedule:

Manuscript submission: April 2014
Peer Review due: May 2014
Revision due: June 2014
Notification of acceptance by the Guest Editor: July 2014
Final manuscripts due: August 2014