Chapter

Introductory Chapter: Receptors P1 and P2 as Targets for Drug Therapy in Humans

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1. Purinergic receptor classification and functions in physiological conditions

One of the most abundant molecules in living cells serving as an intracellular energy source is adenosine-5′-triphosphate (ATP) [1]. Additionally, this molecule acts as the substrate for adenosine 3′,5′-cyclic monophosphate (cAMP) production, which is extensively used in intracellular signaling.

Although there was resistance to recognize the action of ATP in the extracellular medium, nowadays, diverse mechanisms of cellular communication in living organisms have been considered as dependent on purinergic signaling. Numerous cell types released ATP autocrinally as a ubiquitous biologic and physiologic process [2]. A large number of purinergic receptors are activated for extracellular ATP and its metabolic breakdown acting on autocrine and paracrine manner [3, 4]. Thus, adenosine and other nucleotides activate the P1 and P2 receptors, respectively. P1 receptors are selective for adenosine, and P2 receptors are activated by purine and by pyrimidine nucleotides. Adenosine activates A_1, A_{2A}, $A_{2B,}$ and A_3 receptors coupled to G-protein subtypes. Purines and pyrimidines may activate the P2Y receptors (eight subtypes in mammalian $P2Y_{1,}$ $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, and $P2Y_{14}$) coupled to G-protein. P2X receptors are preferentially activated for purines (seven subtypes in mammalian $P2X_1$, $P2X_2$, $P2X_3$, $P2X_4$, $P2X_5$, $P2X_6$, $P2X_7$) forming homotrimers and heterotrimers.

P1 and P2 receptors are abundant and widely distributed in all tissues of the body, mainly in mammals. In physiological conditions, they participate on neurotransmission, neuromodulation, sensory transduction, regulation of heart rate, smooth muscle contraction, bile secretion, endocrine regulation, immune responses, proliferation in development and regeneration, ischemia, and inflammation [5].

2. Purinergic receptor participation in pathological conditions

The immune system uses pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) [6]. Besides pathogens, the immune system also reacts to particles that can cause damage-associated molecular patterns (DAMPs) [7], which are called hazard signaling molecules. Antigen presenters recognize them, once released or produced under stress conditions or cell death, which become activated and generate costimulatory signals and thus initiate immune responses and inflammation [8]. Different chemical agents are

capable of inducing the inflammatory response, even in the absence of infection. Sterile inflammation is marked by neutrophil and macrophage recruitment and for cytokine production such as TNF-α and IL-1β [9]. Nucleotides (ATP, UTP, or ADP) can act as DAMPS in the extracellular medium under stressful conditions and are released with other molecules out of the cell. In the environment, these nucleotides are recognized by a cell expressing purinergic receptors, including the antigen-presenting cells (APCs). Thus, they serve as signaling molecules of danger to APCs. In this context, in an ATP cell release event injured, many classes of receptors (sometimes of different actions) are activated in effector cells and can generate a network of intracellular signaling cascades responsible for late effects [10]. Several studies in recent years have shown that purinergic signaling plays an essential regulatory role in many inflammatory diseases [11]. Additionally, these receptors may modulate diverse diseases such as chronic pain, brain trauma ischemia, epilepsy, Alzheimer disease, amyotrophic lateral sclerosis, depression, anxiety, schizophrenia thrombosis and stroke, dry eye, atherosclerosis, kidney failure, osteoporosis, bladder incontinence, colitis, neurodegenerative diseases, and cancer [12–14].

3. Purinergic receptor as therapeutic targets

Classically, in the function of ubiquitous purinergic receptor expression, the agonists and antagonists for these receptors exhibit a lack of drug selectivity and the possibility of side effect in vivo. However, the advance of medicinal chemistry area in the last decades has developed potent and selective synthetic agonists and antagonists for purinergic receptors. The boost of bioinformatic analysis with power tools allows studying purinergic receptors' structure in details and discovering, in some cases, allosteric modulators with therapeutic window better than orthosteric compounds [15–17].

Undoubtedly, purinergic receptors, P2X receptor, P2Y receptor, and ectonucleotidase pharmacology is an attractive area for pharmacotherapeutic development and, therefore, provides a contemporary understanding of the purinergic signaling in physiological and pathological conditions. Additionally, this content will include of the relationship between purinergic receptors subtypes and ectonucleotidases at molecular, pharmacological, and therapeutic conditions.

We are grateful to all the authors for their valuable contribution and hope that this book could represent, for the scientific community, a solid basis for further studies on purinergic receptors.

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