Biochimica et Biophysica Acta 1828 (2013) 79–93

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Review

The participation of plasma membrane hemichannels to purinergic signaling ☆

Alberto Baroja-Mazo, Maria Barberà-Cremades, Pablo Pelegrín *

Inflammation and Experimental Surgery Unit, CIBERhed, University Hospital "Virgen de la Arrixaca", Fundación Formación Investigación Sanitaria Región Murcia,Murcia, Spain

ARTICLE INFO

Article history:
Received 31 October 2011
Received in revised form 30 December 2011
Accepted 4 January 2012
Available online 12 January 2012

Keywords:
Adenosine receptor
P2X receptor
P2Y receptor
Pannexin
Connexin
ATP release

ABSTRACT

The field of hemichannels is closely related to the purinergic signaling and both areas have been growing in parallel. Hemichannels open in response to a wide range of stressful conditions, such as ischemia, pressure or swelling. Hemichannels represent an important mechanism for the cellular release of adenosine 5′-triphosphate (ATP), which is an agonist of the P2Y and P2X family of purinergic receptors. Therefore, hemichannels are key molecules in the regulation of purinergic receptor activation, during physiological and pathophysiological conditions. Furthermore, purinergic receptor activation can also lead to the opening of hemichannels and the subsequent amplification of purinergic signaling via a positive signaling feedback loop, giving rise to the concept of ATP-induced ATP release. Purinergic receptor signaling is involved in regulating many physiological and pathophysiological processes. P2Y receptors activate inositol trisphosphate and transiently increase intracellular calcium. This signaling opens both connexin and pannexin channels, therefore contributing to the expansion of calcium waves across astrocytes and epithelial cells. In addition, several of the P2X receptor subtypes, including the P2X2, P2X4 and P2X7 receptors, activate select cellular permeation pathways to large molecules, including the pannexin-1 channels, which are involved in the initiation of inflammatory responses and cell death. Consequently, the interplay between purinergic receptors and hemichannels could represent a novel target with substantial therapeutic implications in areas such as chronic pain, inflammation or atherosclerosis. This article is part of a Special Issue entitled: The communicating junctions, roles and dysfunctions.

Contents

Abbreviations: αβmeATP, α,β-methylene ATP; APC, Antigen presenting cell; ATP, Adenosine 5′-triphosphate; BCECs, Bovine corneal endothelial cells; BzATP, 2′,3′-*O*-(benzoyl-4-benzoyl)-ATP; cAMP, Cyclic adenosine 5′-monophasphate; CD39, ENTPD1; CD73, NT5E; CNS, Central nervous system; Cx, Connexin; DAMP, Danger associated molecular pattern; EC, Endothelia cell; EET, Epoxyeicosatrienoic acid; ENTPD1, Ecto-nucleoside triphosphate diphosphohydrolase 1; ERK, Extracellular signal-regulated protein kinases; IHC, Inner hair cells; IP3, Inositol trisphosphate; MAPK, Mitogen activated protein kinase; MHC, Major histocompatibility complex; NMDG, *N*-methyl-D-glucamine; NO, Nitric oxide; NT5E, Ecto-5′-nucleotidase; OHC, Outer hair cells; OoC, Organ of Corti; PAMP, Pathogen associated molecular pattern; PLC, Phospholipase C; PPADS, pyridoxal-phosphate-6-azophenyl-2′,4′-disulphonic acid; RhoA, Ras homolog gene family member A; SMC, Smooth muscle cells; TCR, T-cell receptor; TM, Transmembrane; TNP-ATP, 2′,3′-*O*-(2,4,6-Trinitrophenyl)-ATP; VCAM-1, Vascular cell adhesion molecule 1

☆ This article is part of a Special Issue entitled: The communicating junctions, roles and dysfunctions.

* Corresponding author at: Inflammation and Experimental Surgery Unit, University Hospital "Virgen de la Arrixaca", Fundación Formación Investigación Sanitaria Región Murcia (FFIS), Carretera Madrid Cartagena s/n, 30120 Murcia, Spain. Tel.: +34 968 369 317; fax: +34 968 369 364.
E-mail address: pablo.pelegrin@ffis.es (P. Pelegrín).

0005-2736/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamem.2012.01.002

1. Introduction

1.1. Historic perspective of purinergic signaling pathways

In 1929, Drury and Szent-Gyorgyi described the potent actions of the extracellular application of adenine compounds on the heart [1]. Four decades later, ATP was proposed as the transmitter responsible for non-adrenergic, non-cholinergic transmission in the gut and bladder. In 1972 Burnstock introduced the concept of purinergic signaling [2], in which extracellular purines (most notably ATP, adenosine, and pyrimidine) act as extracellular signaling molecules. Both, pyrimidine and purine nucleotides, are released from cells through several physiologically relevant mechanisms, including diffusion through membrane hemichannels, activation of membrane transporters and vesicular exocytosis [3–6]. In addition, purines and pyrimidines are released from dying cells: this being an early indicator for cell damage [5,7]. Upon release, ATP (and other nucleotides) are enzymatically degraded within seconds by an extended family of ectonucleotidases [8]. This process is physiologically relevant as ATP metabolites are also agonists of purinergic receptors (Fig. 1). These purinergic signaling molecules activate three receptor classes: metabotropic P1 receptors, which are activated by adenosine, while the nucleotide receptors comprise the P2 family and are subdivided into P2Y metabotropic and P2X ionotropic sub-classes (Fig. 1) [6,9–13].

The purinergic signaling is a primitive system, ATP is an ancient and fundamentally important biological molecule. There are purinergic receptors in ancestral green algae and early in the fungi lineage [14,15]. Purinergic signaling is implicated in many neuronal and non-neuronal mechanisms, including exocrine and endocrine secretion, immune responses, inflammation, pain, platelet aggregation and endothelial-mediated vasodilatation [16,17]. In addition, purinergic signaling processes are implicated in mediating cell proliferation, differentiation and death [18,19]. ATP-mediated signaling has been identified in virtually all tissues and cell types and appears to be the most widespread and omnipresent of all known extracellular signaling molecules.

1.2. P1 or adenosine receptors

The P1 class of purinergic receptor was first described in 1989 and comprises four subtypes: A_1, A_{2A}, A_{2B} and A_3 (Fig. 1) [20–25]. The nomenclature used follows the Alexander et al. guide [26]. In common with other G protein-coupled receptors, they contain seven transmembrane (TM) domains of approximately 21 to 28 hydrophobic amino acids composing a α-helix structure. The amino-terminus of the protein is present on the extracellular side of the plasma membrane, while the protein's carboxy-terminus lies on the cytoplasmic side of the membrane. A pocket for the ligand-binding site is formed by the three-dimensional arrangement of the α-helical TM domains, and the agonist is believed to bind within the upper half of this pore [11]. Binding of the agonist to the receptor gives rise to a stable configuration as has been shown by x-ray crystallography with the A_{2A} receptor [27]. The TM domains are connected by three extracellular and three cytoplasmic hydrophilic loops [11]. P1 receptors are coupled to adenylate cyclase signaling pathways in which A_1 and A_3 receptor activations have inhibitory effects on adenylate cyclase through the Gi/o protein α-subunits. Activation of the A_{2A} and A_{2B} receptors stimulates the production of cyclic AMP (cAMP) via adenylate cyclase through the Gs protein [6,22,28].

A number of selective agonists and antagonists have been identified for several of the P1 adenosine receptor subtypes including agonists for the A_1, A_{2A} and A_{2B} receptors, and antagonists for the A_1, A_{2B} and A_3 receptors [11].

1.3. Purinergic P2Y receptors

The first P2Y receptor ($P2Y_1$) was cloned in 1993 [29,30], and since then several other subtypes have been isolated. Eight human P2Y receptor subtypes have so far been identified, the $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$ and $P2Y_{14}$ receptors [12,31] (Fig. 1). A number of putative P2Y receptor subtypes have also been identified but these correspond to non-mammalian orthologs, or receptors with sequence homology to P2Y receptors, but for which there is no functional evidence of activation by nucleotides. Recently, the orphan receptor GPR_{80}/GPR_{99} was named $P2Y_{15}$ receptor on the basis that it would be activated by AMP [32].

Molecular studies have shed light upon the mechanisms of receptor activation. Site-directed mutagenesis of the $P2Y_1$ and $P2Y_2$ receptors has shown that some positively charged residues in TM3, TM6 and TM7 are crucial for receptor activation by nucleotides [33,34]. Furthermore four cysteine residues in the extracellular loops, which are conserved in P2Y receptors, are known to be essential for proper trafficking of the receptor to the cell surface [35].