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Review

Modulation of the neuronal network activity by P2X receptors and their involvement in neurological disorders

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ABSTRACT

ATP is a key energetic molecule, fundamental to cell function, which also has an important role in the extracellular milieu as a signaling molecule, acting as a chemoattractant for immune cells and as a neuro- and gliotransmitter. The ionotropic P2X receptors are members of an ATP-gated ion channels family. These ionotropic receptors are widely expressed through the body, with 7 subunits described in mammals, which are arranged in a trimeric configuration with a central pore permeable mainly to Ca^{2+} and Na^{+}. All 7 subunits are expressed in different brain areas, being present in neurons and glia. ATP, through these ionotropic receptors, can act as a neuromodulator, facilitating the Ca^{2+}-dependent release of neurotransmitters, inducing the cross-inhibition between P2XR and GABA receptors, and exercising by this way a modulation of synaptic plasticity. Growing evidence shows that P2XR play an important role in neuronal disorders and neurodegenerative diseases, like Parkinson's and Alzheimer's disease; this role involves changes on P2XR expression levels, activation of key pathways like GSK3β, APP processing, oxidative stress and inflammatory response. This review is focused on the neuromodulatory function of P2XR on pathophysiological conditions of the brain; the recent evidence could open a window to a new therapeutic target.

Contents

1. Purinergic receptors

Adenosine triphosphate (ATP) is a central metabolic and energetic molecule, which also has some roles in the extracellular milieu, acting as a chemoattractant for immune cells and as a neurotransmitter for cells in the central nervous system [1]. The recognition of the role of ATP as a neurotransmitter was pioneered by the work of Holton [2] and largely by the contribution of Burnstock who proposed in 1972, the existence of purinergic nerves [3] and in 1978, the distinction between 2 families of receptors, one activated by adenosine and the other by ATP/ADP denominated P1 and P2, respectively [4]. It was later determined that P2 family was in fact composed by two subtypes of receptors: P2Y, which are G protein-coupled receptors (GPCR), and P2X who belong to the ligand gated ionotropic channel (LGIC) superfamily [5,6].

P2X receptors conform a unique and distinct LGIC family [7], to date 7 subunits have been cloned from mammals, termed P2X1-7 [8]; the subunits are topologically arranged in a short intracellular N-terminus followed by a transmembrane domain (TM1), a large

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extracellular loop with several conserved cysteines, another transmembrane domain (TM2) and finally an intracellular C-terminus of variable length, as depicted in Fig. 1 [9]. Crystallographic studies confirmed that the receptors are arranged in trimers [9,10], which can be homo- or heterotrimers; currently, is accepted that only subunit P2X6 is unable to conform homotrimeric receptor [11], while the most described heterotrimeric receptors are P2X1/2, P2X1/4, P2X1/5, P2X2/3, P2X2/6 and P2X4/6 [11]. These cationic channels have a high relative permeability to Ca^{2+} compared to Na^{+} and K^{+} [12,13]. This high Ca^{2+} permeability is an important characteristic in order to modulate key neuronal process like exocytosis, mitochondrial function, and pathway signaling. The ion channel is formed by the TM2 segments of each subunit [14] and in the homomeric receptors, the range of sensitivity to ATP, has been described from EC_{50} = 0.07 μM in rat P2X1 to near 100 μM in P2X7, also in rat [15].

Physiologically, the release of ATP is finely tuned by 3 mechanisms and involves: vesicle mediated secretion (Ca^{2+}-dependent) [17], ATP transporters (CFTR, ABC transporters, P-glycoprotein) [18] and channels like connexins or pannexins [19]. The concentration of ATP in the extracellular space has been reported in the range of nano- to micromolar [5]; however millimolar concentrations of ATP could be achieved in the synaptic cleft [19]; reinforcing its role on the synaptic function. Additionally, it has been suggested that a leak in events of cell membrane damage could contribute to extracellular ATP levels, conditioning by this way the synaptic activity [18,20,21]. This last mechanism is important in nociception and some inflammatory pathologies [22], but recently, has been proposed to be part of excitotoxic neurodegenerative mechanisms [21]. The half-life of ATP is estimated in 200 ms [23], being quickly degraded by a complex set of nucleotidases and phosphatases, including ectonucleotide-triphosphatases, phosphodiesterases and ecto-5′-nucleotidase [5,23,24]. In this review, we will focus in how ATP can modulate neural function and the implications of this in the onset and development of neurodegenerative disorders, with special focus on Alzheimer's disease.

2. P2X receptors distribution

Trimeric P2X receptors are assembled in the endoplasmic reticulum (ER), and then trafficked to the cell membrane, this mechanism and the distribution of these receptors is summarized in Fig. 2. The localization of the receptors in the cell depends on the subtype, P2X1 is mainly in the cell surface [25] and studies with chimeric fluorescent receptors demonstrates that the protein is internalized and recycled upon activation [26]. P2X2 is ubiquitous in the neuronal membrane, and low internalization has been observed under sustained ATP stimulation. In parallel, studies with GFP tagged receptors, it has been shown a redistribution of P2X2 at the cell surface of olfactory bulb neurons [27] and also a overexpression on hippocampal embryonic neurons [28]. P2X3 receptors are rapidly internalized upon activation, as observed in HEK293 cells and in neurons from the dorsal horn [29]; interestingly in the same study it was observed that when the receptors were inhibited, they remained in the membrane. Similarly, P2X4 receptors also are internalized upon activation and were trafficked to lysosomes [30]; interestingly, this receptor presents a unique and non-canonical internalization motif [31]. P2X5 and P2X6 are mainly localized in monomeric state in the ER [32]; however, when they heteromerize with P2X2 or P2X4 they can be located at the cell membrane [27]. Finally, P2X7 is distributed mostly in the cell membrane, thanks to its lipid binding sites [33,34], this could be an important element, if we consider that P2X7 has been involved on several pathological conditions on Central Nervous System (CNS) [24].

P2X receptors are widely expressed through the organism, in SNC the 7 subunits are expressed, although with differential levels in distinct area; for example, in some neurons of rat DRG only P2X2 and 3 are expressed [35], while in glia mainly P2X7 is present. However, it is important to note that the level of expression of P2XR depends of the specie, maturational and physiological state, among other consideration; for example, in rat is reported that P2X3 is present in brain from P7 to P14, but not in adult brain [36]; therefore this subject has been already reviewed elsewhere (see [37]).

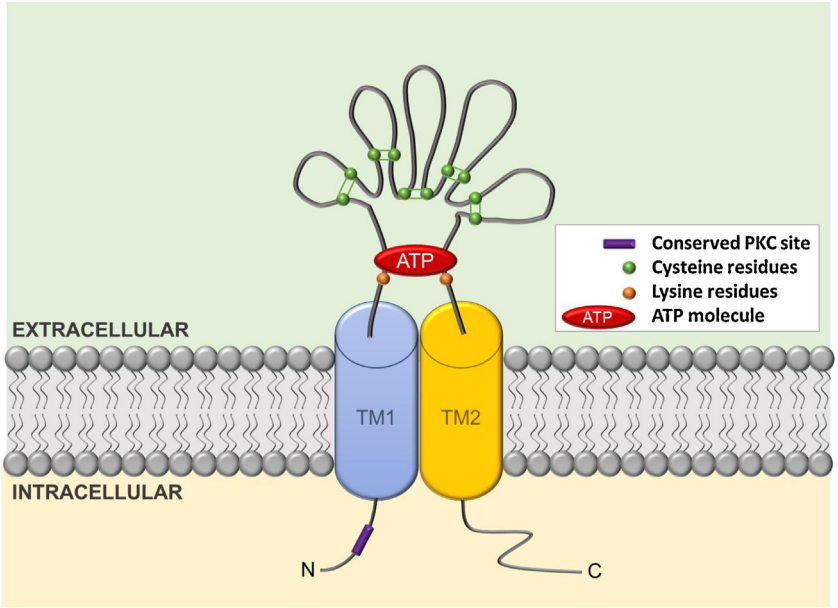

Fig. 1. P2XR subunit topological arrangement. Subunits are arranged in a short intracellular N-terminus which contains a conserved PKC site with important roles in the modulation of the receptor function [7], two transmembrane domains (TM1 and TM2), a large extracellular loop with several conserved cysteines, important for the allosteric regulation of the receptor [16] and a variable length intracellular C-terminus [9].