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·Minireview·

Therapeutic potential of extracellular ATP and P2 receptors in nervous system diseases

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Abstract: Extracellular adenosine 5'-triphosphate (ATP) is a key signaling molecule present in the central nervous system (CNS), and now is receiving greater attention due to its role as a messenger in the CNS during different physiological and pathological events. ATP is released into the extracellular space through vesicular exocytosis or from damaged and dying cells. Once in the extracellular environment, ATP binds to the specific receptors termed P2, which mediate ATP effects and are present broadly in both neurons and glial cells. There are P2X, the ligand-gated ionotropic receptors, possessing low affinity for ATP and responsible for fast excitatory neurotransmission, and P2Y, the metabotropic G-protein-coupled receptors, possessing high affinity for ATP. Since massive extracellular release of ATP often occurs after stress, brain ischemia and trauma, the extracellular ATP is considered relating to or involving in the pathological processes of many nervous system diseases. Conversely, the trophic functions have also been extensively described for the extracellular ATP. Therefore, extracellular ATP plays a very complex role in the CNS and its binding to P2 receptors can be related to toxic and/or beneficial effects. In this review, we described the extracellular ATP acting via P2 receptors as a potent therapeutic target for treatment of nervous system diseases.

Keywords: extracellular ATP; P2 receptors; nervous system diseases

1 Introduction

Extracellular purine and pyrimidines are ubiquitous and their roles as signaling molecules are well established, especially in the case of adenosine 5'-triphosphate (ATP) and adenosine. ATP is currently receiving more attention due to its role as a messenger in the central nervous system (CNS) during different physiological and pathological processes. For instance, in the nervous system, it has been shown that ATP signaling plays a crucial role for embryonic and early postnatal development, synapic plasticity, cognitive functions, and in different pathological states such as neuropathic pain, hyperalgesia, neuroinflammation, injury, ischemia, neurodegenerative disorders, and epilepsy[1]. The potential sources for extracellular ATP in the nervous system include neurons, glia, endothelium, and blood. Extracellular ATP can reach a high concentration, up to the millimolar range, flowing out of cells into the extracellular space, after different kinds of acute CNS injury. In this review, we focused on the role of extracellular ATP through P2 receptors in the CNS, paying particular attention to their therapeutic potential in neural disorders. We also briefly described the mechanism by which the ATP is released into the extracellular space.

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2 ATP: an extracellular signaling molecule in the CNS

Extracellular purines are regarded as the most ancient epigenetic factors that play crucial biological roles in several different tissues[2]. ATP is a biological molecule present in all cells and intracellular organelles, including secretory vesicles, as well as in the extracellular space of several tissues. Extracellular ATP, in particular, is a potent signaling molecule of the CNS, triggering a wide array of events including neurotransmission, hormone secretion, pain and neuroinflammation. Recent findings have demonstrated that ATP is a growth factor participating in cell proliferation, differentiation, regeneration and cellular death. The actions of extracellular ATP as a neurotransmitter or co-transmitter were firstly proposed 30 years ago[3], however, only recently its therapeutic potential has been suggested. The effects of ATP could be mediated by two receptor families belonging to either the P2X (ligand-gated ionotropic receptors) or the P2Y (metabotropic G-protein-coupled receptors) types.

3 P2 receptor subtypes

In the nervous system, P2 receptors are broadly expressed both in neurons and in the cells involved in neuroinflammatory responses, such as astrocytes and microglial cells[4]. Seven P2X receptor subtypes ($P2X_{1\text{-}7}$) have been cloned from mammalian tissue, assembling into ATP-activated ion channels either as homomers or heteromers[2,5]. P2X receptors include two transmembrane spanning regions, an extracellular loop and intracellular N- and C- termini. The extracellular loop contains the ATP binding site and the sites for antagonists and modulators; the residues in the C-terminal play an important role in determining the rate of desensitization[6]. P2X receptors are cation-selective channels with low affinity for ATP. All P2X receptors are permeable to sodium, potassium and calcium[7], resulting in an increase in intracellular Ca^{2+} concentration and depolarization of cell membrane. At the cellular level, P2X are expressed on neurons, astrocytes, oligodendrocytes and microglia and partake in complex of cellular circuits modulating several functions throughout the CNS[8]. P2X receptors have been reported to mediate fast synaptic transmission, neuromodulation[5], cell death and differentiation, and to be the target of tropic agents[9]. Among different P2X receptors, the potency of ATP can vary largely, with EC_{50} values ranging from 50 nmol/L to 300 μmol/L, depending on subunit composition[10].

Eight different mammalian P2Y ($P2Y_{1,2,4,6,11,12,13,14}$) receptor subtypes have been cloned and proven to act as receptors for extracellular nucleotides so far. These metabotropic receptors have seven membrane-spanning regions, the extracellular N-terminus and the intracellular C-terminus, and couple with $G_{q/11}$, G_s and G_i proteins. $P2Y_1$ is a receptor for the endogenous ligands ADP, more than ATP and diadenosine polyphosphates. The $P2Y_{2,4}$ receptors are activated with approximately equal potency by ATP as well as UTP[11]. $P2Y_6$, showing preference for UDP, is a receptor for pyrimidine which is activated specifically by uridine nucleotides and not by adenine nucleosides or nucleotides[12]. The $P2Y_{11}$ subtype is stimulated by agonist with a rank order of potency of ATP>2MeSATP>>ADP, with UTP and UDP inactive[13]. The $P2Y_{12,13}$ subtypes are activated by ADP, whereas ATP is a competitive antagonist for $P2Y_{12}$ or inactive with $P2Y_{13}$[14,15]. A most unusual agonist, UDP-glucose, is the main agonist of $P2Y_{14}$ isoform. Conversely, most P2Y receptors generally act via G proteins coupled to activate phospholipase C (PLC), leading to formation of IP_3 and mobilization of intracellular Ca^{2+}, and to inhibition of adenylyl cyclase (AC). Since they all involve second messenger systems and/or G protein-mediated ionic conductance, the cellular response time of the P2Y receptors is longer than that mediated by the P2X subtypes.

4 Neural release mechanism of ATP

Recent studies provide evidence that ATP as an autocrine/paracrine molecule is released extracellularly in response to a number of stimuli, including reductions in oxygen tension and pH[16-18], as well as mechanical deformation[19,20] and hypotonic stress[21,22]. Translocation of ATP from the intracellular compartment to the extracellular fluid is a fundamental process that provides the substrate for purinergic autocrine and paracrine cell signaling. Although the physiological importance of this process is well recognized, the cellular mechanisms are poorly understood.

The most characteristic features of the nerve terminal are the synaptic vesicles. From very early, it has been thought that these vesicles play an important role in releasing neurotransmitters. Since they appear in clusters at the presynaptic membrane, it was thought that there must have a mechanism that ensured the occurrence of vesicles at this position to account for transmitter release from the organelles. Direct proof of the involvement of vesicles in the release of neurotransmitter came first from ultra structural studies using electron microscopy and showing fusion of vesicles with cell membranes[23]. It is now accepted that exocytosis is the common release mechanism of neurotransmitters[24]. When an action potential arrives at the nerve terminal, the vesicles stored very close to the plasma membrane are triggered to release their content within a fraction of a millisecond. Membrane depolarization produces an increase in Ca^{2+} permeability in the presynaptic membranes and leads to an influx of Ca^{2+} into the axon terminal through voltage-gated Ca^{2+} channels. By some intracellular signal, the sudden flush of Ca^{2+} triggers exocytosis, causing the secretory vesicles to fuse with the cell membrane and release their contents into the extracellular space. At first, it was thought that the principal role of ATP present in vesicles was associated with the storage and the membrane transport of the transmitter or with the process of vesicular exocytosis[25]. However, the kinetics of release of ATP and the transmitter were shown to be of the same magnitude, suggesting that ATP was likely to be released as a neurotransmitter. As a neurotransmitter, there is no reason to suppose that the mechanism of ATP release should be different from the general mechanism of neurotransmitter release. However, some studies proposed additional problems regarding ATP release: its ubiquitous intracellular presence makes it difficult to determine whether its release is selective via a specific mechanism, or non-selective via cytolysis of cells during experimental damage[26]. There is also the possibility that ATP is released from post-junctional sites as well as neuronal sites[27-29]. Numerous studies have demonstrated the co-release of ATP with noradrenaline, where ATP has been localized in both small and large granular vesicles[30,31], or with acetylcholine[32,33]. However, it is still not certain whether the release occurs from a common vesicle population or from independent populations[34]. Different prejunctional modulation of ATP and noradrenaline release raises the possibility that in addition to a common vesicular pool, an independent releasable pool of vesicular or non-vascular ATP also exists[29].

The release of ATP can be promoted by different stimuli such as neuronal cell membrane depolarization by potassium ions or veratridine[35]. Tetrodotoxin, a toxin which specifically blocks Na^+ channels in excitable tissues and is used to block the propagation of action potentials leading to the release of neurotransmitters from nerve terminals, inhibits the release of ATP[36]. A large number of studies have demonstrated the Ca^{2+}-dependent release of ATP. In cultures enriched in cholinergic amacrine-like neurons, the release of ATP is Ca^{2+}-dependent and sensitive to the botulinum neurotoxin A[37]. However, there are also a few studies that have shown a Ca^{2+}-independent release of ATP. For example, the evoked release of ATP from the synaptosomes prepared from rat brain showed that it was independent of the presence of extracellular calcium[35].

5 Neuroprotective and neurotoxic actions of extracellular ATP

The release of ATP and its consequent binding to P2 receptors may most likely contribute alone, or in combination, to a neuropathological event. ATP is released into the extracellular space, either exocytotically or directly from damaged or dying cells. The purines/pyrimidines may indeed reach high extracellular levels, despite the strict control exerted by ectonucleotidases which try to maintain their low physiological concentrations. Once in the extracellular environment, purines/pyrimidines generally mediated dual effects: short-term such as neurotransmission[5], and long-term such as tropic actions[38]. Besides acting alone as a neurotransmitter, neuromodulator or growth factor, ATP is also often co-released with acetylcholine[39], noradrenaline[40] and GABA[41], depending on the specific transmitter receptors of each neuron. It can therefore interact with other neurotransmitters or growth factors at both receptor- and signal transduction-level, thereby modifying their reciprocal effects.

The release of ATP and the existence of multiple P2 re-

ceptor subtypes, their role in cell differentiation and growth, embryonal development and neurogenesis suggest that extracellular nucleotides indeed play important pathophysiological roles. Extracellular ATP *per se* may be toxic for primary neuronal cultures[42], and P2 receptor can mediate and aggravate toxic signaling in many CNS neurons. Similarly, P2 receptor agonists may directly cause lesions in different brain areas, which are reduced by P2 receptor antagonists[43]. There are also reports of direct participation of extracellular ATP and P2 receptor in ischemia stress in various cellular systems[44]. After ischemia, $P2X_{1,2,4,7}$ and $P2Y_1$ are upregulated in neurons or glial cells in various brain regions, and $P2X_7$ especially, appears to be an important element in the mechanisms of cellular damage. *In vitro* ischemia markedly increased $P2X_7$-mediated GABA release in cerebrocortical cell cultures. This was implied to possibly reduce ischemic damage[45]. Nevertheless, targeted deletion of $P2X_7$ receptor subtype or administration of $P2X_7$ receptor antagonists were not cytoprotective in mice *in vivo*[46]. Conversely, long lasting neuroprotection has been demonstrated in the presence of several P2 receptor antagonists in different toxicity models[42,47,48]. Moreover, complete neuroprotection was obtained in organotypic hippocampal slice cultures after oxygen and glucose deprivation by combined blockade of the NMDA receptors, P2X receptor, and MAPKs[49].

In astrocytes, ATP stimulates the sythesis and release of protein trophic factors, acts in combination with growth factors to stimulate proliferation, and contributes to the process of reactive gliosis, a hypertrophic/hyperplastic reaction which enables the injured brain to restore its functions[38,50]. Moreover, astrocytes can sense the severity of damage to the CNS by detecting a changed ATP concentration via activation of P2 receptor types. For instance, P2Y receptor activation enhanced, whereas P2X receptor activation inhibited tumor necrosis factor α (TNFα) release in lipopolysaccharide (LPS) stimulated astrocytes[51].

In microglia, the immune cells of the CNS, purinergic stimulation also occurs and it[48] is dependent on P2 receptor activations. For instance, at low extracellular concentration (≤100 μmol/L), ATP acts via P2Y receptor and $P2X_{1,6}$ to control calcium mobilization within the physiological range. In the case of injury to neurons, however, due to higher ATP concentration, activation of $P2X_7$ in microglia can lead to a significant increase in intracellular calcium concentration. Then microglia is rapidly mobilized and mediates inflammatory responses initiated at sites of damage[52]. $P2X_4$ and $P2X_7$ have been reported to play a particular role in microglial response to injury[4,53].

In conclusion, extracellular ATP plays a very complex role in the repair, remodeling, survival or even cell death occurring in the nervous system after either normal developmental conditions, or injuries and other acute and chronic diseases. All these characteristics indicate that purinergic activation is an interesting target for pharmacological intervention aimed at reducing secondary cell damage.

6 Conclusions

As described in the present review, an increasing number of pathophysiological actions of purinoceptors in the CNS are emerging: specific ligands for purinoceptors may clarify the therapeutic potential of more of these receptors. Because of the widespread simultaneous distribution of several different P2 receptor subtypes in various cell types and tissues, and the still scarce availability of subtype-specific P2 agonists and antagonists, a clear explanation of the role of individual members of the P2 receptors in health and disease of the CNS is still pending since so far. We can not predict that a single subtype of receptor might be exclusively committed to complex specific pathophysiological functions. The field of purinergic research is expanding significantly and a large number of purinergic ligands and their use for treatment of many pathological conditions as diverse as pain, stroke, trauma and depression have been patented. Moreover, the clinical trials begin to be an important avenue to get new insights into the purinergic research: the extension to the neurodegeneration field is now imminent.

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细胞外 ATP 及其 P2 受体在神经系统疾病中的治疗潜能

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Õª Òª：在中枢神经系统中，胞外 ATP 是一种重要的信号转导分子，目前，它在中枢神经系统中的生理及病理作用已经得到了广泛的关注。ATP可以通过囊泡胞吐形式被相关神经细胞释放到细胞外，也可以因为细胞的损伤被直接释放出来。在细胞外环境中，ATP 可以结合到它的特异性 P2 受体上，从而介导各种作用。P2 受体有 P2X 和 P2Y 两种类型，其中 P2X 型受体是一类配体门控型的离子通道型受体，这类受体对 ATP 的亲和力较低，介导快速神经传递作用；P2Y 型受体是一类与代谢相关的 G 蛋白耦联受体，对 ATP 的亲和力高。由于大规模的 ATP 外释现象一般出现在各类应激、脑缺血、脑损伤之后，因此细胞外 ATP 被认为参与了神经系统疾病的病理过程。但是，大量报道也指出了细胞外ATP的营养功能。因此，可以认为细胞外ATP在中枢神经系统中扮演着非常复杂的角色，结合特异性P2受体后，可以引发有害性或有益性的结果。本综述着重叙述了细胞外ATP作为神经系统疾病治疗靶点的潜能。

关键词：细胞外 ATP；P2 受体；神经系统疾病