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REVIEW ARTICLE

P2X ion channel receptors and inflammation

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Abstract Neuroinflammation limits tissue damage in response to pathogens or injury and promotes repair. There are two stages of inflammation, initiation and resolution. P2X receptors are gaining attention in relation to immunology and inflammation. The P2X7 receptor in particular appears to be an essential immunomodulatory receptor, although P2X1 and P2X4 receptors also appear to be involved. ATP released from damaged or infected cells causes inflammation by release of inflammatory cytokines via P2X7 receptors and acts as a danger signal by occupying upregulated P2X receptors on immune cells to increase immune responses. The purinergic involvement in inflammation is being explored for the development of novel therapeutic strategies.

Keywords ATP · P2X4 receptors · P2X7 receptors · Inflammasome · Cytokines

Introduction

Inflammation involves a complex haemostatic mechanism that enables the body to detect and fight foreign antigens and restore tissue integrity. ATP serves as an acute 'danger signal' and behaves as a mediator of inflammation and immunity [1, 2]. Purinergic signalling contributes to the fine tuning of inflammation and immune responses in such a way that the danger to the host is eliminated efficiently with minimal damage to healthy tissues [3]. Brain inflammation occurs following responses to insults, such as bacterial and viral infection, stroke, traumatic injury, and neurodegenerative disorders. During the course of inflammation, there is upregulation of P2X purinoceptors located on immune cells (neutrophils, eosinophils, monocytes, macrophages, mast cells, and lymphocytes). ATP release from injured cells enhances the inflammatory response through increased synthesis of prostaglandin E_2 (PGE_2) [4] via P2X7 receptors [5]. P2X receptor involvement in inflammation also occurs in irritable bowel syndrome [6, 7], lung injury and fibrosis [8, 9], systemic inflammation [10], arthritis [11], fever [12], and rhinosinusitis [13]. Purinergic signalling in different inflammatory cells involves purinoceptor responses in immune cells (see [14]). Microglia are immune cells in the central nervous system (CNS) [15]. They mediate neuroinflammatory responses to insult in response to a variety of triggers, including toxic metabolites and autoimmunity by detection of pathogens [16]. In addition to microglia, astrocytes as well as perivascular monocytes and macrophages invading to sites of insult from the circulation promote neuroinflammation [17]. Neuronal activity also contributes to inflammation [18]. Activation of P2X7 receptors promotes neuroinflammation by causing the release of inflammatory cytokines, such as interleukin (IL)-1β and tumour necrosis factor-α [19–21]. P2X3 receptors are upregulated in the colonic mucosa of humans with inflammatory bowel disease [22]. There is increased release of ATP from endothelial cells during acute inflammation [23]. ATP triggers cytokine release from inflammatory cells, acts as a chemotactic factor and, after breakdown by ectoenzymes to adenosine, is a potent immunosuppressant [24, 25]. ATP may reach a concentration of several hundred micromoles within the interstitium of inflamed tissues [26, 27]. P2X receptors play a central role in inflammation, particularly the P2X7 receptor. P2X1 receptors

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[28, 29] and P2X4 receptors [30] probably also play a role in inflammation and immunity (Fig. 1).

Multiple inflammatory mediators, including cytokines, chemokines, and prostaglandins, are elevated in the cerebrospinal fluid and in post-mortem brain tissues of patients with a history of neuroinflammatory conditions, as well as neurodegenerative diseases [31]. P2X receptors are involved in immune-related neuroinflammatory dysfunctions, including ischaemia and neurodegenerative diseases (see [32]).

Activation of an inflammasome, a protein complex consisting of caspase-1, apoptosis-associated speck-like protein, and nod-like receptor proteins (NLRP1 or NLRP3) [33] expressed in myeloid immune precursor cells is involved. NLRP inflammasomes are activated by the recognition of pathogens-

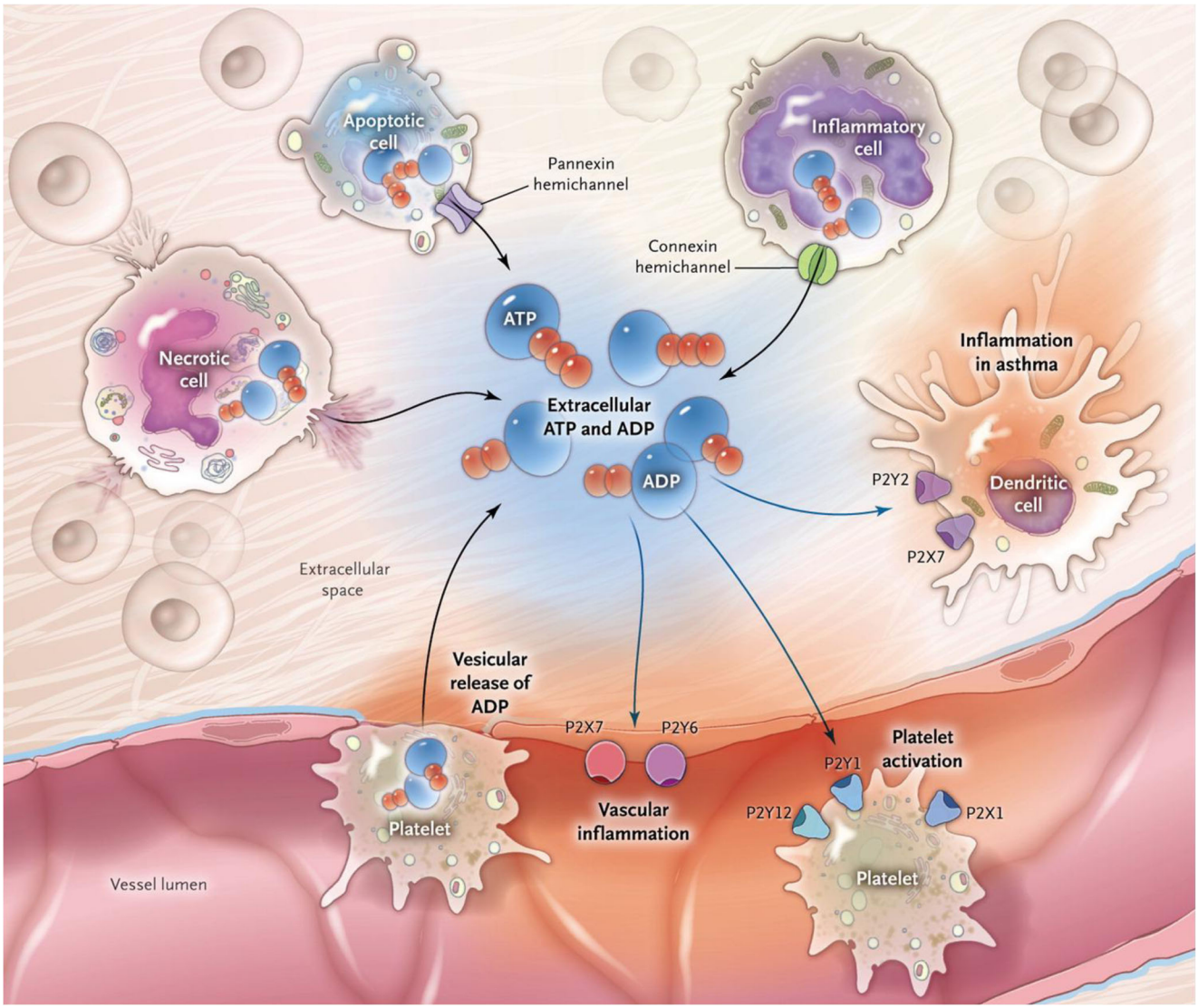

Fig. 1 Release of extracellular adenosine triphosphate (ATP) and adenosine diphosphate (ADP) and activation of ATP (P2) receptors during inflammation. During inflammatory conditions that occur in vascular thrombosis, hypoxia, ischemia, inflammatory bowel disease, and acute lung injury, multiple cell types release nucleotides, typically in the form of ATP or ADP, from the intracellular compartment into the extracellular space. The release of nucleotides includes release of ATP from necrotic cells, pannexin-hemichannel-dependent release of ATP during apoptosis, and release of ATP through connexin hemichannels from activated inflammatory cells such as polymorphonuclear granulocytes (neutrophils). In addition, release of extracellular ATP has been shown to occur through vesicular exocytosis or connexin hemichannels from endothelial and urothelial cells, osteoblasts, and astrocytes, as well as nerves (not shown). An additional source of extracellular nucleotides in inflammatory conditions is provided by activated platelets, which release ATP and ADP through the release of granules and exocytosis. In the extracellular space, these nucleotides function as signalling molecules that can activate P2Y receptors (G protein-coupled receptors) or P2X receptors (ligand-gated ion channels). Examples of nucleotide-receptor signalling in inflammatory conditions include P2Y6- or P2X7-receptor signalling, which mediates vascular inflammation, and P2Y1-, P2X1-, and P2Y12-receptor signalling, which mediate platelet activation. Activation of P2 receptors of the P2Y2 and P2X7 family that are expressed on dendritic cells is thought to play a role in promoting lung inflammation in chronic lung diseases such as asthma (reproduced from [9], with permission from the Massachusetts Medical Society)

associated molecular patterns or damage-associated molecular patterns (DAMPs) [34]. Inflammasomes are involved in P2X7 receptor coupling to IL-1β release [19].

ATP release occurs from damaged cells at the site of injury and from activated immune cells, glial cells, and endothelial cells. ATP release in vivo has also been shown in response to contact allergens [35], irradiation, allograft rejection [36], and intraperitoneal lipopolysaccharide administration [4], as well as mechanical distortion [37, 38]. ATP released during viral infection is an important inflammatory regulator that activates the inflammasome pathway and regulates inflammatory responses [39]. P2X4 receptors were claimed to influence inflammasome activation after spinal cord injury [40]. The secretion of ATP by bacteria infected macrophages leads to activation of P2X7 receptors [41]. Prevention of cell death or ATP release through p38 or AKT activation interfered with inflammasome activation and IL-1β production. Overexpression of P2X7 receptors was reported in the intestinal mucosa of Crohn's (inflammatory) disease patients [42].

Reviews focussing on nucleotide signalling during inflammation are available [14, 43–47].

Inflammation and P2X receptors

Changes in P2X receptor subtype expression in neuroinflammatory conditions in various in vitro and in vivo models have been reported. P2X4 receptors are associated with an early inflammatory mediator, PGE_2 [30]. P2X4 receptors, similar to P2X7, form a large conductance pore on the cell membrane, facilitating ion efflux and subsequent inflammasome activation [5]. The P2X4 receptor may act as an initial trigger, while the P2X7 receptor, in concert with pannexin 1, may amplify the signal [47]. The P2X4 receptor contribution to PGE_2 release in mice is of minor relevance when compared to that of P2X7 receptors [4].

Of the seven P2X subtypes, the P2X7 receptor is the most important for involvement in mediating neuroinflammation [20]. Activation of P2X7 receptors results in DAMP, initiating neuroinflammatory cascades [5]. Further, the formation of the P2X7 receptor pore appears to be necessary for activating the inflammasome [48]. The P2X7 receptor is one of the most potent plasma membrane receptors responsible for the release of inflammatory cytokines of the IL-1 family, IL2, IL6, and IL18 [45, 49, 50]. P2X7 receptor activation is a strong stimulus for IL-18 as well as Il-1β [51, 52] and IL-1α secretion [53]. Microglia are the main source of IL-1β release, but it has also been claimed that IL-1β release from neurons is important [40]. IL-2 synthesis in lymphocytes requires functional P2X receptors [54], probably P2X7 [55, 56]. P2X7 receptors also mediate biglycan-stimulated IL-1β release from mouse macrophages [57]. A P2X7 receptor-P2X4 receptor interaction in the process of IL-1β and IL-18 release has been identified in bone marrow-derived dendritic cells [58]. Smoking contributes to the pro-inflammatory status of perivascular visceral adipose tissue by enhancing the expression and activity of the P2X7 receptor-inflammasome complex [59]. Stimulation of P2X7 receptors drives release of both exosomes and microvesicles from several different cell types relevant to inflammation.

P2X7 receptors are expressed on glial and immune cells of monocyte-macrophage origin and on presynaptic terminals on neurons, with the highest levels on microglia [60–63]. P2X7 receptors, acting via different pathways, play a major role in the promotion as well as in the suppression of inflammation in different pathophysiological conditions ([64, 65] and see [46]). P2X7 receptors mediate transforming growth factor β secretion. P2X7 receptor activation also releases a potent immunosuppressive agent, HLA-G [66, 67] and vascular endothelial growth factor, another major player in inflammation [68]. Another function of P2X7 receptors in inflammation is the activation of transcription factors such as NFkB and NFAT [69, 70]. P2X7 receptor activation opens a cation-specific channel activating several pathways, including the inflammasome, leading to the stress-activated protein kinase pathway that results in apoptosis, and the mitogen-activated protein kinase pathway. Ectonucleotidases control P2X7 receptor function, including the resolution as well as the initial phases of inflammation (see [71]). [^{11}C]-A-740003, a P2X7 receptor antagonist, has been used as a novel tracer of neuroinflammation [72].

P2X7 receptors trigger the activation of the NLRP3 inflammasome, the main intracellular complex involved in the transduction of danger signals and in the initiation of inflammation [73]. The role of the NLRP3 inflammasome in pro-IL-1β processing and pyroptosis places the P2X7 receptor at the centre of cytokine immunology. Since the discovery of the inflammasome [33], whether activation by pathogen- and damage-associated molecular patterns requires a direct, physical, interaction with the scaffold NLR inflammasome proteins has been discussed. Ca^{2+} might be a suitable second messenger responsible for inflammasome activation [39], and this would be consistent with the role of the P2X7 receptor as a trigger of the NLRP3 inflammasome since P2X7 receptor opening drives a large Ca^{2+} influx from the extracellular space.

ATP, the extracellular messenger of cellular injury, accumulates to hundred micromolar levels at sites of injury and inflammation [26, 27]. In the presence of inflammation or stress, there is a fast increase of extracellular ATP to near millimolar levels quickly mediating stimulation of pro-inflammatory pathways [74]. Some P2X7 receptor polymorphisms appear to protect against infection, but others increase the risk of developing chronic inflammatory diseases [75].

Immune cells and inflammation

The participation of P2X receptors in inflammation and immunity is gaining attention probably because of the role played by P2X7 receptors in IL-1β processing and release. All immune cells, whether of the myeloid or lymphoid lineage, express at least one P2X receptor subtype, and many express all seven subtypes [2, 45, 76–81]. Mononuclear phagocytes are the inflammatory cell type where P2X receptor expression has been best characterized [82]. Monocyte/macrophage and myeloid dendritic cells express P2X1, P2X4, and P2X7 receptors [45]. P2X5 receptors are expressed by T lymphocytes. The function of P2X5 receptors in inflammation is not clear. Neutrophils and eosinophils express P2X1, P2X4, and P2X7 receptors, although the level of expression is different in the quiescent or activated state [83–85]. P2X1, P2X4, and P2X7 receptors are expressed on T and B lymphocytes and natural killer cells [45]. ATP released by tissue damage, acts as a danger signal by acting on P2 receptors on immune cells to stimulate the immune response [86]. P2 receptors are present on immune cells and their expression is modulated by inflammatory cytokines [87]. P2X receptors have been implicated in the participation of the immune system in inflammatory pain [88, 89]. P2X1, P2X4, P2X7, and perhaps P2X3 receptors are expressed by mast cells [90, 91]. Mast cells were the cell type in which the properties of the P2X7 receptor were initially observed and characterized by Cockcroft and Gomperts [92]. P2X receptor expression is also present on microglia, both in vitro and in vivo, particularly P2X4 and P2X7 receptors [93, 94]. P2X receptors on mast cells are involved in the pathogenesis of chronic airway allergic inflammation [91].

Inflammatory pain

P2X7 receptors are involved in inflammatory pain [95–99]. There is reduced inflammation-induced hyperalgesia in rats following treatment with oxidized ATP, a P2X7 receptor antagonist [100]. P2X7 receptors play a transductional role in the development of inflammatory pain [101].

A review includes a discussion of the role of P2X3 receptors in inflammatory pain [102]. During the inflammatory process in peripheral tissue, neither prostaglandins nor sympathetic amines can sensitize primary afferent neurons by themselves; they depend on previous neuronal P2X3 receptor activation [103]. Spontaneous and evoked responses of spinal nociceptive neurons are attenuated by P2X3 receptor antagonism in inflamed rats [104]. Data has been presented to indicate that antagonism of spinal P2X3/P2X2/3 receptors regulates an indirect activation of the opioid system to alleviate inflammatory hyperalgesia [105]. P2X4 receptors probably also participate because of their involvement in neuropathic pain [106, 107], which is relevant for inflammation. Mice lacking P2X4 receptors show impaired inflammasome activation [40] and do not develop pain hypersensitivity in response to inflammatory agents, and this is paralleled by a complete absence of PGE_2 in inflammatory exudates [30]. There is also a suggestion that P2X4 receptors might modulate P2X7 receptor activity [56]. P2X7 receptor antagonists reduce inflammatory pain in rats [100, 108–110]. Chronic inflammatory pain was abolished in P2X7 receptor knockout mice [95]. Central sensitization of nociceptive neurons in medullary dorsal horn of rats involves P2X7 receptors [111]. P2X7 receptor antagonism of chronic pain is likely mediated through immunoneural interactions that affect the release of inflammatory cytokines [112]. Inflammatory pain involved in dressing changes of burn patients was relieved by puerarin, an isoflavonoid derived from a Chinese herb [113]. The effects were correlated with the decreased expression of P2X7 receptor mRNA and protein in peripheral blood mononuclear cells in burn patients.

Pathology and inflammation

Purinergic contributions to neuroinflammation in relation to disorders of the CNS are being explored. Pathological neuroinflammation, promoting apoptosis and necrosis, and influencing the synaptic and intrinsic membrane properties of neurons contributes to CNS pathologies [114]. A role for neuroinflammation occurs in neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, stroke, and epilepsy [115]. Neuroinflammation is also a pathological factor in psychiatric mood disorders [116, 117]. The NLRP3 inflammasome is a central mediator of systemic inflammation and a link between psychological stress and the emergence of depression and other psychiatric illnesses [118] and ATP, accumulated following insult, induces NLRP-mediated IL-1β processing [93]. Epidemiological and gene-linking studies have implicated P2X7 in a host of CNS diseases [119, 120]. Neuroimmunological changes occur in psychiatric disorders, including major depressive disorder, bipolar disorder, obsessive compulsive disorder, and schizophrenia. Chronic inflammation associated with diabetes, obesity, or autoimmune diseases increases the risk of psychiatric disorders (see [47]). These disorders are characterized by chronic, low grade, or intermittent inflammation, in contrast to neurodegenerative diseases, where there is acute inflammation in the brain parenchyma. Schizophrenia is considered to be a neurodevelopmental disorder, and foetal neuroinflammation, resulting from maternal infection, is implicated [116]. Enhanced levels of pro-inflammatory cytokines in the brain

and enhanced microglial activation occur in foetal neuroinflammation, leading to abnormal brain maturation.

Associations between susceptibility or resistance to parasites and bacteria and loss- or gain-of-function polymorphisms in the P2X7 receptor indicate that it is important in infectious disease [121]. ATP activation of the NLRP3 inflammasome protects mice against bacterial infection [122]. The P2X7 receptor plays a role in acute and chronic stages of infection as well as a 'danger signal' in the initial stages of inflammation (see [71]).

Therapeutic potential

Purinergic-based therapies may be useful to halt excessive inflammation and promote repair of neuroinflammatory disorders [4, 80, 123, 124].

P2X7 receptor antagonists are promising targets for anti-inflammatory therapy [125, 126], including inflammation in the CNS [11, 95, 100, 127, 128]. In view of its potent pro-inflammatory effect, the analgesic activity of P2X7 receptor blockers is of interest for therapeutic implications [99]. Blockade of P2X7 receptors reduced nociception in animal models of chronic inflammatory pain [96, 125, 129–132]. Relief of inflammatory pain was produced by the P2X7 receptor antagonist, oxidized ATP, in arthritic rats [11]. Blockade by the selective P2X7 receptor antagonist, A-839977, was lost in IL-1αβ knockout mice [133].

P2X3 receptor antagonists have also been suggested to be a therapeutic target for pain therapy [134]. Application of apyrase to CD39-deficient mice prior to ischaemia reduced infarct volumes and neutrophil counts [135, 136]. Kinase inhibitors have been recommended for the treatment of inflammatory and autoimmune disorders, such as rheumatoid arthritis, psoriasis, organ transplantation, and autoimmune diseases [137, 138].

Activation of the purinergic pathway may be implicated in transplantation-related injuries. Following transplantation, ATP, the pro-inflammatory danger signal, is released from damaged cells to promote proliferation of immune cells, T cell activation, and inflammation. Targeting purinoceptors may promote immunosuppression and reduce inflammation. The ectonucleotidases, CD39 and CD73, hydrolyze ATP to the anti-inflammatory mediator adenosine, which suppresses pro-inflammatory cytokine production leading to improved graft survival. The mechanisms of action of several immunosuppressive drugs, such as calcineurin and mTOR inhibitors, involve purinergic signalling. Targeting the purinergic signalling pathway by increasing ectonucleotidase activity and/or boosting short term adenosine-mediated immunosuppression have potential in preventing allograft vascular injury, ameliorating rejection, and promoting tolerance.

Conclusion

P2X receptors mediate the responses to ATP, one of the most ancient evolutionary extracellular messengers (see [139]). ATP is an intracellular molecule, so its release is suited to signal cell distress or injury. This 'danger signal role' of ATP became more and more relevant in multicellular animals. P2X receptors play important roles in pathophysiology (see [140, 141]) and P2X7 receptors, in particular, are vitally involved in inflammation.

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