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Purinoceptors in inflammation: potential as anti-inflammatory therapeutic targets

Maria Elena Ferrero

Department of Human Morphology and Biomedical Sciences, University of the Study of Milan, Milan, Italy

TABLE OF CONTENTS

1. ABSTRACT

Purinergic receptors or purinoceptors are expressed in many mammalian cells and are activated by extracellular purines (adenine, purine nucleotides and nucleosides). Both adenosine (P1) and nucleotide/nucleoside (P2, grouped in P2X and P2Y subtypes) receptors exert important role in the inflammatory processes. The significative up-regulation of many purinoceptors located on the immune cells (neutrophils, eosinophils, monocytes, macrophages, mast cells and lymphocytes) in the course of inflammatory diseases supports the interpretation of their functions. New insights into the involvement of purinoceptors also in the neuro-inflammatory diseases (e.g. conditions of chronic inflammation associated with neurodegenerative diseases) are proposed. The identification of antagonists of purinergic receptors potentially useful to control inflammatory pathways represents the object of many studies reported in the recent literature. Aim of this review is to recapitulate the most recent data and experimental findings that highlight the critical, double edge, effect of these receptors in inflammation, making consistent the possibility to target them to control and regulate inflammation.

2. INTRODUCTION

Extracellular nucleotides released in many tissues, following cell lysis, exocytosis, efflux, cellular stress upon changes in osmolarity and mechanical perturbations, exert their activity by binding to purinergic receptors. The knowledge of the extracellular signalling role for purine compounds (adenine, purine nucleosides and nucleotides) has been developed in many years, as recently reported in an historic overview by Burnstock *et al.* (1). Firstly, extracellular effects of purines were identified both in cardiovascular (2-5) as well as in non-cardiovascular preparations (6, 7); successively, increased evidences of purine effects on the nervous system culminated in the theory of purinergic neurotransmission (1, 8, 9). Further studies have more recently evidenced the role of long-term (trophic) purinergic signalling in cell proliferation, differentiation, motility, and death in development and regeneration (10, 11). Short-term purinergic signalling have been shown implicated in neurotransmission, neuromodulation and neurosecretion (10-12). Moreover, purinergic signal involvements in platelet activation (13, 14), in bone remodelling (15), in the special senses areas (16), in cardiovascular regulation and disease (17) have been described. Purinergic receptor structure and function

has been studied and clarified. Identification of purinoceptors in mammalian tissues as well as their main functional role have been exhaustively reported (1).
In this review, the role of purinoceptors in inflammation is considered and described. Moreover, the possibility to candidate them as possible targets for pharmacologic treatment in inflammatory diseases is proposed and discussed.

3. PURINOCEPTORS

The numerous purinoceptors have been classified into the subtypes P1 and P2 on the basis of pharmacological, biochemical and molecular biological studies (18-20). In several cases, the use of genetic deletion of a single receptor (knock-out mice) has increased the knowledge on the same receptor functions. P1 are adenosine purinoceptors, whereas P2 are purinoceptors for phosphorilated nucleosides (as ADP, ATP) and other related nucleotides. P2 receptors have been further on grouped in ionotropic P2X and metabotropic P2Y subtypes (21).

3.1. Adenosine receptors (P1)

Four subtypes of adenosine receptors are described and characterized: A1, A2A, A2B and A3. They are members of the heterodimeric guanine nucleotide-binding protein (G protein) coupled receptors (GPCR) family A. Since adenosine receptors are widespread throughout the body, they are involved in a variety of physiological processes and pathology including neurological, cardiovascular, inflammatory diseases and cancer (22). Primary sequence and covalent modifications of adenosine receptors, overall three-dimensional structure and comparison to other GPCR, have been recently reviewed (23). In particular, the crystallographic model of the human adenosine A2A receptor could provide new insight to elucidate the relation between structure and function of the adenosine class of GPCR. Each adenosine receptor subtype has revealed a unique binding profile, activation profile, subcellular localization and G protein binding preference. A1 and A2A adenosine receptors have displayed specific physiological role in regulating heart rate, body temperature, locomotor activity, oxygen consumption in mice, in a sex-dependent manner (24). In addition, being adenosine involved in the regulation of digestive functions, A1 and A2A receptors were demonstrated efficient in mediating inhibitory effects of adenosine on the activity of human colon (25). A1, A2A and A2B adenosine receptors activity was shown inhibited by naturally occurring methylxanthines such as caffeine or theophylline (26). The omnipresence of adenosine and A1 and A2A receptors in all nervous system cells (neurons and glia) have suggested their implication in the homeostatic co-ordination of brain function (27). However, much evidence argued for a role of the A1, A2A, A3 adenosine receptors in neurological diseases as Alzheimer's disease, Lesch-Nyhan syndrome, Creutzfeldt-Jakob disease, Huntington's disease, multiple sclerosis, Parkinson's disease (28). A particular role for A2B adenosine receptors has been assigned in regulating platelet function (29) and in damping mucosal inflammation and tissue injury during intestinal ischemia or experimental colitis (30). Finally, A3 receptors, together with A1 receptors, have been shown able to protect astrocytes from hypoxic damage (31), whereas A3 receptor inhibition improved the efficacy of hypertonic saline resuscitation in a mouse sepsis model (32).

3.2. P2 purinoceptors

They have been subdivided in two families (33): 1) P2X purinoceptor subtypes, which are ion channels, and 2) P2Y purinoceptor subtypes, which are G protein-coupled receptors.

3.3. P2X receptors (P2XR)

Seven subtypes of these ATP-gated membrane ion channels have been identified. The recent elaboration of the crystal structure of the zebrafish P2X4 receptor by Gouaux *et al.* (34) has allowed the re-interpretation of channel function at molecular levels and could provide a basis for the structure-based design and study of pharmacological agents (35).The major physiological functions of P2XR are here summarized.

P2X1R: control contraction of the vas deferens and male fertility (36), provide renal microvascular autoregulation (37), promote neutrophil chemotaxis (38), regulate T cell activation in immune synapse (together with P2X4 and pannexin-1 hemichannel-mediated ATP release) (39), modulate heteromeric P2X1/5 receptors by phosphoinositides in astrocytes through the P2X1 lipid-binding domain (40), mediate sympathetic control and paracrine regulation of renal blood flow of renal vascular smooth muscle cell (together with the heteromeric P2X1/4 receptors) (41).

P2X2R: contribute to fast synaptic excitation in myenteric neurons of the mouse small intestine (42), have a role in chemosensory signalling in rat carotid body afferent neurones (together with P2X3R subunits) (43), mediate ventilatory responses to hypoxia (44), are crucial for taste responses in the taste nerves (45).

P2X3R: regulate urinary bladder reflex (46) and peristalsis in the small intestine in mice (47) P2X4R: potentiate hyppocampal synapsis (48) and control vascular tone and remodelling due to impaired flow (49).

P2X5R: their extensive expression within the central nervous system of the mouse suggest the role for extracellular ATP as a fast neurotransmitter; in particular they form together with the P2X1R the functional P2XR in mouse cortical astrocytes (50); moreover, activation of P2X5R expressed on satellite cells regulate the ATP-dependent differentiation of mammalian skeletal muscle (51).

P2X6R: are important, together with P2X3R and P2X5R, for the modulation of amacrine cells in mouse retina (52); are expressed and may be involved in the physiological function of the enteric neurons in the rat gastrointestinal tract probably in heteromeric combination with P2X2R (53); finally are involved (together with

P2X2R) in neuronal differentiation in mitogen-free cultured rat neurospheres (54).

P2X7R: are important in cytokine release (55), in bone remodelling (56), in glia-neuron interactions (57); are involved in short-term physiological regulation of exocrine gland secretion (58). P2XR are also implicated in many physio-pathologic or pathologic conditions, as thrombosis (P2X1R) (59); inflammatory and neuropathic pain: P2X2R and P2X3R (60), P2X4R (60), P2X7R (61, 62); inflammation and renal fibrosis (63); disorders of the central nervous system (P2X4R, P2X7R) (64).

3.4. P2Y receptors

Eight subtypes of these receptors have currently been identified. They exhibit sensitivity to adenine nucleotides ATP and ADP (P2Y1R, P2Y11R, P2Y12R, P2Y13R), to uracil nucleotides UTP and UDP (P2Y2R, P2Y4R, P2Y6R) or to UDP-glucose (P2Y14R) or to both adenine and uracil nucleotides (P2Y2R) (65). Many roles have been attributed to P2YR in physiological and patho-physiological processes. For example, an antihypertensive activity has been shown for P2Y2R through regulation of renal transport mechanisms (66). Both P2Y1R and P2Y12R are rapidly and reversibly modulated in human platelets following ADP activation (67) and antagonism of P2Y12R exerts antiplatelet activity, as obtained by the use of clopidogrel and prasugrel (68). P2Y12R are also involved in inflammatory and neuropathic pain (69), P2Y4R in chronic pain (70), as well as in cancer because a P2Y2R-dependent pathway has been demonstrated able to induce reactive oxygen species production, resulting in increased tumor growth (71). It is likely that different receptors have distinct roles in cell physiology and pathology. Accumulating evidence suggests that extracellular nucleotides, depending on their concentration, activate and signal through distinct receptors, triggering cellular changes that modulate cell function. The activation pathway is so far poorly identified, but activation of such receptors elevates cytosolic Ca^{2+} concentration [Ca^{2+}] (i).

4.PURINERGIC SIGNALLING AND INFLAMMATION

In this section general considerations about the involvement of different purinergic signalling in inflammation are reported.

4.1. Adenosine and inflammation

Extracellular adenosine can signal through each adenosine receptor (AR): A1AR, A2AAR, A2BAR and A3AR. Expression of AR is under dynamic regulation in many cell types (platelets, lymphocytes, eosinophils, neutrophils, mast-cells and macrophages) during many forms of physiological and pathological stress including inflammation (72). Stimulation of A1AR provokes pro-inflammatory effects, whereas stimulation of A2AAR and A3AR has anti-inflammatory effects; in particular, the usefulness of A3AR up-regulation in the treatment of patients affected by rheumatoid arthritis has suggested this receptor as a therapeutic target (72). Stimulation of A2BAR favours the release of pro-inflammatory cytokines and cell degranulation, but this receptor is endowed also of anti-inflammatory properties. Recently, extracellular adenosine has been implicated as anti-inflammatory signalling molecule during lipopolysaccharide (LPS)-induced acute lung injury in mice. The main source of extracellular adenosine is the coordinated two-step enzymatic conversion of nucleotides via the ectopyrase (CD39) and the ecto-5'-nucleotidase (CD73): their expression on the pulmonary tissues and neutrophils after LPS exposure attenuated pulmonary neutrophil accumulation, suggesting the role for adenosine in reducing LPS-induced inflammation (73). However, a detrimental role of elevated adenosine levels in studies investigating chronic pulmonary diseases has been previously described (74, 75).

4.2. A1AR involvement in inflammation

AR are differently involved in the inflammatory processes.evertheless selective A1AR antagonists targeting renal microcirculation represent novel pharmacologic agents that are currently under development for the treatment of acute and chronic heart failure, hepatorenal syndrome, hypotension on dialysis and nephropathy due to radiocontrast use (76), emerging studies evidence the role of A1AR in inflammation. In an allergic mouse model of asthma, A1AR have been shown responsible for altered vascular reactivity, increased airway hyper-responsiveness and systemic inflammation (77). A1AR have been shown able to regulate neutrophil trafficking and microvascular permeability in LPS-induced lung injury (78), confirming the involvement of adenosine in LPS-induced acute lung injury (73). Antinociceptive properties of the neuromodulator adenosine have been shown, through activation of A1AR. Such activation was responsible for the long lasting antinociceptive effects due to treatment of mice with recombinant CD73 (which induced hydrolysis of AMP to adenosine, followed by A1AR activation) in experimental models of both inflammatory and neuropathic pain (79). Noteworthy, A1AR expression mediated local antinociceptive effects of acupuncture, the procedure commonly used to relieve pain (80).

4.3. A2AAR involvement in inflammation

Both A1AR and A2AAR are involved in neuro-inflammatory processes. They have been shown able to regulate the pre-synaptic release of glutamate, whose extracellular increase has been associated with chronic neuro-inflammation. Indeed, consumption of caffeine, which is an antagonist of A1AR and A2AAR, reduced the risk of Alzheimer's and Parkinson's diseases. It has been shown that adenosine exerts a role in the propagation of inflammation and caffeine may reduce microglia activation directly by blocking adenosine receptor on microglia: e.g. caffeine attenuated the number of activated microglia within the hippocampus of rats affected by LPS-induced and age-related inflammation (81). Inosine also, an endogenous purine which is the first metabolite of adenosine in a reaction catalyzed by adenosine deaminase, has been shown able to reduce pain-related behaviour in mice by acting on A1AR and A2AAR as well as through blockade of the protein kinase C pathways (82). A2AAR alone have been shown able to modulate neuro-inflammation and traumatic brain injury upon influence of

glutamate levels in cultured microglial cells (83). Moreover, the deficiency of A2AAR in leukocytes enhanced their homing ability and increased the formation of the arterial neointima after injury (84). Induction of A2AAR on iNKT (invariant natural killer T cells) and NK cells reduced pulmonary inflammation and injury in mice with sickle cell disease (85). Interestingly, DNA methylation regulated A2AAR gene transcription and, subsequently, A2AAR constitutive cell surface expression levels (86).

4.4. A2BAR involvement in inflammation

Adenosine has been proposed as a "stopping" signal for the immune response during excessive inflammatory conditions affecting not only the pathogens but also the infected or neighboring tissues (87). Among AR, only A2BAR appear up-regulated during hypoxia (88), because contain the hypoxia inducible factor (HIF-1α) binding site in its promoter region (89). Indeed, A2BAR may play a key role in response to extracellular adenosine under hypoxic conditions, whereas A2AAR may regulate the response during inflammation in the absence of hypoxia. The infection induced with intracellular bacteria as *Chlamydia trachomatis* in cervical epithelial cells (HeLa cells) was reversibly retarded by prolonged exposure of infected cells to extracellular adenosine. This effect was mediated by the A2BAR and was dependent on an increase in the intracellular cAMP levels, but was independent of cAMP-dependent protein kinase (PKA) (90). Cultured endothelia or epithelia exposed to inflammatory mediators showed time-dependent induction of the A2BAR. Analogously, *in vivo* studies in mice bearing endotoxic-induced lung injury promoted induction of A2BAR transcript. Moreover, functional studies of LPS-induced murine lung injury demonstrated that pharmacological inhibition or genetic deletion of the A2BAR was associated with dramatic increase in lung inflammation and histologic tissue injury (91). These studies suggest that A2BAR are potential therapeutic target in the treatment of endotoxin-induced forms of acute lung injury. Other studies have shown that A2BAR protect against mortality and inflammatory response of mice following polymicrobial sepsis (92). Finally, taking into account that the atherosclerosis process is a chronic inflammation, it seems to be important to highlight the role for A2BAR in regulating platelet function. Recently, it has been demonstrated that platelet A2BAR are up-regulated under stress *in vivo*, play a significant role in regulating ADP receptor expression and inhibit agonist-induced platelet aggregation (29).

4.5. A3AR involvement in inflammation

Following the identification of the trimeric G-protein Gi3 as the cellular target of basic secretagogues that activate mast cell independently of IgE-receptors, it has been shown that, coupling with Gi3, the A3AR stimulate multiple signalling pathways in human mast cells. Such stimulation could lead to up-regulation of cytokines, chemokines and growth factors. Stimulation induced by direct binding to A3AR could be mediated also by contact with T cell membranes (93). In addition, selective activation on neutrophils of A3AR inhibited superoxide production and chemotaxis (the movement of cells toward chemical gradients) of these cells: indeed, the suppression of neutrophil function was mediated by the inhibition of the monomeric GTPase Rac (94). Furthermore, the antiapoptotic effects exerted by glucocorticoids in monocytes, resulting in differentiation to an anti-inflammatory phenotype, was shown as promoted by stimulation of A3AR (95). Simultaneous activation of A2AAR and A3AR ameliorated chronic experimental colitis (96), whereas selective activation of A1AR, A2AAR and A3AR provided significant protection against lung ischemia-reperfusion injury, via the reduction of TNF-α and decreased neutrophil sequestration (97). A role for A3AR has been shown for eosinophil degranulation in a n model of mouse pulmonary inflammation and fibrosis (98), whereas attenuation of pulmonary inflammation in A2BAR knockout mice has been described (99).

4.6. P2 receptors and inflammation

Many P2 receptors (P2R) are involved in the course of inflammatory processes. The leukocyte chemotaxis plays an essential role in generating and delivering immune responses and is a critical component of inflammation. Recent investigations have shown that macrophages move in a gradient of the chemoattractant complement fraction C5a through the release of ATP and autocrine "purinergic feedback loops" that involve receptors for ATP (P2Y2R), for ADP (P2Y12R) and adenosine (A2AAR, A2BAR an A3AR). The inhibition of purinergic receptors as well as degradation of ATP and ADP induced by apyrase were able to block chemotaxis (100). Interestingly, the uptake of apoptotic bodies derived from dying cells (phagocytosis) by macrophages and clearance of such bodies seem to be modulated by purinergic receptor agonists. In fact ATP, ADP, alpha, beta-methylene ATP, 3'-O-(4-benzoyl) benzoyl ATP, UTP and UDP increased macrophage phagocytosis, which was inhibited by pre-treatment with some P2 receptor antagonists. These data have suggested that engagement of the P2X1R or P2X3R by extracellular nucleotides released from dying cells increased the ability of macrophages to bind apoptotic bodies, thus enhancing their capacity to internalize and present antigens (101). In a rat model of systemic inflammation provoked by LPS-induced septic shock, pre-treatment with an inhibitor of the ADP receptors (the clopidogrel, able to inhibit platelet function) reduced the levels of inflammatory markers as interleukin-6 (IL-6) and TNF-alpha and the signs of inflammation at the levels of lung and other tissues (102).

The recent studies on the inflammasome have highlighted the role of P2X receptors. The inflammasome is a multpiprotein complex that mediates the activation of caspase-1, which promotes secretion of the pro-inflammatory cytokines IL-1-beta and IL-18, as well as "pyroptosis", a form of cell death induced by bacterial pathogens. Members of the NOD (nucleotide binding and oligomerization domain)-like receptor (NLRP) family are critical components of inflammasome that link microbial and endogenous "danger" signals to caspase-1 activation (103). Several diseases are associated with dysregulated activation of caspase-1 and secretion of IL-1-beta. The

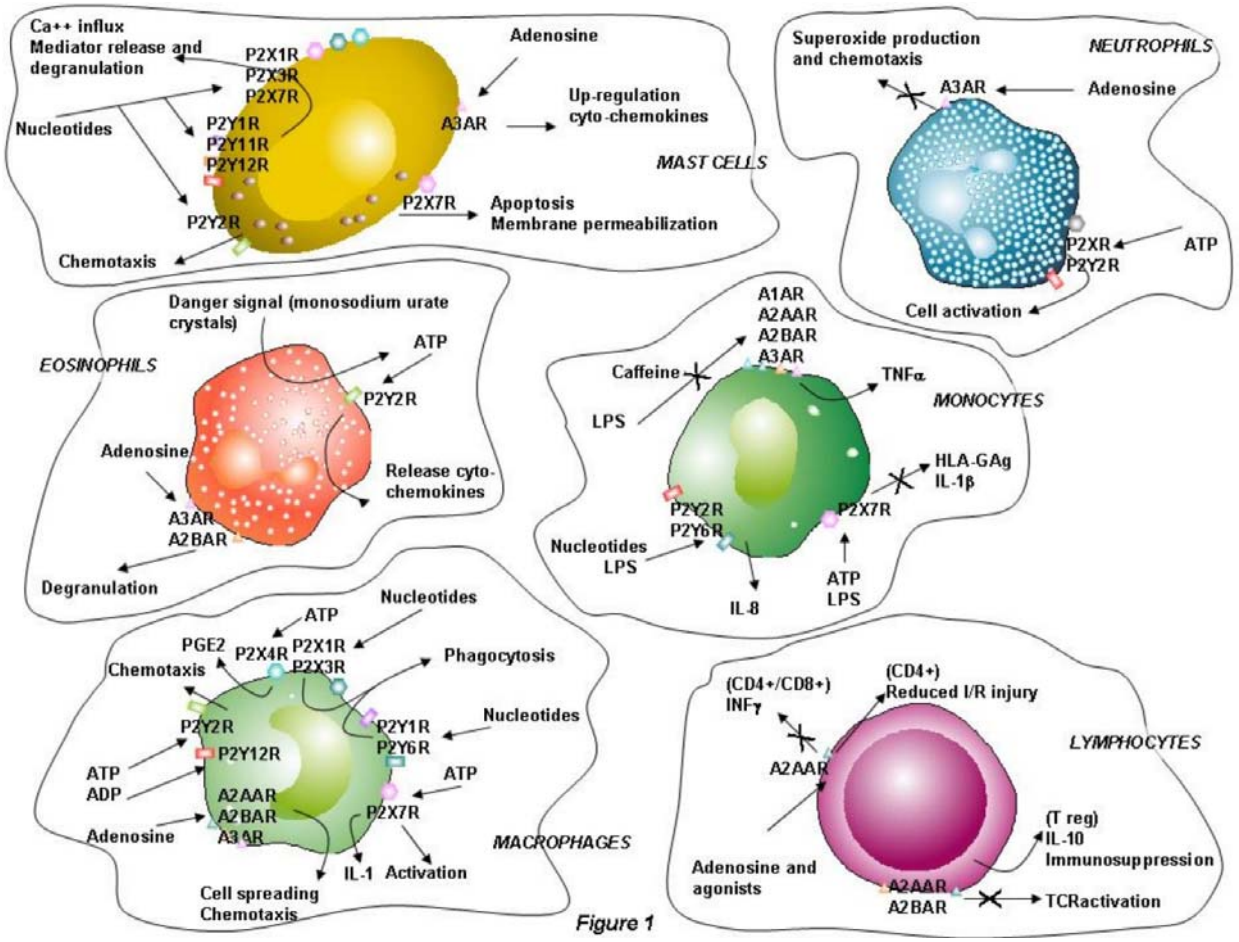

Figure 1. Immune cell function mediated by purinoceptors. The main purinoceptors expressed on each immune cell are reported. Activation or inhibition of cells and induction of main effector functions, following binding of receptor agonists, are represented. Abbreviations: AR=adenosine receptors; P2XR and P2YR= P2X and P2Y receptors; TNF-alpha=tumor necrosis factor alpha; IL-1 b=Interleukin 1-beta; HLA-G Ag=HLA-G Antigens; I/R= ischemia/reperfusion; T reg=T regulatory cells, PGE2=prostaglandin E2. References: (1, 101) (mast cells); (94, 107) (neutrophils); (98, 99, 110) (eosinophils); (1, 111-114) (monocytes); (100, 101, 104-106, 116, 117) (macrophages); (118-122) (lymphocytes). =Activation; X=inhibition

danger signal byglican (a ubiquitous leucine-rich repeat proteoglycan of the extracellular matrix) has been shown effective in activating the NLRP3 inflammasome via Toll-like receptors and P2X4/P2X7R on macrophages (104), suggesting a new attractive role for P2XR. Moreover, the ATP-dependent activation of P2X7R has been demonstrated useful to trigger the elimination of *Toxoplasma gondii* from infected macrophages through ROS production (105). In addition, P2X4R have been shown able to mediate prostaglandin E2 release by resident macrophages of inflamed tissues and initiate inflammatory pain (106). Thus both P2X7R and P2X4R might represent useful therapeutic targets in the immune/inflammatory responses.

5. PURINOCEPTORS ON IMMUNE CELLS

The immune cells responsible for inflammatory reactions display both adenosine and P2 receptors, which have a role in cell activation and effector functions. This section reports specifically the role of purinergic receptors on each immune cell involved in inflammation. Indeed, the main purinergic receptors responsible for activation or inhibition of the immune/inflammatory cells are reported and summarized in the Figure 1.

5.1. Mast cells

They are recognized as the key components of allergic inflammatory reactions, but are also implicated in the pathogenesis of chronic inflammatory diseases, in wound healing, in fibrosis, thrombosis/fibrinolysis and in innate immunity. The involvement of A3AR has been previously reported (93). Many different P2 receptor subtypes are expressed on mast cells, depending of the distinct species (human, mouse or rat) and sources (different anatomic site) of the cells (107). The main P2 receptor-mediated responses of mast cells are: membrane permeabilization and Ca^{2+} influx mainly via P2X7R,

degranulation via P2X7R, P2Y1R and P2Y2R, intracellular signalling via P2X1R, P2X3R, P2X7R, P2Y1R and P2Y12R, cytokine/chemokine expression and secretion via P2X1R, P2X3R, P2X7R, P2Y1R, P2Y11R and P2Y12R, chemotaxis via P2Y2R receptors and apoptosis via P2X7R receptors (107).

5.2. Neutrophils

The involvement of A3AR has been above reported (94). Neutrophils are recently been shown able to release ATP in response to exogenous stimuli such as formylated bacterial peptides and inflammatory mediators as IL-8, C5a complement, leukotriene B4. Specifically, stimulation of the formyl peptide receptor led to ATP release through pannexin-1 hemichannels (responsible for rise in cytosolic calcium); formyl peptide receptors colocalized with P2Y2R (the most abundant in human neutrophils) on the cell surface to form a purinergic signalling system that facilitated neutrophil activation (108, 109).

5.3. Eosinophils

The role of A3AR has been above reported (98, 99). Eosinophils incubated with the endogenous danger signal crystalline uric acid released ATP. The latter acted in autocrine manner via P2 receptors (in particular P2Y2R) to stimulate production of cyto-/chemokines by eosinophils (110).

5.4. Monocytes

Other than in isolated human and murine, also in equine peripheral blood monocytes, LPS and TNF-alpha up-regulated the expression and functional activity of A2AAR (111). Moreover, adenosine receptors are involved in the caffeine modulation of TNF-alpha production by cord blood monocytes (112). Extracellular ATP, acting via the P2X7R, impaired the expression and secretion of HLA-G Antigens (which are currently defined as nonclassical HLA class Ib molecules) in human monocytes in an IL-10-dependent fashion (113). Concomitant activation of P2Y2R and P2Y6R on monocytes have been shown required for IL-8-dependent neutrophil migration (114). Recently it has been proposed the contribution of P2YR to immunocytes microglia activation and their late phagocytosis in the central nervous system (115).

5.5. Macrophages

As reported above, it has been shown that autocrine purinergic receptor signalling is essential for macrophage chemotaxis (100) and that purinergic receptor agonists modulate phagocytosis and clearance of apoptotic cells in macrophages (101). The macrophage activation via P2X7R has been demonstrated: indeed, millimolar ATP was able to induce macrophage death in a concentration dependent manner but the anthraquinone emodin inhibited such death by antagonizing P2X7R (116). The P2X7R-mediated killing of the intracellular parasite *Toxoplasma gondii* has been shown both in human and murine macrophages (105, 117).

5.6. Lymphocytes

A2AAR activation on CD4+ lymphocytes (other than on neutrophils) has been demonstrated able to attenuate lung ischemia reperfusion injury (118). Moreover, A2AAR activation on CD4+ and CD8+ cells has been determined expansion of cells lacking effector functions (119). Signaling via A2AAR and A2BAR on CD8+ cells resulted in inhibition of TCR (T cell receptor)-triggered activation and of many effector functions. Specifically, hypoxia inducible factor 1(HIF-1) and A2AAR in T effector cells not only inhibited the TCR-induced production of pro-inflammatory cytokines, as INF-gamma, but also re-directed the inflammatory repertoire of the T effector cell produced cytokines toward an anti-inflammatory repertoire. Specifically, maximal immunosuppression and re-direction of immune response have shown to be possible in T regulatory cells only if the TCR-triggered activities were combined with and/or enhanced by the HIF-1-driven and adenosine receptor-mediated immunosuppressive mechanisms (120). P2X1R, P2X2R, P2X4R and P2X7R have been identified on B lymphocytes, but their significance deserves further investigations (121). In addition, the P2X7R involvement in *Trypanosoma cruzi* infection through the induction of CD4+/CD8+ double positive cells in thymus has been proposed (122).

6.THE SPECIFIC ROLE OF PURINERGIC RECEPTORS IN NEURO-INFLAMMATION AND PAIN

It is known that inflammation and immunity have a key role in a vast range of central nervous system diseases. Signals endogenous to the nervous system, as extracellular nucleotides and nucleosides released upon injury, have been identified to be responsible for initiating neuro-inflammation by acting on purinergic receptors: the latter are expressed on neurons, oligodendrocytes and on the two types of glial cells involved in inflammatory reactions (microglia and astrocytes). Indeed, purinergic signals severely affect neuro-inflammation (115, 123, 124). Modulation of ischemic brain injury and neuro-inflammation by A2AAR has been described as well as a novel role for glutamate in the modulation of neuro-inflammation and traumatic brain injury by the same receptors (83, 125). The role of caffeine and other A2AAR antagonists in attenuating LPS-induced neuro-inflammation in rats has confirmed these data (81, 126). The molecular pathway in mouse and human microglia responsible of converting ATP-driven process of extension into a process of retraction during inflammation has been reported: such chemotactic reversal was driven by concomitant A2AAR up-regulation and P2Y12R down-regulation (127). Some P2 receptors (P2X4R, P2X7R, P2Y6R) localized on microglia have been shown up-regulated in mouse models of amyotrophic lateral sclerosis, indicating the pro-inflammatory action of such receptors (128). In particular, P2XR, have been recognized to affect neuronal cell death through their ability to regulate the processing and release of IL-1-beta, a key mediator in neuro-degeneration, other than in chronic inflammation and chronic pain (129). Interestingly, P2X7R over-expression was associated to microglial activation and proliferation (130). In addition, the neuronal soma-satellite glial cell interactions in sensory ganglia have suggested the participation of purinergic

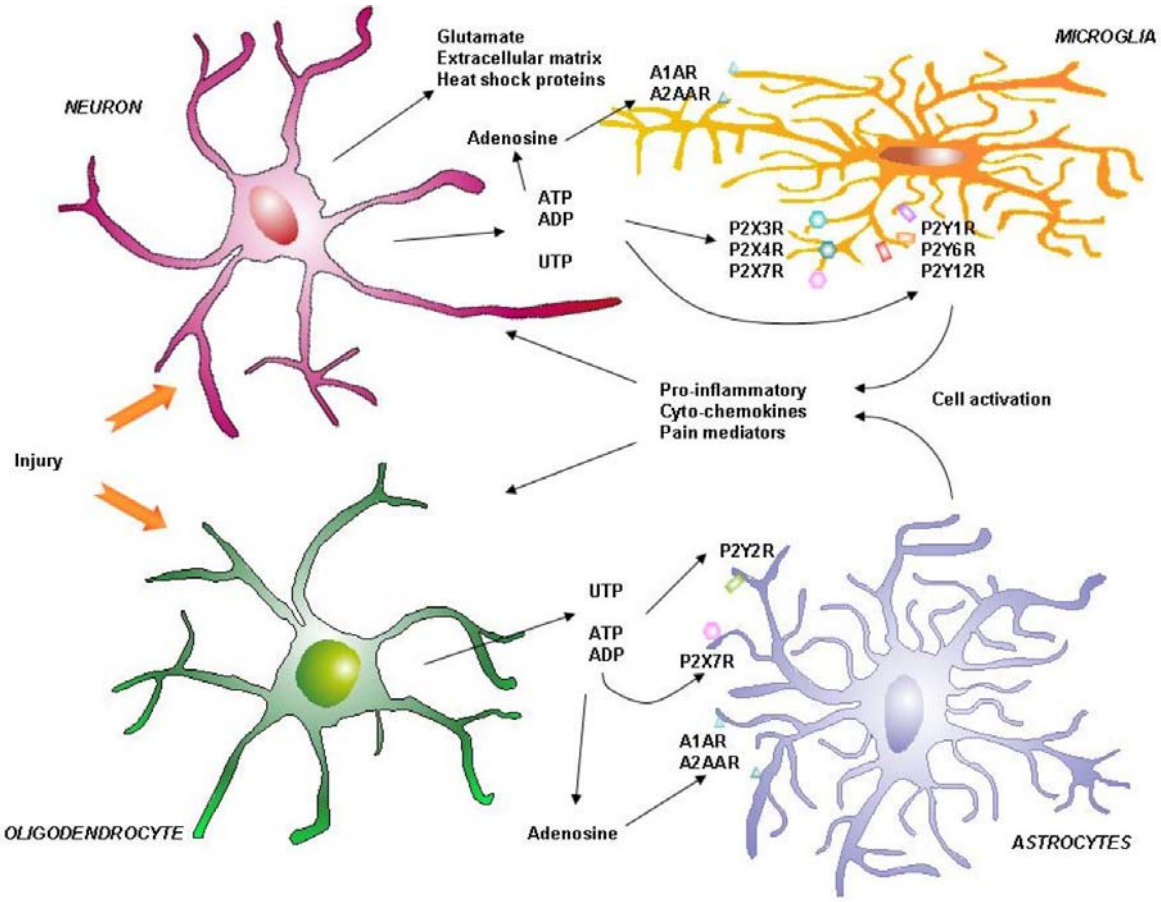

Figure 2. Inflammatory network in the central nervous system via purinoceptors. A schematic representation of the main cell interactions in the central nervous system, following damage to neurons, and involving purinergic receptors, is reported. Damage (injury) to neural cells can activate the release of mediators from the same cells. Released nucleotides provokes activation via purinoceptors of astrocytes and microglia, which produce cyto-chemokines able to re-activate neural cells. Abbreviations: AR=adenosine receptors; P2XR and P2YR=P2X and P2Y receptors

receptors in these intracellular communications (131). Finally, an involvement of P2Y1R (132) and P2Y12R (133) over than of P2X4R, P2X7R, and P2Y6R have been proposed in microglial activation. A particular role for P2X7R and P2YR have been shown in the inflammatory pathways in astrocytes (134, 135). Chemotaxis through P2Y12 receptors of microglia as well as phagocytosis through P2Y6R, following nucleotide release from damaged neurons, have been reported (136).

Since pain represents an important component in the inflammatory processes, a brief relief on pain transmission mediation by purinergic receptors may be useful. Purinoceptors have been identified in central (neurones, astroglia, oligodendroglia and microglia) and peripheral nervous system (sensory, sympathetic, parasympathetic, enteric neurones) (1). P2XR and P2YR have been described not only on sensory neurons but also on their peripheral and central terminals in dorsal root, nodose, trigeminal, petrosal, retinal and enteric ganglia. During inflammatory processes, ATP released from damaged cells and from sensory nerves of inflamed tissues is able to stimulate purinergic receptors of nociceptive neurons, thus initiating a nociceptive signalling. Indeed, purinergic mechanisms are enhanced in inflammatory conditions. Several works have highlighted the contribution of both adenosine receptors (69, 80), and P2XR or P2YR to pain transmission (70, 137-140) both in central and peripheral nervous system.

The main cell activations in the central nervous system, mediated by purinergic receptors, are schematically reported in the Figure 2. It is noteworthy that some cyto-chemokines released from the glial cells could be able to further activate neurons and oligodendrocytes which are also endowed of purinergic receptors. In the context of identification of P2XR expression on nociceptive neurons and on their peripheral terminals, we hypothesized some years ago the role of such receptors in the inflammatory pain transmission. Our studies have focused on the role of extracellular ATP interaction with P2X7R, able to mediate ATP cytolytic activity on macrophages: for this, we have tested the relief of inflammatory pain induced by the P2X7R inhibitor periodated oxidized ATP (oATP),

showing that oATP inhibited inflammatory pain in arthritic rats through the inhibition of P2X7R expression on peripheral nerves as well as on endothelial cells (141, 142). Moreover, we demonstrated that local, oral and intravenous administration of a single dose of oATP reduced thermal hyperalgesia in inflamed hind paws of rats and that, following oATP treatment, the expression of some pro-inflammatory cytokines within the inflamed tissues markedly decreased on vessels and inflamed cells, associated with an impairment in P2X7 expression (143). The anti-hyperalgesic effect of oATP was also demonstrated in mouse models of visceral and neuropathic pain (144). Accordingly, others showed the efficacy of oATP treatment in preventing ATP excitotoxicity in oligodendrocytes, that resulted in improvement of experimental autoimmune encephalomyelitis (145). More recently, the anti-hyperalgesic effects of P2X7R blockade by a selective antagonist, in an inflammatory pain model in mice, has been shown mediated by blocking the release of IL-1-beta (146).

7 PURINERGIC RECEPTOR ANTAGONISTS: THEIR ROLE IN INFLAMMATORY DISEASES

The expression of many purinergic receptors on immune/inflammatory cells and their implications in immune/inflammatory reactions have emphasized the research of compounds able to antagonize or specifically block the involved receptors. For instance, due to the documented role of adenosine receptor subtypes in a number of the characteristic features of asthma, new molecules with high affinity and high selectivity for such human receptors designed to control the airway inflammatory component of asthma have been developed and currently tested in clinical trials (147, 148). Concomitantly, some A2AAR antagonists as caffeine were shown able to diminish adenosine-mediated immunosuppression, thus increasing inflammatory tissue damage secondary to enhanced immunity, but to enhance the immunomodulatory pathway useful to prevent inflammatory tissue destruction (149). Neuroprotection against inflammatory neurotoxicity and neurodegeneration associated with neuro-inflammation has been induced by caffeine and A2AAR antagonists in animal models of Parkinson's disease (150). Accordingly, chronic caffeine consumption prevented memory disturbance in different animal models of memory decline mimicking Alzheimer's disease (151).

Extracellular ATP is the most known agonist of P2 receptors and can induce inflammation by binding to them and acting as a "danger signal". It has been recently demonstrated that endogenous ATP contributed to smoke-induced lung inflammation and then development of emphysema in mice via the purinergic receptor subtypes, such as P2Y2R (152). Recently, an interesting pathogenetic mechanism of chronic obstructive pulmonary disease (COPD) ATP-mediated has been reported (153). Based on this proposed model, cigarette smoke could activate lung and bronchial epithelial cells to produce chemokines able to recruit neutrophils to the lung tissue; cigarette smoke could also induce neutrophils to release ATP which, acting mainly through P2X7R, activates inflammasome pathway in epithelial cells and macrophages, favouring the release of IL-1-beta, thereby inducing chronic stages of the disease. Involvement of both P2X and P2Y purinergic signalling in pain, has also increased the literature regarding current developments of compounds for the therapeutic treatment of pain, including inflammatory pain (69, 154, 155).

A recent review reports the new patented compounds able to bind each P2XR (P2X1R-to P2X7R) which could be attractive targets for novel therapeutics in areas comprising chronic inflammation and pain (156). However, among the receptor antagonists proposed as useful to reduce inflammation, the most studied and evaluated for clinical and research purposes seem to be the P2X7 receptor antagonists. In particular, the arise of inflammation in the central nervous system from a number of neurodegenerative disorders and tumors, as well as from ischemic and traumatic brain injury, mediated by the release of extracellular adenine nucleotides activating P2X7 receptors, has highlighted the interest in compounds able to reduce neuronal cell death by inhibiting the inflammation. Indeed, recent patents on P2X7R antagonists and their potential for reducing central nervous system inflammation have been published (157, 158). The results regarding the P2X7R antagonists overcome the data related to the inflammation "in se". In fact, ischemic damages causing oligodendrocyte death, myelin disruption and axon dysfunction mediated by P2X7R activated by ATP released during ischemia has permit to propose such receptors as therapeutic target to limit tissue damage in cerebrovascular diseases (159). Moreover, the identification of P2X7R expression in neuroblastoma cells, in which the receptor-mediated Ca^{++} signal appeared important in maintaining cellular viability and growth, has encouraged the development of P2X7 selective antagonists to treat neuroblastoma (160). A recent review has focused the role of oATP in the treatment of some experimental models of inflammatory/immune diseases, reporting also patents related to the proposed effects of oATP in such diseases (161). The recent progress in the development of adenosine receptor ligands as anti-inflammatory drugs has been previously reported (162). The above cited reviews (156, 157, 161) exhaustively report the recently patented compounds antagonists of each P2XR subtype and in particular of P2X7R.

8 CONCLUSION AND PERSPECTIVE

Extracellular nucleotides are important players in regulating inflammatory response through the binding to purinergic receptors. The activation of such receptors plays many roles in various pathologic processes. In particular, the expression of purinergic receptors on immune cells have suggested for their important functions in the inflammatory/immune diseases. Indeed, endogenous nucleotides, released upon inflammatory injury by the cells of inflamed tissues, can in turn stimulate the release of pro-inflammatory cyto-chemokines from immune cells, upon binding with purinoceptors. The development of compounds able to activate or limit purinergic receptor expression during inflammation may be relevant to

modulate the inflammatory processes. To this aim, a better knowledge of purinergic signal role in inflammation is mandatory. However, the hypothesis to control inflammatory diseases by regulating the purinergic receptor expression is at present very promising, and may offer a rational basis to design targeted therapies.

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Send correspondence to: Maria Elena Ferrero, Department of Human Morphology and Biomedical Science, Università degli Studi di Milano, Facoltà di Medicina e Chirurgia, Via Mangiagalli 31, 20133, Milano, Italy, Tel: 039-02-50315333, Fax: 039-02-50315338, E-mail: mariaelena.ferrero@unimi.it

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