The potential of P2X7 receptors as a therapeutic target, including inflammation and tumour progression

Geoffrey Burnstock1,2,3 & Gillian E. Knight1

Abstract Seven P2X ion channel nucleotide receptor subtypes have been cloned and characterised. P2X7 receptors (P2X7R) are unusual in that there are extra amino acids in the intracellular C terminus. Low concentrations of ATP open cation channels sometimes leading to cell proliferation, whereas high concentrations of ATP open large pores that release inflammatory cytokines and can lead to apoptotic cell death. Since many diseases involve inflammation and immune responses, and the P2X7R regulates inflammation, there has been recent interest in the pathophysiological roles of P2X7R and the potential of P2X7R antagonists to treat a variety of diseases. These include neurodegenerative diseases, psychiatric disorders, epilepsy and a number of diseases of peripheral organs, including the cardiovascular, airways, kidney, liver, bladder, skin and musculoskeletal. The potential of P2X7R drugs to treat tumour progression is discussed.

Keywords Pain · Infection · Cancer · CNS disorders · Cardiovascular · Airways · Diabetes · Kidney · Bladder · Liver · Gut · Immune cells

Introduction

P2X receptors are a family of ionotropically gated ATP receptors. They are cation-selective channels, equally permeable to Na+ and K+ and with significant Ca2+ permeability. Seven mammalian subunits have been cloned to date (P2X1-7) that form either functional homo- or heterotrimers. When three molecules of ATP bind to a P2X receptor, the pore opens within milliseconds, allowing the cations to flow. P2X7 receptors (P2X7R) differ in that they have extra amino acids in the intracellular C terminus and are bi-functional. The binding of ATP within milliseconds induces the opening of a channel selective for small cations, and within seconds, a larger pore opens, which allows permeation by molecules with a mass of up to 900 Da (leading to the release of inflammatory cytokines and apoptosis) (see [1, 2]).

An important review was published about the development of P2X7R antagonists for anti-inflammatory therapy, including therapeutic potential and recent discoveries [3]. More recent reviews about P2X ion channel receptors and inflammation [1] and the P2X7R as a therapeutic target [4] have been published. This review is focused largely on the recent interest since 2014 about the involvement of P2X7R in inflammation and tumour progression.

P2X7R and inflammation

P2X7R have been implicated in the regulation of inflammation [5] and virtually all immune cell types (both of innate and adaptive immunity, including lymphocytes, macrophages, monocytes, neutrophils, basophils, dendritic cells, eosinophils and mast cells) express P2X7R [6]. They therefore represent significant therapeutic potential. A review was published in 2015 that discussed those P2X7R antagonists that exhibited...
promising therapeutic potential for the treatment of inflammatory diseases, pain and cancer [7]. Other reviews have been published that highlight the involvement of P2X7R in neuroinflammation and how medicinal chemists are working to identify centrally penetrant antagonists [8, 9]. For instance, GSK1482160 is a potent P2X7R antagonist with blood-brain barrier penetration, which has the ability to be radiolabelled with \(^{13}\)C. This allows it to be potentially useful as a biomarker of neuroinflammation [10], since P2X7R may mediate the neuroinflammation and cognitive impairment that can result following surgery [11]. Another review explored the role of P2X7R in fibrosis, the pathological outcome of most chronic inflammatory diseases [12].

Activation of P2X7R is associated with immune responses, including allergic inflammation [13]. ATP released from damaged or infected cells causes inflammation by activation of P2X7R and subsequent release of inflammatory cytokines, such as interleukin (IL)-1\(\beta\), thereby acting as a danger signal by activating P2X7R on immune cells to increase immune responses [14]. An example of this is seen in enteric epithelial cells in conditions of inflammation of the gut (see [1]; Fig. 1). Pulmonary neutrophils are the inflammatory cells that are initially recruited during lung injury. Antagonism of the P2X7R with AZ106006120, or knockout (KO) of the receptor, reduced neutrophil infiltration and pro-inflammatory cytokine levels in a mouse model of acute lung injury [16]. Human and murine neutrophils express functional P2X7R, which mediate NLRP3 inflammasome-dependent IL-1\(\beta\) secretion [17]. Nanobodies are small, single-domain antibody fragments and a mouse nanobody, 13A7, was shown to block gating of the P2X7R channel on T cells and macrophages in vivo and is proposed as a new drug candidate for inflammatory disorders [18].

**P2X7R in inflammation, infection and immunity**

Extracellular ATP is an endogenous danger signal that activates inflammatory responses in immune cells. The role of P2X7R in infectious inflammatory diseases has been reviewed [8, 19, 20]. P2X7R are needed for the development of the inflammatory response associated with sepsis in mice [21, 22] and Brilliant Blue G (BBG; a selective antagonist for mouse P2X7R that is blood-brain barrier permeable and safe) was shown to ameliorate sepsis-induced brain damage [23]. Also in mice, P2X7R downstream of caspase-11 play a critical role for pyroptosis and susceptibility to sepsis induced by the non-canonical inflammasome [24].

The use of P2X7R agonists in conjunction with low molecular weight anti-bacterial medicines has been proposed for the treatment of multi-drug-resistant tuberculosis [25]. P2X7R antagonists are potential tools for the treatment of *Clostridium perfringens* type C [26] and *Porphyromonas gingivalis* [27] infections. P2X7 activation was shown to be protective during severe *Escherichia coli* infection in mice [28]. Similarly, ATP release from infected macrophages and subsequent activation of P2X7R are critical for IL-1-dependent host protection from *Bacillus anthracis* [29]. The role of P2X7R and ectonucleotidases in infectious inflammatory diseases has been reviewed [20].

Evidence was presented to show that mouse P2X7R are involved in containing the parasitic protozoan *Toxoplasma gondii* spread in vivo, by stimulating inflammation [30]. The dysfunction of P2X7R is likely to contribute to morbidity due to human schistosomiasis, a chronic inflammatory disease [31]. P2X7R-deficient mice were more susceptible to *Leishmania amazonensis* infection than wild type (WT) mice, suggesting that P2X7R play a key role in parasite control by regulating T effector cells and inflammation [32].

P2X7R activation regulates inflammatory responses during acute viral infection in mice [33]. Upregulated expression of P2X7R on peripheral blood mononuclear cells provides anti-viral immunity in patients against hepatitis C virus [34], while activation of P2X7R participates in the exacerbated immune response that occurs during influenza virus infection in mice [35]. P2X7R play a role in control of dengue virus-2 infection and KN62 appeared to have anti-viral and anti-inflammatory actions in infected human monocytes [36]. Purinergic receptors, particularly P2X7, have been identified as key mediators
of human immunodeficiency virus-1 (HIV-1) infection and inflammation [37] and ATP induces rapid release of HIV-1 from virus containing compartments of human macrophages [38]. In HIV-1 infection, abnormalities in neuron-glial interactions result in neuronal damage. HIV-1 Tat induces neuronal apoptosis and augments the expression of P2X7R in astrocytes. Oxidised ATP (oxATP), A-438079 and BBG attenuated apoptosis and augments the expression of P2X7R in astrocytes. HIV-1 Tat induces neuronal apoptosis and may be novel tools for therapeutic management of neuroAIDS [39].

A valuable review discusses the role of purinergic signalling in autoimmunity and highlights a role for P2X7R in systemic lupus erythematosus [40]. P2X7R activation deleted intestinal T cells by apoptosis and suppressed T cell-induced colitis in mice [41]. P2X7R are expressed on peripheral lymphocytes and may influence the immune profile from patients with the indeterminate form of Chagas disease [42].

**P2X7R and inflammatory neuropathic pain**

The earlier literature about the involvement of P2X7R in neuropathic pain has been reviewed [43].

Genetically determined P2X7R pore formation was shown to regulate variability in chronic pain sensitivity [44]. P2X7R activation by endogenous ATP contributes to the development of inflammatory hyperalgesia. Removal of the P2X7R gene or P2X7R antagonists, such as BBG and oxATP, abolished chronic inflammatory and neuropathic pain in animal models (see review by Alves et al. [45]). Inflammatory pain that occurs in burn patients following dressing changes was relieved by puerarin treatment, which was claimed to act by decreasing the expression levels of P2X7R mRNA and protein in peripheral blood mononuclear cells [46]. P2X7R activation in vivo was involved in the development of central sensitisation in an acute inflammatory pain animal model (see [1]).

P2X7R antagonists were shown to have analgesic activity in a rat model of neuropathic pain. P2X7R expressed by microglia mediate neuropathic pain, which is reduced by antagonists, such as A-740003 and A-438079 [47]. Central nervous system (CNS)-penetrant P2X7R antagonists may be beneficial for the treatment of persistent pain by targeting microglia. Resveratrol was shown to be neuroprotective against neuropathic pain mediated by P2X7R expressed on satellite glial cells of the dorsal root ganglia (DRG) [48].

**P2X7R and tumour progression**

A review covering the early literature about the involvement of purinergic signalling and cancer, including discussion about the roles of the P2X7R in a variety of tumours, is available [49].

P2X7R are a key mediator of inflammation and cancer invasion/metastasis and P2X7R antagonists are potential anti-metastatic agents [50]. A feature of some cancer cells is the high level of expression of P2X7R, which, depending on the tumour type, can mediate either proliferation or cell death (see [51]). Thus, P2X7R activation may have effects on anti-tumour immunity that are opposed to a direct effect on tumour growth. It was also pointed out in this review that there is increased release of ATP, promoting cancer cell migration and metastasis. High levels of extracellular ATP accumulate in tumour interstitium and high ATP doses inhibit migration of endothelial cells from human breast carcinoma, via the activation of P2X7R [52]. Human pancreatic duct adenocarcinoma cells in vitro express high levels of P2X7R protein and AZ10606120 inhibited cell proliferation [53]. ATP activation of P2X7R triggers immunogenic signalling, which converts dying cancer cells into an effective anti-cancer vaccine [54]. P2X7R activation is linked to elevated expression of inflammation promoting factors, tumour cell migration, increase in [Ca²⁺], and membrane depolarisation in malignant gliomas (see [55]; Fig. 2). Evidence has been presented to suggest that P2X7R antagonists are promising therapeutic tools for the treatment of osteosarcoma [56]. Growth of experimental tumours is strongly inhibited by P2X7R antagonism of both cancer and immune cells (see [57]). A non-functional P2X7R, nP2X7R, is expressed on cancer cells and has been proposed as a novel therapeutic target for human cancer [58, 59]. A phase I clinical trial has recently demonstrated that nP2X7R-targeted antibodies were a novel, safe and tolerable topical therapy for basal cell carcinoma [60]. P2X7R activation induces apoptosis in acute myeloid leukaemia cells but not in normal hematopoietic stem cells [61].

ACN human neuroblastoma cells express P2X7R, which is a regulator of its growth and angiogenesis, and AZ10606120 and A-740003 reduced ACN-derived tumour growth in nude mice so P2X7R may be a novel therapeutic target for treatment of neuroblastoma [62, 63]. P2X7R are expressed on human malignant glioma and C6 cells [55, 64, 65] and high P2X7R expression has been correlated with progression-free survival and overall survival [66]. P2X7R activation caused release of inflammatory cytokines by macrophages exposed to glioma-conditioned medium that was prevented by A-740003 [67]. A P2X7R agonist, 2'(3')-O-(4-benzoylbenzoyl)-ATP (Bz-ATP), enhanced the temozolomide anti-tumour effect on human cultured glioblastoma stem cells [68].

Autocrine release of ATP and activation of P2X7R influence the metastatic migration of human lung cancer H292 and PC-9 cells [69], and in immunodeficient mice, migration of transplanted HTB177 and HTB183 lung cancer cells was reduced by A-438079 [70]. The role of P2X7R in tumour progression is complex and studies show contradictory effects of P2X7R activation. For instance, an increase in survival of non-small cell lung cancer patients with high P2X7R expression was observed [71], although low P2X7R expression resulted in greater mRNA (miR-21) expression in the non-small
cell lung cancer tumours. Thus, the high levels of miR-21 expression in these cancer patients may be a consequence of P2X7R downregulation and resultant promotion of tumour progression. These results agree with the study by Souza and colleagues [72], which showed that defective P2X7R expression following miR-21 activation by a K-Ras mutation, led to reduced tumour-killing activity, resulting in a poorer prognosis. P2X7R are expressed in pancreatic cancer PancTu-1 Luc cells and antagonists, such as AZ10606120, are likely to be effective therapeutic agents [53]. Other antagonists, A-438079 and A-740003, reduced inflammation associated with colitis but increased tumour incidence in a mouse model of colitis-associated cancer [73]. In P2X7R-transfected human embryonic kidney cells and CT26 colon carcinoma, there was enhanced tumourigenesis when the cells were inoculated into either immunodeficient or immunocompetent mice, respectively. It was shown that in tumours derived from B16 mouse melanoma or ACN human neuroblastoma cell lines, tumour growth was inhibited by oxATP [74]. The anthraquinone, emodin, suppressed the invasiveness of the highly invasive breast cancer cell line MDA-MB-435s, by antagonizing P2X7R [75]. ATP increased [Ca^{2+}]i in breast tumour cells and high concentrations produced apoptosis via P2X7R. ATP-mediated activation of the human breast cancer cell line T47D resulted in an increase in cell migration and the development of metastases, suggesting a potential therapeutic role for P2X7R antagonists [76]. P2X7R expression is a prognostic indicator for postoperative cancer-specific survival of patients with clear-cell renal cell carcinoma [77].

Decreased expression of P2X7R is associated with the development of cervical cancer. In women, decreased expression of P2X7R is found in endometrial epithelial pre-cancerous lesions. Activation of P2X7R-dependent apoptosis with BzATP may be a chemotherapeutic approach to prevent cell growth of pre-cancerous and early cancerous epithelial lesions [78]. Clearly, while ATP and P2X7R activation induced
apotomop of tumour cells in some models, in others it accelerated tumour growth.

It is known that there are many polymorphisms of the P2X7R [79, 80], which, in addition to resulting in a loss of function, may alter the activity of the receptor. Expression of non-functional cytolytic P2X7R was found in all pathology specimens of prostate cancer examined [81]. P2X7R were not expressed in normal tissues from patients with no evidence of cancer, suggesting that the appearance of P2X7R is an early marker of prostate cancer. The expression of P2X7R is increased by hypoxia and hypoxia-driven increase in P2X7R enhances invasion and migration of tumour cells [82].

UV-B irradiation destroys P2X7R, as well as melanoma. UV-B irradiation destroys P2X7R, by directly killing epithelial cells and by reducing P2X7R mRNA by degrading the protein, and may contribute to the malignant transformation of keratinocytes [83]. P2X7R were expressed in the necrotic centre of nodular basal cell carcinomas in and apoptotic cells in superficial multifocal and infiltrative cells. ATP could apoptosis of cultured A431 human squamous cell carcinoma cell line via P2X7R and application of BzATP inhibited the formation of skin papillomas and carcinomas in mice [84]. There was increased expression of P2X7R in patients with superficial spreading melanomas, which were later shown to be functional, and it was suggested that they are the potential for melanoma therapy. A low pH environment (like that seen in solid tumours) induced ATP release from B16 melanoma cells to increase proliferation via P2X7R and oxATP inhibited tumour growth in B16 melanoma-bearing mice [85]. In P2X7R KO mice, tumour progression of B16 melanoma was accelerated, showing that P2X7R are critical to support an anti-tumour immune response as well as restricting tumour growth and metastatic diffusion [86]. γ-Irradiation, which causes growth arrest and death of tumour cells, induced P2X7R-dependent ATP release from the B16 melanoma cells. P2X7R KO mice were susceptible to bone cancer pain and had an earlier onset of pain-related behaviours. The majority of human osteosarcomas express P2X7R isoforms A and B and the expression of either isofrom is differentially coupled to cell growth and activity [87]. P2X7R are involved in cancer-induced bone pain and A839977 was suggested as a useful analgesic tool in a rat model of cancer-induced bone pain [88].

Activation of P2X7R can either promote cellular survival or induce cytotoxicity and depends on the stimulus intensity of ATP to control the ion channel or the P2X7-dependent large pore functions. How these two opposite effects are controlled is not fully understood. Recently, a feedback loop was described showing that sustained activation of P2X7R results in the release of active matrix metalloproteinase 2, which stops ion channel and large pore responses in several different cell types, including macrophages and human tumour cells. This effect may be an important fine-tuning of P2X7R functions. The authors suggested that P2X7R antagonists could be useful as in treating inflammatory diseases and cancers [89].

As the tumour microenvironment contains very high concentrations of ATP, adenosine is also present in high concentrations, following enzymatic breakdown of ATP by CD39 and CD73. Both ATP and adenosine contribute to immunosuppression or immunostimulation of the host, and stimulation of growth or cytotoxicity of the tumour, depending on the receptors activated. Thus, targeting specific receptor subtypes produces different effects, for example targeting CD73 or A2A receptors reduced immunosuppression and potently inhibited tumour growth [90]. As has been described above, growth of experimental tumours is also strongly inhibited by targeting P2X7R of cancer and immune cells (see [57]).

P2X7R and diseases of the CNS

The role of P2X7R in diseases related to neuroinflammation and the use of centrally penetrant antagonists has been highlighted [1, 11, 14, 18, 91–94]. Blockade of P2X7R may serve as a therapeutic target in alleviating the degree of inflammation seen in neurodegenerative and neoplastic conditions [95]. Figure 3 is a schematic showing P2X7R-mediated pathways of common disease mechanisms in CNS disorders of different aetiology. P2X7R are upregulated in various disease conditions and stress signals elicit activation, which can lead to excitotoxicity, neuroinflammation, neuronal damage, reactive astrogliosis or neuroplasticity, contributing to disease pathology (see [92]).

Neurodegenerative diseases

Attention has been directed recently towards the use of P2X7R antagonists for the treatment of neurodegenerative diseases, which are often associated with inflammation and damage to both neurons and glia [96–99]. P2X7R antagonists were neuroprotective in an animal model of Alzheimer’s disease (AD). P2X7R trigger α-secretase-dependent processing of the amyloid precursor protein to generate β-amyloid peptides, which are present in the amyloid plaques in AD. Inhibition of P2X7R in vivo reduces amyloid plaques through glycogen synthase kinase 3β and secretases. BBG improved cognition in an animal model of AD and inhibited amyloid-β-induced loss of filopodia and dendrite spines in cultured hippocampal neurons [100]. The control of amyloid plaque formation in vivo by P2X7R was reviewed in 2015 [97] and discussed further in 2017 [101]. It was suggested that P2X7R contribute to Parkinson’s disease (PD) pathogenesis through a triple effect on synaptotoxicity, gliosis and neurotransitivity, indicating therapeutic potential of P2X7R antagonists for PD [102–104]. BBG was neuroprotective in an intranigral lipopolysaccharide (LPS) animal model of PD [104]. P2X7R are involved in multiple sclerosis (MS) and in the animal model of
MS, experimental autoimmune encephalomyelitis (see [105]), where increased expression of P2X7R protein was shown in brain homogenates. Genetic variants in P2X7R affect susceptibility to MS [106, 107]. Altered P2X7R level and function in mouse models of Huntington’s disease were reported and BBG prevented neuronal apoptosis and reduced body weight loss and motor-coordination deficits [108].

Inflammation features in the pathogenesis of amyotrophic lateral sclerosis (ALS). The potential of antagonism with BBG for the treatment of ALS was proposed, but it was claimed that the treatment was gender-dependent, although this varied in different studies using the SOD1-G93A mouse model of ALS: more effective in males [109], more effective in females [110] and no difference between the sexes [111]. Similarly, the pathogenesis of ALS was shown to differ in different studies. In P2X7R KO-SOD1-G93A mice, onset of the disease occurred more rapidly than in WT mice, with increased astrogliosis, microgliosis, motorneuron loss, induction of pro-inflammatory markers and activation of mitogen-activated protein kinase (MAPK) pathways [112]. In a later study by this group using the same mouse model of ALS, BBG reduced neuroinflammation at late pre-symptomatic phases of the disease, enhanced motor neuron survival and reduced microgliosis in the lumbar spinal cord [111]. These differences may be due to the timing of the receptor block, complete absence of the receptor in the KO study, as opposed to antagonising the receptor prior to symptoms showing in the latter study. Ca^{2+} abnormalities in ALS exist in both motor neurons and immune cells. Reduction of P2X7R expression on peripheral blood mononuclear cells from ALS patients led to calcium dysregulation, a feature of ALS [112].

Fig. 3 Common disease mechanism by P2X7 receptor (P2X7R)-mediated pathways in central nervous system (CNS) disorders of different etiology. P2X7R are expressed on nerve terminals, astrocytes and microglia, and they are upregulated in various disease conditions. Stress signals such as hypoxia/ischemia (metabolic limitations), mechanical injury and bacterial or chemical toxins elicit the endogenous activation of P2X7R and lead to a self-amplifying ATP release and to further activation of P2X7R on neighbouring cells. Following the influx of Ca^{2+} through the receptor ion channel complex, P2X7R activation (i) releases glutamate from nerve terminals and astrocytes by both exocytic and non-exocytic mechanisms, which may give rise excitotoxicity; (ii) leads to the posttranslational processing of pro-interleukin-1β (pro-IL-1β) to the leaderless, mature IL-1β and to its further release by the NLRP3 inflammasome and that of other cytokines, which contribute to neuroinflammation; (iii) enhance reactive oxygen species (ROS) production and thereby aggravate protein misfolding and neuronal damage; (iv) leads directly or indirectly to cell death and the following reactive astrogliosis; and (v) directly or indirectly downregulates the production of brain-derived neurotrophic factor (BDNF) and the subsequent neuroplasticity. These key mechanisms could be manifested and contribute to disease pathology in Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD), status epilepticus (SE), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), stroke, pain and mood disorders in different forms and proportion, depending on the etiology. Abbreviations: GLU, glutamate, ROS, reactive oxygen species. (Reproduced from [92], with permission from Elsevier)
Psychiatric disorders

Activation of microglial P2X7R causes inflammation and brain penetrant P2X7R antagonists are being developed since microglial P2X7R are being increasingly recognised as a therapeutic target for the treatment of neurological and psychiatric diseases [113]. A review on this subject is available [114].

There is increased neuronal death via P2X7R and pannexin 1 channels in cultured cerebral cortex from prenatal LPS-exposed mice, which suggested a link to an increased risk of developing neurological disorders, including schizophrenia, in the offspring (see [115]). P2X7R, mediating neuroinflammation via the activity of microglia, may play a role in bipolar disorder and offer therapeutic possibilities (see [116]). Anti-depressant effects of chrysopanol (a natural anthraquinone) via inhibition of P2X7R has been reported in an LPS animal model of depression [117]. Similarly, BBG had anti-inflammatory and anti-depressant effects in mice after LPS administration [118].

Acute restraint stress activates the inflammasome via release of ATP and stimulation of P2X7R in a mouse model of stress-related mood disorders [119] and the antagonist A-804598 was shown to have an impact on the neuroimmune and behavioural consequences of stress in a rat model [120]. The P2X7R-Gln460Arg variant has been associated with mood disorders and co-expression of WT P2X7R with the polymorphic variant Gln460Arg transfected into HEK293 human cells was found to impair receptor function [121].

Neuroprotection from injury

There are reviews that discuss the importance of inflammation and the involvement of purinergic signalling in the responses to brain injury [8] and of the P2X7R in particular [1, 14]. P2X7R antagonists are a promising therapeutic tool for the treatment of cerebral ischaemia (see [122, 123]). BBG reduced delayed neuronal cell death in the hippocampal CA1 region after ischaemia/reperfusion injury and it was found that systemic administration of P2X7R antagonists improved recovery after spinal cord injury. The neuroprotective action of the P2X7R antagonist, GS1370319A, acts by inhibiting the assembly of the NLRP3 inflammasome in glial cells [124, 125]. ATP enhanced radiation-induced brain injury through microglial activation via P2X7R-mediated release of inflammatory mediators, such as cyclooxygenase-2, tumour necrosis factor-α (TNF-α) and IL-6, and P2X7R antagonists were suggested as a potential strategy for the treatment of patients with radiation-induced brain injury [126]. Activation of P2X7R in the hippocampus following traumatic brain injury was thought to imply cognitive impairment in rats [127], while A-438079 provided neuroprotection toward neurological disorders, including stroke, traumatic brain injury and subarachnoid haemorrhage, as well as preserving blood-brain barrier integrity [128].

Recent papers have recognised a role for P2X7R antagonists for the treatment of epilepsy, including drug-resistant epilepsy [8, 129, 130]. P2X7R antagonism produced lasting reduction in the development of spontaneous seizures and inhibited glial inflammatory responses in mouse models of experimental temporal lobe epilepsy [131] and pentylenetetrazol-induced seizures [132]. However, in pilocarpine-induced status epilepticus in mice, blockade of central P2X7R increased the number of seizures and their severity [133]. P2X7R are considered as a target for the treatment of hypoxic/ischaemic encephalopathy and other causes of neonatal seizures since in A-438079-treated mice, seizure number, EEG power and spiking during hypoxia as well as molecular markers of inflammation and microglia were reduced [130].

Cardiovascular diseases

The long non-coding RNA (lncRNA), NONRATT021972, targeted using a small interfering RNA (siRNA), decreased the upregulation of P2X7R in the superior cervical ganglion and improved cardiac function after myocardial ischaemia in rats [134]. Myocardial ischaemic injury facilitated sympathoexcitatory action via P2X7R and it was suggested that P2X7R antagonists may be useful for the treatment of coronary heart disease as expression of P2X7R is increased during coronary ischaemia-reperfusion [135]. Microglial P2X7R in the rat hypothalamic paraventricular nuclei regulate the sympathoexcitatory responses in acute myocardial infarction and gene knockdown of P2X7R with P2X7-siRNA, or inhibition with BBG, reduced mRNA and protein expression of IL-1β and TNF-α [136]. P2X7R involvement in dilated cardiomyopathy has been reported in P2X7R KO mice [137]. A-740003 reduced experimental autoimmune myocarditis in a mouse model, suggesting a treatment for clinical myocarditis [138]. P2X7R in the kidney play a role in hypertension and it has been suggested that P2X7R antagonists may have promise as clinical anti-hypertensive agents. In atherosclerotic mice, P2X7R are over-expressed whereas P2X7R KO mice were found to have less plaque formation and decreased leukocyte recruitment following ATP stimulation [139]. P2X7R are prothrombotic and genetic KO of the P2X7R gene is protective in a mouse model of carotid artery thrombosis. Vasomotor dysfunction was caused by sub-failure overstretch injury in rat abdominal aorta via activation of P2X7R and this suggested that the use of antagonists for the treatment of vascular stretch injury in humans may be beneficial [140].

Diseases of the airways

Inflammation occurs in most diseases of the airways, including asthma, chronic obstructive pulmonary disease, cystic fibrosis, dyspnea, allergy, infection and injury. P2X7R are a target for therapeutic intervention in lung hypersensitivity reactions associated with chronic inflammatory responses. Extracellular ATP was recognised as a danger signal activating P2X7R in lung
inflammation and fibrosis and P2X7R antagonists were proposed as a novel therapeutic approach in humans to control IL-1β production and fibrosis in lung injury [141] as well as in silicosis, an occupational lung disease, following a study in a mouse model [142]. Attenuated P2X7R function gives protection from asthma and is age-related, being most effective in young boys. P2X7R have also been implicated in the pathophysiology of allergy-induced lung inflammation. Targeting P2X7R on haematopoietic cells, namely dendritic cells or eosinophils, may be a therapeutic approach for the treatment of allergic asthma. The anti-allergic anti-histamine, oxatomide, is claimed to also act as a P2X7R antagonist in N18TG2 and J774 cells [13]. BBG prevented neurogenic pulmonary oedema after subarachnoid haemorrhage in rats by attenuating inflammation [143]. Cigarette smoke activates P2X7R signalling, which appears to be involved in the pathogenesis of emphysema, and induces ATP and inflammatory cytokine release from neutrophils via P2X7R activation [144]. Polymorphisms of the P2X7R gene are associated with the risk and prognosis of human tuberculosis [145]. Data was presented to support the view that P2X7R antagonists should be used to treat the aggressive forms of tuberculosis [146]. ATP, released by activated macrophages and damaged cells, modulates lung inflammation in pneumonia in cattle. Both epithelial cells and pulmonary microvascular endothelial cells expressed mRNA for P2X7R, as did alveolar macrophages, which, when stimulated, activate the proinflammatory IL-1 to IL-5 cytokine cascade. P2X7R are involved in the pathophysiology of LPS-induced lung injury [147] and there is upregulation of pulmonary P2X7R in both acute and chronic lung injury in mice where P2X7R deletion was shown to be lung protective [148]. Pulmonary neutrophils are the initial inflammatory cells to be recruited during lung injury and are crucial for innate immunity. In contrast, pathological recruitment of neutrophils results in lung injury and P2X7R antagonists were shown to reduce neutrophil infiltration and proinflammatory cytokine levels [16].

Gut disorders

Extracellular nucleotides and their receptors are involved in the pathogenesis of inflammatory bowel disease (IBD), which includes two main forms, namely ulcerative colitis (UC) and Crohn’s disease (CD). P2X7R are involved in colonic motor dysfunction associated with bowel inflammation in rats [149] and are over-expressed in gut mucosa of patients with CD [150]. P2X7R KO mice were protected against gut inflammation, while in WT mice, ATP via P2X7R triggers the death of mucosal regulatory T cells [151]. Oestrogen receptor β activation may play a therapeutic role in IBD by downregulation of P2X7R [152]. Reviews discussing the role of P2X7R in IBD are available [15, 153]. UC differentially affects P2X7R-expressing enteric neurons based on their chemical codes [154]. In a later paper, it was shown that trinitrobenzene sulfonic acid-induced UC in rats affected secretory and vasodilatory neurons, enteric sensory neurons and enteric glia of the submucosal plexus expressing P2X7R [155]. ATP mediates inflammatory responses in dextran sulfate sodium-induced UC in mice via P2X7R signalling and A-438079 down-regulated the production of proinflammatory cytokines and attenuated the colitis [156]. There is increased expression of P2X7R in the inflamed mucosa in CD in humans and animal models, suggesting that P2X7R may be a target for treatment of CD [151, 156, 157]. Purinergic signalling is involved in gastrointestinal motility disorders, such as diarrhoea and constipation. P2X7R activity was enhanced in enteric glia that were isolated from mice with long-term morphine treatment, which can result in colonic inflammation [158].

Diseases of the kidneys

Increased expression of P2X7R in renal hypertension, polycystic kidney disease (PKD) and glomerulonephritis is opening up novel purinergic possibilities for the treatment of kidney failure (see [159, 160]). A-438079 protected against ischaemic acute kidney injury in mice [161]. P2X7R are expressed in collecting duct cysts in the cph/cph mouse model of congenital PKD, and mRNA and protein increased as the disease developed. ATP inhibits renal cyst growth, via P2X7R and oxATP, and A-438079 reduced cyst formation via MAPK-dependent pathways in a zebrafish model of PKD [162]. P2X7R expression has been demonstrated in both experimental and human glomerulonephritis, which suggests that P2X7R antagonists may have therapeutic potential [163]. P2X7R deficiency attenuated renal injury in experimental glomerulonephritis in mice. BBG attenuated nephritis by inhibiting inflammasome activation in a mouse model of lupus nephritis [164]. There is predominant P2X7R control of glomerular haemodynamics in angiotensin-II hypertension [165]. While P2X7R are only weakly expressed in healthy kidney, they are significantly upregulated in hypertension [166], antagonism of which would reduce interstitial inflammation, prevent interstitial cell death and improve blood pressure control. P2X7R antagonism prevented the development of salt-sensitive hypertension and renal injury in Dahl salt-sensitive rats [167]. P2X7R expression was increased in human kidneys with type 2 diabetes and activation of P2X7R evoked renal inflammation and injury in the high-fat diet model of metabolic syndrome, suggesting that P2X7R antagonists might be useful therapeutically for diabetic nephropathy [168]. P2X7R activation contributes to the high prevalence of kidney disease found in diabetics [160].

Diseases of the lower urinary tract

Localised inhibition of P2X7R at the spinal cord inflammatory injury site in a rat model reduced microglia numbers and improved neurogenic bladder dysfunction [169]. P2X7R,
expressed by macrophages and neutrophils in the bladder submucosa, are increased in cyclophosphamide-induced haemorrhagic cystitis in mice and treatment with A-438079 or genetic ablation of this receptor reduced the tissue levels of IL-1β and TNF-α and reduced nociceptive behaviour [170]. It was shown that 7 days after unilateral ureteral obstruction in WT mice there was increased expression of P2X7R associated with inflammation and fibrogenic responses in the cortex [171]. It was suggested that there is a potential role for P2X7R antagonists to prevent renal interstitial fibrosis [172].

Diseases of the liver

In mouse models of acetaminophen (APAP)-induced inflammation, liver injury after overdose involved P2X7R activation [173] resulting in hepatic caspase-1 and migration of neutrophils into the liver, suggesting that ATP may play a pivotal role in the development of inflammasomes after APAP overdose [174]. A-438079 was reported to be protective against APAP-induced liver injury, by an effect on metabolic activation and cell death pathways, rather than on involvement of inflammasomes [175]. Blockade of the P2X7R-NLRP3 inflammasome axis is a potential therapeutic target for liver fibrosis [176]. In mice with induced autoimmune hepatitis, activation of P2X7R on natural killer T cells was shown to inhibit naive but stimulate activated cells, resulting in suppression or stimulation of the autoimmune hepatitis [177]. P2X7R-mediated responses participate in infection of human hepatocytes by hepatitis delta virus and hepatitis B virus. P2X7R mediate leptin-induced GLUT4 function in mice stellate cells in non-alcoholic steatohepatitis [178]. P2X7R may be a major component of the purinergic signalling complex in hepatitis C virus-induced liver pathogenesis [34].

Musculoskeletal diseases

P2X7R proteins were upregulated on dystrophic myoblasts of mdx mice (a mouse model of Duchenne muscular dystrophy) and it was suggested that antagonists to these receptors may be of potential therapeutic benefit [186] as treatment with BBG or oxATP slowed the progression of disease in the mouse model [187]. The P2X7R has received the most attention in relation to the treatment of osteoporosis [188]. P2X7R plays an important role in both cortical and cancellous bone mass augmentation. They were shown to mediate stimulation of periosteal and cancellous bone formation and inhibition of cancellous bone resorption during growth [188]. Single nucleotide polymorphisms (SNPs) of the P2X7 gene are associated with fracture risk, decrease in bone mineral density and osteoporosis [189]. P2X7R are also involved in the chain of events leading to the formation of human osteoclasts, and P2X7R antagonists may have therapeutic roles in bone diseases with an increase in osteoclast number, such as Paget’s disease [190]. P2X7R antagonists may be useful for the management of osteoporosis and with disorders of remodelling, where there is reduced bone mass [191]. Different polymorphic variants of the P2X7R are associated with high or reduced periprosthetic osteolysis in the long-term complication of total hip arthroplasty due to osteoarthritis [192]. Cross-talk between P2X7R and Wnt/β-catenin pathways may modulate...
osteoabl activity in response to mechanical loading [193]. Treatment with AZD9056, a selective P2X7R antagonist, produced pain-relieving and anti-inflammatory effects in rats with osteoarthritis [194]. ATP, via P2X7R, induced higher levels of IL-1β in blood samples from rheumatoid arthritis (RA) patients compared to controls. It was suggested that mononuclear cells from these patients were more sensitive to ATP stimulation, perhaps due to genetic polymorphism in the P2X7R gene [195]. P2X7R play a role in the pathogenesis of RA and systemic lupus erythematosus. Human rheumatoid synoviocytes express P2X7R mRNA and protein. Animal models of arthritis have provided evidence for an in vivo role for the P2X7R in the progression of inflammatory disease. In P2X7R KO mice, there was a reduced incidence and severity of anti-collagen-induced arthritis symptoms; therefore, targeting the P2X7R may be a promising treatment for RA [196]. Block of P2X7R signalling in the collagen-induced arthritis animal model of RA inhibited peripheral inflammatory tissue destruction. P2X7R antagonists have been explored for the treatment of inflammatory pain in joints [197]. Charcot-Marie-Tooth 1A is a demyelinating hereditary neuropathy and A-438079 improved the clinical phenotype of the disease in a rat model and was recommended for its treatment [198]. A review was published about P2X7R antagonists in rodent models of musculoskeletal and other disorders [199].

**P2X7R and diabetes**

Type 1 and type 2 diabetes are inflammatory diseases. P2X7R KO in mice prevents streptozotocin (STZ)-induced type 1 diabetes and the levels of proinflammatory mediators (IL-1β, interferon-γ and nitric oxide) did not increase [200]. P2X7R-pannexin 1 channels impair bone mechanosignalling in osteocytes associated with type 1 diabetes that affects osteoblast function and maintenance of bone health [201]. In STZ-induced diabetic animals, P2X7R located on glucagon-containing α cells in pancreatic islets increase and they migrate centrally to take the place of the missing insulin-containing β cells [202]. OxATP in mice has been proposed as a therapeutic tool to cause immunsuppression and tolerance induction in pancreatic islet transplantation [203, 204]. LncRNA NONRATT021972 siRNA decreases the expression of P2X7 mRNA and protein in DRG, thereby reducing mechanical and thermal hyperalgesia in type 2 diabetic rats [205]. ATP concentrations and P2X7R expression were increased in glial cells in rats with painful diabetic neuropathy [206]. Diabetic sympathetic neuropathy in type 2 diabetic rats was improved by reducing the expression of P2X7R with LncRNAuc.48+ siRNA in superior cervical ganglia [207]. Different P2X7R polymorphisms are associated with pain sensitivity for diabetic neuropathic pain patients, such that patients with the gain-of-function SNP report more severe pain, whereas those with a loss-of-function SNP report less pain when the pain was tested and scored [208]. P2X7R antagonists may be a useful coadjuvant treatment to delay the progression of diabetic nephropathy [209].

**Conclusions**

It is clear from the recent literature that P2X7R antagonists are potential effective therapeutic agents for the treatment of inflammatory diseases and cancer. There is a problem, however, concerning the many polymorphic forms of the human P2X7R, as care must be taken in identifying those patients that would most benefit by the available antagonists, as different antagonists are not always effective agents at some of the polymorphic types (see [210]). There is an explosion of interest in developing centrally penetrant P2X7R antagonists and their therapeutic explorations in clinical trials [211–213]. The relation between inflammation elicited by P2X7R activation and the immune system needs further exploration. Apart from the potential of the therapeutic use of P2X7R antagonists for CNS disorders (including neurodegenerative diseases, brain injury, psychiatric diseases, epilepsy and neuropathic pain), there is increasing recognition of their use for the treatment of diseases of the heart, lung, gut, kidney, liver and bladder. The reasons for dual roles of P2X7R mediating cell proliferation and apoptotic cell death need further investigation of the mechanisms involved.

The purinergic signalling field is now well established and much known about the physiological roles played by this system. The emphasis now is on the pathophysiology and therapeutic potential of purinergic signalling (see [214, 215]). For example, clopidogrel (trade name Plavix) and ticagrelor (trade name Brilique) are P2Y₁₂ receptor antagonists that inhibit platelet aggregation and are widely used for the treatment of thrombosis and stroke (see [216]).

Characterisation of the P2Y class (see [217]) made it possible to identify specific agonists of the P2Y₂ receptor, which evokes mucus secretion. A new, long-lasting agonist, diquafosol (Diquas), has been developed by Inspire Pharmaceuticals [218]. Diquas was launched by Santen in Japan in 2010, with Inspire Pharmaceuticals.

Through the cloning of the P2X₃ ion channel receptor located on nociceptive sensory nerves [219] and later the discovery of the involvement of these channels in signalling pain (see [220]), a new target for pain relief is receiving attention from the pharmaceutical industry. Roche and, more recently, Afferent Pharmaceuticals have developed AF-219, a specific P2X₃ antagonist, which is a promising new analgesic, orally bioavailable and stable in vivo [221]. AF-219 is currently in phase 2 clinical trials for the treatment of three painful disorders: osteoarthritis; interstitial cystitis/bladder pain syndrome and idiopathic chronic cough. Four phase 1 studies of AF-219 have demonstrated that the compound is safe and well
tolerated and the phase 2 clinical trials were completed earlier this year [222]. Antagonism of P2X3 receptors on primary afferent neurons is a novel analgesic approach that has been pursued by leading pharmaceutical companies for the last 15 years. Over 600 patents are currently held which relate to the P2X3 receptor and pain (https://patentscope.wipo.int/search/en/result.jsf). There are currently investigations into the potential therapeutic use of purinergic compounds for osteoporosis, irritable bowel syndrome, atherosclerosis, kidney failure and cancer.

Since P2X7R-mediated inflammation is associated with a wide range of diseases, medicinal chemists in research institutes, universities and drug companies are optimistic that P2X7R antagonists are promising tools for the treatment of inflammatory diseases and more than 70 patents have been filed in the last few years by Glaxo, AstraZeneca, Roche, Janssen and Abbott, to name a few. For instance, Abbot filed a patent from the use of A-438079 in disease models of affective disorders and status epilepticus, while Abbott filed for triazole-based compounds for the CNS disorders and as a therapeutic strategy to treat spinal cord injury and the University Hospitals of Cleveland claimed in vitro and in vivo effects of P2X7R antagonists in epithelial cancer and papilloma (see [213]).

As mentioned above, a major challenge is to understand which polymorphic variations of the P2X7R have relevance to which disease and to fit patients with different polymorphisms to the P2X7R antagonist that would have the greatest efficacy for that variant. For example, the responses of human leukocytes to GSK1370319A were significantly altered, directly related to the SNP genotype, there being a 6.7-fold difference in the inhibition of ATP-stimulated IL-1β release by GSK1370319A between individuals with the homozygous gain- and loss-of-function genotypes [223]. A correlation was found between some gain-of-function and loss-of-function P2X7R SNPs, transfected into HEK-293 cells, and the expression of the channel protein. A change in both channel and pore function was described for the mutant P2X7R in parallel to the protein levels, although the agonist and antagonist sensitivity was not altered. The presence of the gain-of-function SNP (rs208294 (His155Tyr) and rs1718119 (Ala348Thr)) in female patients with diabetic peripheral neuropathy was associated with higher pain intensity scores [208]. Recently, mutations and molecular modelling studies have identified an allosteric binding site forming at the subunit interface at the apex of the receptor, distinct from the ATP-binding pocket, that regulates access of antagonists, such as AZ10606120, to the allosteric site. This allosteric pocket may provide novel targets for P2X7R drug development [224, 225], although the effect of polymorphic variations on the allosteric site has not been elucidated yet.

Also, more needs to be discovered about the relation of inflammatory diseases to the immune system where lymphocytes, macrophages, monocytes, neutrophils, basophils, dendritic cells, eosinophils and mast cells all express P2X7R (see [6]).

It seems likely that a breakthrough will occur about the use of P2X7R antagonists for a variety of diseases in the future, including, in particular, neurodegenerative diseases and cancer and the description of the crystal structure of mammalian P2X7R can only help in this endeavour [225, 226].

In addition to the therapeutic potential of P2X7R antagonists, P2X3R antagonists look extremely promising for the treatment of chronic cough, visceral pain, bladder disorders and hypertension. Exploration of the use of purinergic drugs for the treatment of obesity is also well worth pursuing.

Funding The writing of this review article was not financially supported.

Compliance with ethical standards

Conflict of interest Geoffrey Burnstock declares that he has no conflict of interest.

Gillian E. Knight declares that she has no conflict of interest.

Ethical approval This review article does not contain any studies with human participants or animals performed by either of the authors.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Burnstock G (2016) P2X ion channel receptors and inflammation. Purinergic Signalling 12:59–67
2. Volonté C, Apolloni S, Skaper SD, Burnstock G (2012) P2X7 receptors: channels, pores and more. CNS & Neurological Disorders-Drug Targets 11:705–721
3. Mehta N, Kaur M, Singh M, Chand S, Vyas B, Silakari P, Bahia MS, Silakari O (2014) Purinergic receptor P2X7: a novel target for anti-inflammatory therapy. Bioorg Med Chem 22:54–88
4. Burnstock G (2013) Purinergic signalling: pathophysiology and therapeutic potential. Keio J Med 62:63–73
5. Di Virgilio F, Dal Ben D, Sarti AC, Giuliani AL, Falzoni S (2017) The P2X7 receptor in infection and inflammation. Immunity 47:15–31
6. Burnstock G, Boezaart A-JM (2014) Purinergic signalling and immune cells. Purinergic Signal 10:529–564
7. Baudelet D, Lipka E, Millet R, Ghinet A (2015) Involvement of the P2X7 purinergic receptor in inflammation: an update of antagonists series since 2009 and their promising therapeutic potential. Curr Med Chem 22:713–729
8. Beamer E, Gölöncséf F, Horváth G, Bekő K, Otokocsci L, Koványi B, Sperlágh B (2016) Purinergic mechanisms in neuroinflammation: an update from molecules to behavior. Neuropharmacology 104:94–104
9. Rech JC, Bhattacharya A, Letavic MA, Savall BM (2016) The evolution of P2X7 antagonists with a focus on CNS indications. Bioorg Med Chem Lett 26:3838–3845

10. Territo PR, Meyer JA, Peters JS, Riley AA, McCarthy BP, Gao M, Wang M, Green MA, Zheng QH, Hutchins GD (2017) Characterization of 11C-GSK1428160 for targeting the P2X7 receptor as a biomarker for neuroinflammation. J Nucl Med 58:458–465

11. Zheng B, Lai R, Li J, Zuo Z (2017) Critical role of P2X7 receptors in the neuroinflammation and cognitive dysfunction after surgery. Brain Behav Immun 61:365–374

12. Gentile D, Natale M, Lazzerini PE, Capecchi PL, Laghi-Pasini F (2015) The role of P2X7 receptors in tissue fibrosis: a brief review. Purinergic Signal 11:435–440

13. Yoshida K, Ito M, Matsuoka I (2015) P2X7 receptor antagonist activity of the anti-allergic agent oxatomide. Eur J Pharmacol 767:41–51

14. Giuliani AL, Sarti AC, Falzoni S, Di Virgilio F (2017) The P2X7 receptor-interleukin-1 liaison. Front Pharmacol 8:123

15. Diezmos EF, Bertrand PP, Liu L (2016) Purinergic signaling in gut inflammation: the role of connexins and pannexins. Front Neurosci 10:311

16. Mishra A, Guo Y, Zhang L, More S, Weng T, Chintagari NR, Huang C, Liang Y, Pushparaj S, Gou D, Breshares M, Liu L (2016) A critical role for P2X7 receptor-induced VCAM-1 shedding and neutrophil infiltration during acute lung injury. J Immunol 197:2828–2837

17. Karmakar M, Katsnelson MA, Dubyak GR, Pearlman E (2016) Neutrophil P2X7 receptors mediate NLRP3 inflammasome-dependent IL-1β secretion in response to ATP. Nat Commun 7:10555

18. Danquah W, Meyer-Schewinger C, Rissiek B, Pinto C, Serracant-Prat A, Amadi M, Iacenda D, Knop JH, Hammel A, Bergmann P, Schwarz N, Assunção J, Rotthier W, Haag F, Tolosa E, Bannas P, Nolte F (2016) Nanobodies that block gating of the P2X7 ion channel. Sci Transl Med 8:366na162

19. Di Virgilio F, Vuerich M (2015) Purinergic signaling in the immune system. Auton Neurosci 191:117–123

20. Morandini AC, Savio LE, Coutinho-Silva R (2014) The role of P2X7 receptor in infectious inflammatory diseases and the influence of ectonucleotidases. Biomed J 39:316–324

21. Csóka B, Németh ZH, Toró G, Idzkó M, Zech A, Koscsó B, Spolarics Z, Antonioli L, Cseri K, Erdélyi K, Pacher P, Haskó G (2015) Extracellular ATP protects against sepsis through macrophage P2X7 purinergic receptors by enhancing intracellular bacterial killing. FASEB J 29:3626–3637

22. Santana PT, Benjamim CF, Martinez CG, Kurtenbach E, Takiya CM, Coutinho-Silva R (2015) The P2X7 receptor contributes to the development of the exacerbated inflammatory response associated with sepsis. J Innate Immun 7:417–427

23. Savio LE, Andrade MG, de Andrade Mello P, Santana PT, Moreira-Souza AC, Kolling J, Longoni A, Feldbrügge L, Wu Y, Wyse AF, Robson SC, Coutinho-Silva R (2016) P2X7 receptor signaling contributes to sepsis-associated brain dysfunction. Mol Neurobiol

24. Yang D, He Y, Munoz-Planillo R, Liu Q, Núñez G (2015) Caspase-11 requires the pannexin-1 channel and the purinergic P2X7 pore to mediate pyroptosis and endotoxic shock. Immunity 43:923–932

25. Soares-Bezerra RJ, Pinho RT, Bisaggo RC, Benévolo-de-Andrade TC, Alves LA (2015) The search for new agonists to P2X7R for clinical use: tuberculosis as a possible target. Cell Physiol Biochem 37:409–418

26. Nagahama M, Seike S, Shirai H, Takagishi T, Kobayashi K, Takehara M, Sakurai J (2015) Role of P2X7 receptor in Clostridium perfringens beta-toxin-mediated cellular injury. Biochim Biophys Acta 1850:2159–2167

27. Almeida-da-Silva CL, Morandini AC, Ulrich H, Ojcius DM, Coutinho-Silva R (2016) Purinergic signaling during Porphyromonas gingivalis infection. Biomed J 39:251–260

28. Greve AS, Skals M, Fagerberg SK, Tonnis W, Ellermann-Eriksen S, Evans RJ, Linkermann A, Praetorius HA (2017) P2X2, P2X4, and P2X7 receptor knock out mice expose differential outcome of sepsis induced by α-haemolysin producing Escherichia coli. Front Cell Infect Microbiol 7:113

29. Ali SR, Timmer AM, Bilgrami S, Park EJ, Eckmann L, Nizet V, Karin M (2011) Anthrax toxin induces macrophage death by p38 MAPK inhibition but leads to inflammasome activation via ATP leakage. Immunity 35:34–44

30. Corrêa G, Almeida Lindeberg C, Moreira-Souza AC, Savio LE, Takiya CM, Marques-da-Silva C, Vommaro RC, Coutinho-Silva R (2017) Inflammatory early events associated to the role of P2X7 receptor in acute murine toxoplasmosis. Immunobiology 222:676–683

31. Silva CL (2016) Purinergic signaling in schistosomal infection. Biomed J 39:316–325

32. Figliauro VO, Chaves SP, Savio LE, Thorstenberg ML, Machado Salles E, Takiya CM, D'Impeiró-Lima MR, de Matos Guedes HL, Rossi-Bergmann C, Coutinho-Silva R (2017) The role of the P2X7 receptor in murine cutaneous leishmaniasis: aspects of inflammation and parasite control. Purinergic Signal 13:145–152

33. Lee BH, Hwang DM, Palaniyar N, Grinstein S, Philpott DJ, Hu J (2012) Activation of P2X7 receptor by ATP plays an important role in regulating inflammatory responses during acute viral infection. PLoS One 7:e35812

34. Manzoor S, Akhtar U, Naseem S, Khalid M, Mazhar M, Parvaiz F, Khaliq S (2016) Ionotropic purinergic receptors P2X4 and P2X7: proviral or antiviral? An insight into P2X receptor signaling and hepatitis C virus infection. Viral Immunol 29:401–408

35. Leyva-Grado VH, Ermler ME, Schotsaert M, Gonzalez MG, Gillespie V, Lim JK, Garcia-Sastre A (2017) Contribution of the purinergic receptor P2X7 to development of lung immunopathology during influenza virus infection. MBio 8:e00229-e00217

36. Corrêa G, Lindeberg daC, Fernandez-Santos C, Gandini M, Pettingia PF, Coutinho-Silva R, Kubelka F (2016) The purinergic receptor P2X7 role in control of dengue virus-2 infection and cytokine/chemokine production in infected human monocytes. Immunobiology 221:794–802

37. Swartz TH, Dubyak GR, Chen BK (2015) Purinergic receptors: key mediators of HIV-1 infection and inflammation. Front Immunol 6:585

38. Graziano F, Desdouts M, Garzetti L, Podini P, Alfano M, Rubartelli A, Furlan R, Benaroch P, Poli G (2015) Extracellular ATP induces the rapid release of HIV-1 from virus containing compartments of human macrophages. Proc Natl Acad Sci U S A 112:E3265–E3273

39. Twari M, Monika VRK, Menon M, Seth P (2015) Astrocytes mediate HIV-1 Tat-induced neuronal damage via ligand-gated ion channel P2X7R. J Neurochem 132:464–476

40. Di Virgilio F, Giulian AL (2016) Purinergic signalling in autoimmunity: a role for the P2X7R in systemic lupus erythematosus? Biomed J 39:326–338

41. Hashimoto-Hill S, Friesen L, Kim M, Kim CH (2017) Contraction of intestinal effector T cells by retinoic acid-induced purinergic receptor P2X7. Mucosal Immunol 10:912–923

42. Souza DV, Dos Santos JT, Cabral FL, Barbisan F, Azevedo ML, Dias Carli LF, de Avila BS, Dos Santos Jaques IA, Rosa Leal DB (2017) Evaluation of P2X7 receptor expression in peripheral lymphocytes and immune profile from patients with indeterminate form of Chagas disease. Microb Pathog 104:32–38

43. Burnstock G (2013) Purinergic mechanisms and pain—an update. Eur J Pharmacol 716:24–40
44. Sorge RE, Trang T, Dorfman R, Smith SB, Beggs S, Ritchie J, Austin JS, Zaykin DV, Vander MH, Costigan M, Herbert TA, Yarkoni-Abitbol M, Tichauer D, Livneh J, Gershon E, Zheng M, Tan K, John SL, Slade GD, Jordan J, Woolf CJ, Peltz G, Maixner W, Diatченко W, Selzter Z, Salter MW, Mogil JS (2012) Genetically determined P2X7 receptor pore formation regulates variability in chronic pain sensitivity. Nat Med 18:595–599

45. Alves LA, Bezerra RJ, Faria RX, Ferreira LG, da Silva Frutuoso V (2013) Physiological roles and potential therapeutic applications of the P2X7 receptor in inflammation and pain. Molecules 18: 10953–10972

46. Zhang J, Li X, Gao Y, Guo G, Xu C, Li G, Liu S, Huang A, Tu G, Peng H, Quo S, Fan B, Zhu Q, Yu S, Zheng C, Liang S (2013) Effects of puerarin on the inflammatory role of burn-related pathological pain mediated by P2X7 receptors. Burns 39:610–618

47. Tsuda M (2017) P2 receptors, microglial cytokines and chemokines, and neuropathic pain. J Neurosci Res 95:1319–1329

48. Xie J, Liu S, Wu B, Li G, Rao B, Zou L, Ye Z, Zhao T, Zhao S, Schmalzing G, Hausmann R, Nie H, Li G, Liang S (2017) The protective effect of resveratrol in the transmission of neuropathic pain mediated by the P2X7 receptor in the dorsal root ganglia. Neurochem Int 103:24–35

49. Burnstock G, Di Virgilio F (2013) Purinergic signalling in cancer. Purinergic Signalling 9:491–540

50. Park JH, Williams DR, Lee JH, Lee SD, Lee JH, Ko H, Lee GE, Kim S, Lee JM, Abdelrahman A, Muller CE, Jung DW, Kim YC (2016) Potent suppressive effects of 1-piperidinylimidazole based novel P2X7 receptor antagonists on cancer cell migration and invasion. J Med Chem 59:7410–7430

51. Ferrari D, Malavasi F, Antonioli L (2017) A purinergic trail for cancer and stellate cells. Int J Cancer 139:2540–2552

52. Avanzato D, Genova T, Fiorio PA, Bernardini M, Bianco S, Bussolati B, Mancardi D, Giraudo E, Maione F, Cassoni P, Castellano I, Munaron L (2016) Activation of P2X7 and P2Y11 purinergic receptors inhibits migration and normalizes tumor-derived endothelial cells via cAMP signaling. Sci Rep 6:32602

53. Giannuzzo A, Saccomano M, Napp J, Maione F, Cassoni P, Castellano I, Munaron L (2016) Activation of P2X7 and P2Y11 purinergic receptors inhibits migration and normalizes tumor-derived endothelial cells via cAMP signaling. Sci Rep 6:32602

54. Garg AD, Krysko DV, Vandenabeele P, Agostinis P (2016) Extracellular ATP and P2X7 receptor exert context-specific immunomodulatory effects after immunogenic cancer cell death. Cell Death Dis 7:e2097

55. Marrone FB, Gehring MP, Nicoletti NF (2016) Calcium channels and associated receptors in malignant brain tumor therapy. Mol Pharmacol 90:403–409

56. Yadav M, Singh A, Rizvi N, Ali S, Salma S, Kumar V, Hussain SR (2015) The role of P2X7R in purinoreceptor osteosarcoma. Advances in Modern Oncology Research 1:88–96

57. Di Virgilio F, Adinolfi E (2017) Extracellular purines, purinergic receptors and tumor growth. Oncogene 36:293–303

58. Barden JA, Gildey-Baird A, Teh LC, Rajasekariah G-H, Pedersen J, Christensen NI, Spielman D, Ashley DM (2016) Therapeutic targeting of the cancer-specific cell surface biomarker nP2X7. J Clin Cell Immunol 7:432

59. Barden JA, Yuksei A, Pedersen J, Danieleitto S, Delprado W (2014) Non-functional P2X7: a novel and ubiquitous target in human cancer. J Clin Cell Immunol 5:327

60. Gilbert SM, Gidley Baird A, Glazer G, Barden JA, Glazer A, Teh LC, King J (2017) A phase I clinical trial demonstrates that nP2X7-targeted antibodies provide a novel, safe and tolerable topical therapy for basal cell carcinoma. Br J Dermatol 177:117–124

61. Salvestrini V, Orecchioni S, Talarico G, Raggioi F, Mazzetti C, Bertolini F, Orioli E, Adinolfi E, Di Virgilio F, Pezzi A, Cavo M, Lemoli RM, Curti A (2017) Extracellular ATP induces apoptosis through P2X7R activation in acute myeloid leukemia cells but not in normal hematopoietic stem cells. Oncotarget 8:5895–5908

62. Amoroso F, Capece M, Rotondo A, Cangelosi D, Ferrarin M, Franceschini A, Raffaghello L, Pistoia V, Varesio L, Adinolfi E (2015) The P2X7 receptor is a key modulator of the PI3K/GSK3β/VEGF signaling network: evidence in experimental neuroblastoma. Oncogene 34:5240–5251

63. Gomez-Villafuertes R, Garcia-Huerta P, Diaz-Diezamendi J, Miras-Portugal MT (2015) P2X7/Akt signaling pathway triggers P2X7 receptor expression as a survival factor of neuroblastoma cells under limiting growth conditions. Sci Rep 5:18417

64. Monif M, O’Brien TJ, Drummond KJ, Reid CA, Liubinovs D, Williams DA (2014) P2X7 receptors are a potential novel target for anti-glioma therapies. Journal of Inflammation 11:25

65. Fang J, Chen X, Wang S, Xie T, Du X, Liu H, Wang S, Li X, Chen J, Zhang B, Liang H, Yang Y, Zhang W (2015) The expression of P2X7 receptors in EPCs and their potential role in the targeting of EPCs to brain gliomas. Cancer Biol Ther 16:498–510

66. Gehring MP, Kipper F, Nicoletti NF, Sperotto ND, Zanin R, Sávigny J, Battistini AM (2015) Involvement of purinergic system in the release of cytokines by macrophages exposed to glioma-conditioned medium. J Cell Biochem 116:721–729

67. D’Alimonte I, Nargi E, Zuccarini M, Lamartini P, Di Iorio P, Giuliani P, Ricci-Vitiani L, Pallini R, Cacciaglì F, Ciccarelli R (2015) Potentiation of temozolomide antitumor effect by purine receptor ligands able to restrain the in vitro growth of human glioblastoma stem cells. Purinergic Signal 11:331–346

68. Takai E, Tsukamoto M, Harada H, Kojima S (2014) Autocrine signaling via release of ATP and activation of P2X7 receptor influences motile activity of human lung cancer cells. Purinergic Signal 10:487–497

69. Schneider G, Glaser T, Lameu C, Bdellaseta-Ismael A, Sellers ZP, Moniuszko M, Ulrich H, Ratayczak MZ (2015) Extracellular nucleotides as novel, underappreciated pro-metastatic factors that stimulate purinergic signaling in human lung cancer cells. Mol Cancer 14:201

70. Boldrini L, Giordano M, Ali G, Melfi F, Romano G, Lucchi M, Fontanini G (2015) P2X7 mRNA expression in non-small cell lung cancer: MicroRNA regulation and prognostic value. OncoLett 9:449–453

71. Souza CO, Santoro GF, Figliuolo VR, Nanini HF, de Souza HS, Castelo-Branco MT, Abalo AA, Paiva MM, Coutinho CM, Coutinho-Silva R (2012) Extracellular ATP induces cell death in human intestinal epithelial cells. Biochim Biophys Acta 1820:1867–1878

72. Hofman P, Cherrulis-Vicini J, Bazin M, Ilić M, Juhébetere X, Gilson E, Schmid-Alianna A, Boyer O, Adriouch S, Vouret-Craviari V (2015) Genetic and pharmacological inactivation of the purinergic P2X7 receptor dampens inflammation but increases tumor incidence in a mouse model of colitis-associated cancer. Cancer Res 75:835–845

73. Adinolfi E, Raffaghello L, Giuliani AL, Cavazzini L, Capece M, Chiozza P, Bianchi G, Kroemer G, Pistoia V, Di Virgilio F (2012) Expression of P2X7 receptor increases in vivo tumor growth. Cancer Res 72:2957–2969

74. Jelassi B, Anchelin M, Chamouton J, Cayuela ML, Clarysse L, Li X, Jond J, Liang LH, Roger S (2013) Anthraquinone emodin inhibits human cancer cell invasiveness by antagonizing P2X7 receptors. Carcinogenesis 34:1487–1496

75. Xia J, Yu X, Tang L, Li G, He T (2015) P2X7 receptor stimulates breast cancer cell invasion and migration via the AKT pathway. OncoL Rep 34:103–110
Shemon AN, Sluyter R, Fernando SL, Clarke AL, Dao-Ung LP, Fuller SJ, Stokes L, Skarratt KK, BJ G, Wiley JS (2009) Genetics of the P2X7 receptor and human disease. Purinergic Signal 5:257–262

Gorodeski GI (2009) P2X7-mediated chemoprevention of epithelial cancers. Expert Opin Ther Targets 13:1313–1332

Fuller SJ, Stokes L, Skarratt KK, BJ G, Wiley JS (2009) Genetics of the P2X7 receptor and human disease. Purinergic Signal 5:257–262

Shemon AN, Sluyter R, Fernando SL, Clarke AL, Dao-Ung LP, Skarratt KK, Saunders BM, Tan KS, BJ G, Fuller SJ, Britton WJ, Petrou S, Wiley JS (2006) A Thr357 to Ser polymorphism in homozygous and compound heterozygous subjects causes absent or reduced P2X7 function and impairs ATP-induced mycobacterial killing by macrophages. J Biol Chem 281:2079–2086

Slater M, Danieletto S, Gilday-Airad A, Teh LC, Barden JA (2004) Early prostate cancer detected using expression of non-functional cytotactic P2X7 receptors. Histopathology 44:206–215

Tafani M, Schito L, Pellegrini L, Villanova L, Marle G, Anwar T, Rosa R, Indelicato M, Fini M, Pucci B, Russo MA (2011) Hypoxia-increased RAGE and P2X7R expression regulates tumor cell invasion through phosphorylation of Erk1/2 and Akt and nuclear translocation of NF-κB. Carcinogenesis 32:1167–1175

Ruzsnavszky O, Telek A, Gönczi M, Balogh A, Remenyik E, Sperlagh B, Illes P (2014) P2X7 receptor: an emerging target in the central nervous system. Curr Med Chem 22:819–844

Adinolfi E, Capece M, Franceschini A, Falzoni S, Giuliani AL, Pezzi M, Calella M, Ghiyash A, Motta C, Capri M, Anwar T, Tafani M, Schito L, Pellegrini L, Villanova L, Marle G, Anwar T, Rosa R, Indelicato M, Fini M, Pucci B, Russo MA (2011) Hypoxia-increased RAGE and P2X7R expression regulates tumor cell invasion through phosphorylation of Erk1/2 and Akt and nuclear translocation of NF-κB. Carcinogenesis 32:1167–1175

Ruzsnavszky O, Telek A, Gönczi M, Balogh A, Remenyik E, Sperlagh B, Illes P (2014) P2X7 receptor: an emerging target in the central nervous system. Curr Med Chem 22:819–844

Adinolfi E, Capece M, Franceschini A, Falzoni S, Giuliani AL, Rotondo A, Sarti AC, Bonora M, Syberg S, Corigliano D, Pinton P, Jorgensen NR, Abelli L, Emionite L, Raffaghello L, Pistoia V, Pevarello P, Bovolenta S, Tonnari P, Pardo L, Yee IM, Criscuoli MG, Huang X, Ou A, Milligan CJ, Petrou S, Lea R, Taylor BV, Stankovich J, Butzkueven H, Gresle

Burnstock G (2015) Physiological roles of P2X receptors in the central nervous system. Curr Med Chem 22:819–844

Sperlagh B, Illes P (2014) P2X7 receptor: an emerging target in the central nervous system. Curr Med Chem 22:819–844

Cisneros-Mejorado A, Perez-Samartin A, Gottlieb M, Maturé C (2015) ATP signaling in brain: release, excitotoxicity and potential therapeutic targets. Cell Mol Neurobiol 35:537–547

Pevarello P, Bovolenta S, Tonnari P, Z a L, Severi E, Torino D, Vitalone R (2017) P2X7 antagonists for CNS indications: recent patent disclosures. Pharm Pat Anal 35:1–6

Monif M, Reid CA, Powell KL, Drummond KJ, O’Brien TJ, Williams DA (2016) Interleukin-1β has trophic effects in microglia and its release is mediated by P2X7R pore. J Neuroinflammation 13:173

Metzger MW, Walser SM, Apriole-Garcia F, Dedic N, Chen A, Holsboer F, Arzt E, Wurst W, Deussing JM (2017) Genetically dissecting P2rx7 expression within the central nervous system using conditional humanized mice. Purinergic Signal 13:153–170

Miras-Portugal MT, Diaz-Hernandez JJ, Gomez-Villafuertes R, Diaz-Hernandez M, Artalejo AR, Gualix J (2015) Role of P2X7 and P2Y2 receptors on α-secretase-dependent APP processing: control of amyloid plaques formation “in vivo” by P2X7 receptor. Cell Struct Funct 13:176–181

Sáez-Orellana F, Godoy PA, Bastidas CY, Silva-Grecchi T, Guzmán L, Aguayo LG, Fuentealba J (2016) ATP leakage induces P2XR activation and contributes to acute synaptic excitotoxicity induced by soluble oligomers of β-amyloid peptide in hippocampal neurons. Neuropsychopharmacology 100:116–123

Woods LT, Ajit D, Camden JM, Erb L, Weisman GA (2016) Purinergic receptors as potential therapeutic targets in Alzheimer's disease. Neuropharmacology 104:169–179

Chen X, Hu J, Jiang L, Xu S, Zheng B, Wang C, Zhang J, Wei X, Chang L, Wang Q (2014) Brilliant Blue G improves cognition in an animal model of Alzheimer's disease and inhibits amyloid-β-induced loss of filopodia and dendrite spines in hippocampal neurons. Neuroscience 279:94–101

Burnstock G (2017) Purinergic signalling and neurological diseases: an update CNS Neurol Disord Drug Targets 16:257–265

Carmo MR, Menezes AP, Nunes AC, Piássavo A, Rolò AP, Palmíere CM, Cunha RA, Canas PM, Andrade GM (2014) The P2X7 receptor antagonist Brilliant Blue G attenuates contralateral rotations in a rat model of Parkinsonism through a combined control of synaptotoxicity, neurotoxicity and gliosis. Neuropharmacology 81:142–152

Jörg M, Scanmell PJ, Capuano B (2014) The dopamine D2 and adenosine A2A receptors: past, present and future trends for the treatment of Parkinson's disease. Curr Med Chem 21:3188–3210

Wang XH, Xie X, Luo XG, Shang H, He ZY (2017) Inhibiting purinergic P2X7 receptors with the antagonist brilliant blue G is neuroprotective in an intranigral lipopolysaccharide animal model of Parkinson's disease. Mol Med Rep 15:768–776

Burnstock G (2015) Purinergic signalling in neuroregeneration. Neuro Regeneration Research 10:1919

Bj G, Field J, Dutertre S, Ou A, Kilpatrick TJ, Lechner-Scott J, Scott R, Lea R, Taylor BV, Stankovich J, Butzkueven H, Gresle M, Laws SM, Petrov S, Hoffman S, Akkad DA, Graham CA, Hawkins S, Glaser A, Bedik SK, Hillert J, Maturé C, Antiguedad A, Wiley JS (2016) A rare P2X7 variant Arg307Gln with absent pore formation function protects against neuroinflammation in multiple sclerosis. Hum Mol Genet 24:5644–5654

Sadovnik AD, Bj G, Traboulsi AL, Bernales CQ, Encarnacion M, Yee IM, Criscuoli MG, Huang X, Ou A, Milligan CJ, Petrov S, Wiley JS, Vilarino-Guell C (2017) Purinergic receptors P2RX4 and P2RX7 in familial multiple sclerosis. Hum Mutat 38:736–744

Díaz-Hernández M, Domenico J, Sánchez-Nogueiro J, Gómez-Villafuertes R, Canals JM, Alberich J, Miras-Portugal MT, Lucas JJ (2009) Altered P2X7-receptor level and function in mouse models of Huntington's disease and therapeutic efficacy of antagonist administration. FASEB J 23:1893–1906

Cervetto C, Frattaroli D, Maura G, Marcoli M (2013) Motor neuron dysfunction in a mouse model of ALS: gender-dependent effect of P2X7 antagonism. Toxicology 310:69–77

Bartlett R, Sluyter V, Watson D, Sluyter R, Yerbury JJ (2017) Altered P2X7-receptor level and function in mouse models of Huntington's disease and therapeutic efficacy of antagonist administration. FASEB J 23:1893–1906
111. Apolloni S, Amadio S, Parisi C, Matteucci A, Potenza RL, Armida M, Popoli P, D’Ambrosi N, Volonté C (2014) Spinal cord pathology is ameliorated by P2X7 antagonism in a SOD1-mutant mouse model of amyotrophic lateral sclerosis. Dis Model Mech 7:1101–1109

112. Apolloni S, Amadio S, Montilli C, Volonté C, D’Ambrosi N (2013) Ablation of P2X7 receptor exacerbates gliosis and motor neuron death in the SOD1-G93A mouse model of amyotrophic lateral sclerosis. Hum Mol Genet 22:4102–4116

113. Bhattacharya A, Biber K (2016) The microglial ATP-gated ion channel P2X7 as a CNS drug target. Glia 64:1772–1787

114. Catanzaro JM, Hueston CM, Deak MM, Deak T (2014) The impact of P2X7 receptor antagonists in selected seizure models. PLoS One 11:e0156468

115. Avendano BC, Montero TD, Chávez CE, von Bernhardi R, Orellana JA (2015) Prenatal exposure to inflammatory conditions increases Cx43 and Panx1 unopposed channel opening and activation of astrocytes in the offspring on neuronal survival. Glia 63:2058–2072

116. Barron ML, Werry EL, McGregor IS, Kassiou M (2014) P2X7 in bipolar and depressive disorders. In: Weiss N, Koschak A (eds) Pathologies of calcium channels. Springer Berlin Heidelberg, Berlin, Heidelberg, pp 635–661

117. Zhang K, Liu J, You X, Kong P, Song Y, Cao L, Yang S, Wang W, Fu Q, Ma Z (2016) P2X7 as a new target for chrysophanol to treat lipopolysaccharide-induced depression in mice. Neurosci Lett 613:60–65

118. Ma M, Ren Q, Zhang JC, Hashimoto K (2014) Effects of brilliant blue G on serum tumor necrosis factor-α levels and depression-like behavior in mice after lipopolysaccharide administration. Clin Psychopharmacol Neuropsych 12:31–36

119. Iwata M, Ota KT, Li XY, Sakaue F, Li N, Dutheil S, Banasr M, Jimenez-Pacheco A, Diaz-Mendez M, Arribas-Blázquez M, Sanz-Rodriguez A, Olivos-Oré LA, Artalejo AR, Alves M, Letavic M, Miras-Portugal MT, Conroy RM, Delaney N, Farrell MA, O’Brien DF, Bhattacharya A, Engel T, Henshall DC (2016) Transient P2X7 receptor antagonism produces lasting reductions in spontaneous seizures and gliosis in experimental temporal lobe epilepsy. J Neurosci 36:5920–5932

120. Fischer W, Franke H, Krügel U, Müller H, Dinkel K, Lord B, Letavic MA, Henshall DC, Engel T (2016) Critical evaluation of P2X7 receptor antagonists in selected seizure models. PLoS One 11:e0156468

121. Rezmer K, Gao P, Araújo MG, Khan MT, Liu J, Rong W, Tang Y, Franke H, Krügel U, Fernandes MJ, Iles P (2016) Pilocarpine-induced status epilepticus increases the sensitivity of P2X7 and P2Y1 receptors to nucleotides at neural progenitor cells of the juvenile rodent hippocampus. Cereb Cortex 27:3568–3585

122. Tu G, Zou L, Liu S, Wu B, Lv Q, Wang S, Xue Y, Zhang C, Yi Z, Zhang X, Li G, Liang S (2016) Long noncoding NONRATT021972 siRNA normalized abnormal sympathetic activity mediated by the upregulation of P2X7 receptor in superior cervical ganglia after myocardial ischemia. Purinergic Signal 12:521–535

123. Granado M, Amor S, Montoya JJ, Monge L, Fernández N, García-Villalón AL (2015) Altered expression of P2Y2 and P2X7 purinergic receptors in the isolated rat heart mediates ischemia-reperfusion injury. Vascul Pharmacol 73:96–103

124. Du D, Jiang M, Liu M, Wang J, Xia C, Guan R, Shen L, Ji Y, Zhu D (2015) Microglial P2X7 receptor in the hypothalamic paraventricular nuclei contributes to sympathoexcitatory responses in acute myocardial infarction rat. Neurosci Lett 587:227–232

125. Martinez CG, Zamith-Miranda D, da Silva MG, Ribeiro KC, Brandão IT, Silva CL, Diaz BL, Bellio M, Persechini PM, Kurtenbach E (2015) P2X7 purinergic signaling in dilated cardio-myopathy induced by auto-immunity against muscarinic M2 receptors: autoantibody levels, heart functionality and cytokine expression. Sci Rep 5:16940

126. Zempo H, Sugita Y, Ogawa M, Watanabe R, Suzuki J, Isobe M (2015) A P2X7 receptor antagonist attenuates experimental autoimmune myocarditis via suppressed myocardial CD4+ T and macrophage infiltration and NDPH oxidase 2/4 expression in mice. Heart Vessels 30:527–533

127. Stachon P, Heidenreich A, Merz J, Hoppe N, Bode C, Idzko M, Zirlik A (2016) Deficiency of purinergic receptor P2X7 reduces atherosclerosis in mice. Circulation 134(Suppl 1):A16502

128. Luo W, Guth CM, Jolayemi O, Duvall CL, Brophy CM, Cheung-Flynn J (2016) Subfailure overstretch injury leads to reversible functional impairment and purinergic P2X7 receptor activation in intact vascular tissue. Front Bioeng Biotechnol 4:75

129. Gicquel T, Le Dare B, Boichet E, Lagente V (2017) Purinergic receptors: new targets for the treatment of gout and fibrosis. Fundam Clin Pharmacol 31:136–146
142. Monção-Ribeiro LC, Faffé DS, Santana PT, Vieira FS, da Graca CL, Marques-da-Silva C, Machado MN, Caruso-Neves C, Zin WA, Borojевич R, Takiya CM, Coutinho-Silva R (2014) P2X7 receptor modulates inflammatory and functional pulmonary changes induced by silica. PLoS One 9:e101085

143. Chen S, Zhu Z, Klebe D, Bian H, Kraft PR, Tang J, Zhang J, Zhang JH (2014) Role of P2X purinoceptor 7 in neurogenic pulmonary edema after subarachnoid hemorrhage in rats. PLoS One 9:e89042

144. Lucattelli M, Ciccó S, Muller T, Lommatzsch M, De Cunto G, Cardini S, Sundas W, Grimm M, Zeiser R, Durk T, Zissel G, Söröricht S, Ferrari D, Di Virgilio F, Virchow JC, Lungarella G, Idzkó M (2011) P2X7 receptor signaling in the pathogenesis of smoke-induced lung inflammation and emphysema. Am J Respir Cell Mol Biol 44:423–429

145. Zheng X, Li T, Chen Y, Pan H, Li Z (2016) Estrogen receptor beta (ERβ) plays a crucial role in P2X7 receptor function in smoking. PLoS One 11:e0150868

146. Amaral EP, Ribeiro SC, Lanes VR, Almeida FM, de Andrade MR, Zheng X, Li T, Chen Y, Pan H, Zhang Z, Dai Y, Wang J (2017) Purinergic Signalling (2018) 14:1

147. Ma B, Jiang Q, Li W, Li Z (2016) Role of P2X7 receptor in rat experimental colitis. Acta Histochem 118:429–436

148. Hafner S, Wagner K, Weber S, Gröger M, Wepler M, McCook O, Kurashima Y, Kiyono H, Kunisawa J (2015) Pathophysiological role of P2X7 receptor in rat experimental colitis. Acta Histochem 119:171–179

149. Turnier-CM, Lam F, Lai P-C, Tarzi RM, Bystock G, Houseyry VT, Unwin RJ (2007) Increased expression of the pro-apoptotic ATP-sensitive P2X7 receptor in experimental and human glomerulonephritis. Nephrol Dialysis Transplantation 22:386–395

150. Moncado-Ribeiro LC, Cagido VR, Lima-Murad G, Santana PT, Riva DR, Borojевич R, Zin WA, Cavalcante MC, Riva L, Brandão-Lima AC, Takiya CM, Faffé DS, Coutinho-Silva R (2011) Lipopolysaccharide-induced lung injury: role of P2X7 receptor. Respir Physiol Neurobiol 179:314–325

151. Hafner S, Wagner K, Weber S, Gröger M, Wepler M, McCook O, Scheuerle A, Stahl B, Huber-Lang M, Jung B, Calzia E, Georgieff H, Möller P, Frick M, Rademacher P, Wagner F (2017) Role of the purinergic P2X7 receptor in P2X4 receptor after blunt chest trauma in cigarette smoke-exposed mice. Shock 47:193–199

152. Antonioli L, Giron MC, Colucci R, Pellegrini C, Sacco D, Caputi V, Orso G, Tuccori M, Scarpignato C, Blandizzi C, Formai M (2014) Involvement of the P2X7 purinergic receptor in colonic motor dysfunction associated with bowel inflammation in rats. PLoS One 9:e116253

153. Neves AR, Castelo-Branco MT, Figliuolo VR, Bernardazzi C, Buongusto F, Yoshimoto A, Nanini HF, Coutinho CM, Carreiro AJ, Coutinho-Silva R, de Souza HS (2014) Overexpression of ATP-activated P2X7 receptors in the intestinal mucosa is implicated in the pathogenesis of Crohn’s disease. Inflamm Bowel Dis 20:444–457

154. Figliuolo VR, Savio LEB, Safiya H, Nanini H, Bernardazzi C, Abalo A, de Souza HSP, Kanellopoulos J, Bobe P, Coutinho C, Coutinho-Silva R (2017) P2X7 receptor promotes intestinal inflammation in chemically induced colitis and triggers death of mucosal regulatory T cells. Biochim Biophys Acta 1863:1183–1194

155. Ma B, Jiang Q, Li W, Li Z (2016) Estrogen receptor beta (ERβ) activation plays a therapeutic role in murine models of inflammatory bowel disease (IBD) via inhibiting P2X7 and P2X3 receptors. J Pathol 231:342–353

156. Munoz A, Yazdi IK, Tang X, Rivera C, Taghipour N, Grossman RG, Boone TB, Tasciotti E (2017) Localized inhibition of P2X7R at the spinal cord injury site improves neurogenic bladder dysfunction by decreasing urethralial P2X3R expression in rats. Life Sci 171:67–73

157. Wertheimer M, Gade A, Kang M, Hauser HF, Dewey WL, Al-Aghbari H (2017) Connexin-purinergic signaling in enteric glia mediates the prolonged effect of morphine on constipation. FASEB J 31:2649–2660

158. Zhou J, Wang H, Dai C, Wang H, Zhang H, Huang Y, Wang S, Gaskin F, Yang N, SM F, Zhao TC, Zhuang S (2015) P2X7 blockade attenuates lupus nephritis by inhibiting NLRP3/ASC/caspase-1 activation. Arthritis Rheum 67:3176–3185

159. Franco M, Bautista-Perez R, Cano-Martinez A, Pacheco U, Santamaria J, Del Valle-Mondragon L, Perez-Mendez O, Navar LG (2017) Physiopathological implications of P2X1 and P2X7 receptors in regulation of glomerular hemodynamics in angiotensin II-induced hypertension. Am J Physiol Renal Physiol: apjrenal.00663.02016

160. Menzies RJ, Unwin RJ, Bailey MA (2015) Renal P2 receptors and hypertension. Acta Physiol (Oxf) 213:232–241

161. Xi X, Naito Y, Hirokawa G, Weng H, Hiura Y, Takahashi R, Iwai N (2012) P2X7 receptor antagonist attenuates the hypertension and renal injury in Dahl salt-sensitive rats. Hypertens Res 35:173–179

162. Sollott S, Menini S, Rossi C, Ricci C, Santini E, Blasetti Fantauzzi C, Iacobini C, Pugliese G (2013) The purinergic P2X7 receptor participates in renal inflammation and injury induced by high-fat diet: possible role of NLRP3 inflammasome activation. J Physiol 591:324–335

163. Munoz A, Yazdi IK, Tang X, Rivera C, Taghipour N, Grossman RG, Boone TB, Tasciotti E (2017) Localized inhibition of P2X7R at the spinal cord injury site improves neurogenic bladder dysfunction by decreasing urethralial P2X3R expression in rats. Life Sci 171:67–73

164. Martins JP, Silva RB, Coutinho-Silva R, Takiya CM, Battistini AM, Morrone FB, Campos MM (2012) The role of P2X7 purinergic receptors in inflammatory and nociceptive changes accompanying cyclopenthamide-induced haemorrhagic cystitis in mice. Br J Pharmacol 165:183–196

165. Gonçalves RG, Gabrieli L, Rosário A Jr, Takiya CM, Ferreira ML, Chiarini LB, Persechini PM, Coutinho-Silva R, Leste M Jr (2006) The role of purinergic P2X7 receptors in the inflammation and fibrosis of unilateral ureteral obstruction in mice. Kidney Int 70:1599–1606

166. Xiao HT, Li SY, Liu W, Li N, Meng G, Yang N, Chen X, Zhou YG, Shen HY (2013) The effects of adenosine A3R receptor knockout on renal interstitial fibrosis in a mouse model of unilateral ureteral obstruction. Acta Histochem 115:315–319
183. Greig A VH, Cuthill S, Linge C, Clayton E, Burnstock G (2006) Altered responsiveness to extracellular ATP enhances acetonaminophen hepatotoxicity. Cell Commun Signal 11:10

184. Hoque R, Sohail MA, Salhanick S, Malik AF, Ghani A, Robson SC, Mehal WZ (2012) P2X7 receptor-mediated purinergic signaling promotes liver injury in acetonaminophen hepatotoxicity in mice. Am J Physiol Gastrointest Liver Physiol 302:G171–G179

185. Jiang S, Zhang Y, Zheng JH, Li X, Yao YL, YL W, Song SZ, Sun P, Nan JX, Lian LH (2017) Potentiation of hepatic stellate cell activation by extracellular ATP is dependent on P2X7R-mediated NLRP3 inflammasome activation. Pharmacol Res 117:82–93

186. Kavamura H, Aswad F, Minagawa A, Govindarajan S, Denny G (2006) P2X7 receptors regulate NK T cells in autoimmune hepatitis. J Immunol 176:2152–2160

187. Chandrashekaran V, Das S, Seth RK, Dattaroy D, Alhasson F, Amaral SS, Oliveira AG, Marques PE, Quintão JL, Pires DA, Purinergic Signalling (2018) 14:1

188. Varley I, Greeses JP, Sale C, Friedman E, Moran DS, Yanovich R, Wilson PJ, Garland A, Hughes DC, Stellingwerff T, Ranson C, Fraser WD, Gallagher JA (2016) Functional polymorphisms in the P2X7 receptor gene are associated with stress fracture injury. Purinergic Signalling 12:103–113

189. Agrawal A, Buckley KA, Bowers K, Furber M, Gallagher JA, Garland A (2010) The effects of P2X7 receptor antagonists on the formation and function of human osteoclasts in vitro. Purinergic Signal 6:307–315

190. Jorgensen NR, Boynaems JM, Di Virgilo F (2011) European meeting "P2 receptors: new targets for the treatment of osteoporosis". Purinergic Signal 7:275–276

191. Zanin RF, da Silva GL, Erig T, Sperotto ND, Leite CE, Coutinho-Silva R, Batastini AM, Morrone FB (2015) Decrease of serum adenine nucleotide hydrolysis in an irritant contact dermatitis mice model. J Invest Dermatol 139:1338–1347

192. Weber FC, Esser PR, Miller T, Ganses J, Pellegrati P, Simon MM, Zeiser R, Ildzko M, Jakob T, Martin SV (2010) Lack of the purinergic receptor P2X7 results in resistance to contact hypersensitivity. J Exp Med 207:2609–2619

193. Zanin RF, da Silva GL, Tergo ND, Leite CE, Coutinho-Silva R, Batistini AM, Morrone FB (2015) Decrease of serum adenosine nucleotide hydrolysis in an irritant contact dermatitis mice model: potential P2X7R involvement. Mol Cell Biochem 404:221–228

194. Gazzerro E, Baldassari S, Assereto S, Fruscione F, Pistorio A, Panicucci V, Volpi S, Perruzza L, Fiorillo C, Minetti C, Traggiai E, Grassi F, Bruno C (2015) Enhancement of muscle T regulatory cells and improvement of muscular dystrophic process in mdx mice by blockade of extracellular ATP/P2X2 axis. Am J Pathol 185:3349–3360

195. Sinadinos A, Young CN, Al-Khalidi R, Teti A, Kalinski P, Mohamad S, Floriot L, Henry T, Tezzi G, Jiang T, Wurtz O, Górecki DC (2015) P2RX7 purinoceptor: a therapeutic target for ameliorating the symptoms of duchenne muscular dystrophy. PLoS One 11:e0155107

196. Liu S, Zou L, Xie J, Xie W, Wen S, Xie Q, Gao Y, Li G, Zhang C, Xu C, Xu H, Wu B, Lv Q, Zhang X, Wang S, Xue Y, Liang S (2016) LncRNA NONRA TT021972 siRNA regulates neuropathic ameliorating the symptoms of duchenne muscular dystrophy. Cell Death Dis 7:2160

197. Bartlett R, Stokes L, Sluyter R (2014) The P2X7 receptor channel: potential P2X7R involvement. Mol Cell Biochem 404:221–228

198. Kostic TM, Schwarz P, Jorgensen NR The P2X7 receptor: a key player in immune-mediated bone loss? Scic World J 2014, 2014:10

199. Agrawal A, Buckley KA, Bowers K, Furber M, Gallagher JA, Garland A (2010) The effects of P2X7 receptor antagonists on the formation and function of human osteoclasts in vitro. Purinergic Signal 6:307–315

200. Jorgensen NR, Boynaems JM, Di Virgilo F (2011) European meeting "P2 receptors: new targets for the treatment of osteoporosis". Purinergic Signal 7:275–276

201. Zanin RF, da Silva GL, Erig T, Sperotto ND, Leite CE, Coutinho-Silva R, Batastini AM, Morrone FB (2015) Decrease of serum adenine nucleotide hydrolysis in an irritant contact dermatitis mice model. J Invest Dermatol 139:1338–1347

202. Weber FC, Esser PR, Miller T, Ganses J, Pellegrati P, Simon MM, Zeiser R, Ildzko M, Jakob T, Martin SV (2010) Lack of the purinergic receptor P2X7 results in resistance to contact hypersensitivity. J Exp Med 207:2609–2619

203. Zanin RF, da Silva GL, Tergo ND, Leite CE, Coutinho-Silva R, Batistini AM, Morrone FB (2015) Decrease of serum adenosine nucleotide hydrolysis in an irritant contact dermatitis mice model: potential P2X7R involvement. Mol Cell Biochem 404:221–228

204. Gazzerro E, Baldassari S, Assereto S, Fruscione F, Pistorio A, Panicucci V, Volpi S, Perruzza L, Fiorillo C, Minetti C, Traggiai E, Grassi F, Bruno C (2015) Enhancement of muscle T regulatory cells and improvement of muscular dystrophic process in mdx mice by blockade of extracellular ATP/P2X2 axis. Am J Pathol 185:3349–3360

205. Sinadinos A, Young CN, Al-Khalidi R, Teti A, Kalinski P, Mohamad S, Floriot L, Henry T, Tezzi G, Jiang T, Wurtz O, Górecki DC (2015) P2RX7 purinoceptor: a therapeutic target for ameliorating the symptoms of duchenne muscular dystrophy. PLoS One 11:e0155107

206. Liu S, Zou L, Xie J, Xie W, Wen S, Xie Q, Gao Y, Li G, Zhang C, Xu C, Xu H, Wu B, Lv Q, Zhang X, Wang S, Xue Y, Liang S (2016) LncRNA NONRA TT021972 siRNA regulates neuropathic ameliorating the symptoms of duchenne muscular dystrophy. Cell Death Dis 7:2160
pain behaviors in type 2 diabetic rats through the P2X7 receptor in dorsal root ganglia. Mol Brain 9:44

206. Liu W, Ao Q, Guo Q, He W, Peng L, Jiang J, Hu X (2017) miR-9 mediates CALHM1-activated ATP-P2X7R signal in painful diabetic neuropathy rats. Mol Neurobiol 54:922–929

207. Wu B, Zhang C, Zou L, Ma Y, Huang K, Lv Q, Zhang X, Wang S, Xue Y, Yi Z, Jia T, Zhao S, Liu S, Xu H, Li G, Liang S (2016) LncRNA uc.48+ siRNA improved diabetic sympathetic neuropathy in type 2 diabetic rats mediated by P2X7 receptor in SCG. Auton Neurosci 197:14–18

208. Liu W, Ao Q, Guo Q, He W, Peng L, Jiang J, Hu X (2017) miR-9 mediates CALHM1-activated ATP-P2X7R signal in painful diabetic neuropathy rats. Mol Neurobiol 54:922–929

209. Rodrigues AM, Bergamaschi CT, Fernandes MJ, Paredes-Gamero EJ, Buri MV, Ferreira AT, Araujo SR, Punaro GR, Maciel FR, Nogueira GB, Higa EM (2016) LncRNA uc.48+ siRNA improved diabetic sympathetic neuropathy in type 2 diabetic rats mediated by P2X7 receptor in SCG. Auton Neurosci 197:14–18

210. Caseley EA, Muench SP, Roger S, Mao HJ, Baldwin SA, Jiang LH (2014) Non-synonymous single nucleotide polymorphisms in the P2X receptor genes: association with diseases, impact on receptor functions and potential use as diagnosis biomarkers. Int J Mol Sci 15:13344–13371

211. Barniol-Xicota M, Kwak SH, Lee SD, Caseley E, Valverde E, Jiang LH, Kim YC, Vázquez S (2017) Escape from adamantane: scaffold optimization of novel P2X7 antagonists featuring complex polycycles. Bioorg Med Chem Lett 27:759–763

212. Müller CE (2015) Medicinal chemistry of P2X receptors: allosteric modulators. Curr Med Chem 22:929–941

213. Park JH, Kim YC (2017) P2X7 receptor antagonists: a patent review (2010-2015). Expert Opin Ther Pat 27:257–267

214. Burnstock G (2006) Pathophysiology and therapeutic potential of purinergic signaling. Pharmacological Reviews 58:58–86

215. Burnstock G (2007) Physiology and pathophysiology of purinergic neurotransmission. Physiol Rev 87:659–797

216. Zhang Y, Zhang S, Ding Z (2017) Role of P2Y12 receptor in thrombosis. In: Islam MS (ed) Thrombosis and embolism: from research to clinical practice: volume 1. Springer International Publishing, Cham, pp 307–324, https://doi.org/10.1007/5584_2016_123

217. Ralevic V, Burnstock G (1998) Receptors for purines and pyrimidines. Pharmacol Rev 50:413–492

218. Matsumoto Y, Ohashi Y, Watanabe H, Tsubota K (2012) Efficacy and safety of diquafosol ophthalmic solution in patients with dry eye syndrome: a Japanese phase 2 clinical trial. Ophthalmology 119:1954–1960

219. Chen CC, Akopian AN, Sivilotti L, Colquhoun D, Burnstock G, Wood JN (1995) A P2X purinoceptor expressed by a subset of sensory neurons. Nature 377:428–431

220. Burnstock G (2016) Purinergic receptors and pain—an update. Frontiers in Medicinal Chemistry 9:3–55

221. Gever JR, Rothschild S, Henningsen R, Martin R, Hackos D, Panicker S, Rubas W, Oglesby I, Dillon MP, Milla ME, Burnstock G, Ford APD (2010) AF-353, a novel, potent orally bioavailable P2X3/P2X2/3 receptor antagonist. Br J Pharmacol 160:1387–1398

222. Abdulqawi R, Dockry R, Holt K, Layton G, McCarthy BG, Ford AP, Smith JA (2015) P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. Lancet 385:1198–1205

223. McHugh SM, Roman S, Davis B, Koch A, Pickett AM, Richardson JC, Miller SR, Wetten S, Cox CJ, Karpe F, Todd JA, Bullmore ET (2012) Effects of genetic variation in the P2RX7 gene on pharmacodynamics of a P2X(7) receptor antagonist: a prospective genotyping approach. Br J Clin Pharmacol 74:376–380

224. Allsopp RC, Dayl S, Schmid R, Evans RJ (2017) Unique residues in the ATP gated human P2X7 receptor define a novel allosteric binding pocket for the selective antagonist AZ10606120. Sci Rep 7:725

225. Karasawa A, Kawate T (2016) Structural basis for subtype-specific inhibition of the P2X7 receptor. Elife 5:e22153

226. Kasuya G, Yamaura T, Ma XB, Nakamura R, Takemoto M, Nagumo H, Tanaka E, Dohmae N, Nakane T, Yu Y, Ishitani R, Matsuzaki O, Hattori M, Nureki O (2017) Structural insights into the competitive inhibition of the ATP-gated P2X7 receptor channel. Nat Commun 8:876