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Review Article

P2X7 Receptors in Neurological and Car Disorders

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Abstract

P2X receptors are ATP-gated cation channels that mediate fast ex and spinal cord. Several P2X receptor subtypes, including P2X7, selectivity during prolonged exposure to ATP, which results in a ch daltons. The P2X7 receptor was originally described in cells of her and Na+ and Ca2+ and Na+ ions as well as the release of proi neuronal cell death through their ability to regulate the processin neurodegeneration, chronic inflammation, and chronic pain. Activa chronic inflammation, and chronic pain. Activation of P2X7 recep receptor-deficient mice have substantially attenuated inflammato chronic inflammatory pain. Moreover, P2X7 receptor activity, by re may be involved in the pathophysiology of depression. Apoptotic including atherosclerosis, restenosis, and hypertension, and may cells, P2X7 receptor activation, proinflammatory cytokine producti the P2X7 receptor may be viewed as a gateway of communication systems.

1. Introduction

The role of extracellular ATP and purinoceptors in cytokine regul
rapidly expanding area of research. ATP can act as a neurotransm
subclass P2X_7 on immune cells suggests that it also regulates i
addition, activation of this receptor has dramatic cytotoxic prop
cytokine production and release, propose that it can act as an
pathological insults in both nervous and other (e.g., cardiovascular

Neurodegeneration is the underlying basis of many disorders in
sclerosis, Parkinson's, Alzheimer's, and Huntington's dise
Alzheimer's disease (AD) has previously been viewed as an ep
damaged neurons provoke an activation response from glia. Accu
and points to a more active role of neuroinflammation in pathc
nervous system (CNS), glial cells (microglia, astroglia, and oligoc
roles for neurons but also in the healthy brain often respond
inflammatory processes. These processes are kept in check
neuroprotective responses that return the brain to homeostasis. C
result in a more severe and chronic neuroinflammatory cycle that
disease [1]. The delicate balance in this homeostasis can be c
initiating factors that result in disease (i.e., the neuroinflammation

Figure 1: The inflammatory cycle and neuro
point. In Alzheimer's disease, the neuroinf
activation of microglia and astrocytes in resp
beta (Aβ). Glia proinflammatory responses ac
α, IL-1β, S100β), chemokines (macrophage inf
oxidative stress-related molecules (nitric oxide
and/or death and can further propagate the inf

Clinical evidence in support of neuroinflammation as a pharmacolo
such as AD, comes from epidemiological and genetic linkage data
inflammatory drugs is correlated with a protective effect against A
proinflammation mediators are associated with increased risk [4].
expressed an array of inflammatory mediators, including cytokines
the disorder [5]. Neuroinflammation has been documented also in
from Parkinson's disease, multiple sclerosis, human immunod
various prion diseases [6–9], as well as cerebral ischemia [10],
[12]. The ability of P2X_7 receptor activation to regulate cytokine
other neurological disorders, for example, pain and depressior
Collectively these observations propose that excessive P2X_7 rec
constitutes a viable target for the discovery and development of
the current biology and cellular signaling pathways of P2X_7 recepto
receptor in neurological/psychiatric and cardiovascular diseases
antagonism.

2. P2X_7 Receptor Biology

Virtually all cell types express plasma membrane receptors fo
Presently, 15 members have been cloned and are classified into tw
and P2X receptors [13, 14]. P2X receptors function as ATP-gatec
K^+, and Ca^{2+} [15]. The ability of P2X receptors to act as direct

voltage-gated Ca^{2+} channels underlies their multiple roles in Ca^{2} channels are oligomeric complexes composed of protein subunits $P2X_1$ through $P2X_7$) expressed in mammalian and other ver conformation of the $P2X_7$ receptor channel appears to be a trim intrinsic dilation of the channel [13] or $P2X_7$ receptor-mediated dov

All functional P2X receptor subtypes display a very high selectivity The $P2X_7$ receptor is unusual among the P2X receptor family in th the formation of a reversible plasma membrane pore permeable property is likely due to the receptor's extended carboxy tern diverse range of cellular responses including phospholipase A_2, p (MAPK), and nuclear factor-kappa B (NF-κB) (Figure 2) [13].

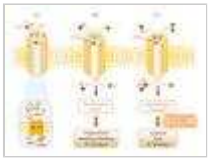

Figure 2: Structure and signaling functions receptor is a trimer [18], with the three prote channel pore. The subunits all share a comm spanning domains (TM1 and TM2), a large e containing 10 similarly spaced cysteines and amino termini. (b) Brief ATP activation (<10 s reversible channel opening that is permeable also triggers a series of cellular responses membrane blebbing, along with signaling ca Continued stimulation results in the formati facilitates the uptake of cationic molecules up frequently used as a tool to measure channel p fluorescent signal upon DNA binding). Furthe results in the induction of apoptosis/cell lysis. mainly through the activation of IL-1β convert of the $P2X_7$ receptor triggers the efflux of K^+ enzyme, leading to cleavage of pro-IL-1β to m

$P2X_7$ receptors are selectively expressed on cells of hematopo monocytes, peripheral macrophages, dendritic cells, T- and B-ly Within the CNS, functional $P2X_7$ receptors are localized on microgl 20]. The existence of functional $P2X_7$ receptors on peripheral or c poor selectivity of both antibodies and ligands targeting the rat P2 (dorsal root), $P2X_7$ receptors appear to be selectively localized characterized activity of the $P2X_7$ receptor is its role in interleukin- that have been primed with substances such as bacterial end activation of $P2X_7$ receptors in some cell types results in the physiological significance of this "highly stimulated" state of the P

The only known physiological activator of the $P2X_7$ receptor is receptor requires near millimolar concentrations of ATP ($EC_{50} \cong 3$ in the millimolar range, acute cell injury or death will cause massiv activated immune cells [25], macrophages [26], microglia [27], concentrations of nucleotide di- and tri-phosphates into the extrac increase significantly under inflammatory conditions in vivo [30] that ATP levels sufficient to activate the $P2X_7$ receptor may be r

proinflammatory cytokines and bacterial products up-regulate P2X
extracellular ATP [32, 33].

Deletion of $P2X_7$ abolishes the ability of extracellular ATP to induc
X_7 receptor-deficient mice are protected against symptom deve
antibody-induced arthritis [35]. Disruption of the $P2X_7$ receptor ge
pain [36], and may play a role in the pathophysiology of AD [37
receptor gene and both neuropsychiatric [38] and cardiovascular
in later sections.

3. $P2X_7$ Receptor Signaling

In macrophages/monocytes, $P2X_7$ receptor stimulation rapidly act
[40], extracellular signal-regulated kinase (ERK-1/2), and p38 M
benzoyl-benzoyl)ATP (BzATP) activates the same pathways in m
translocation of NF-κB in mouse BV-2 microglia [42]. Dephosphor
by calcineurin exposes a nuclear localization sequence, permitting
[43]. In N9 cells, ATP activates NFAT via the $P2X_7$ receptors in a
response element- (CRE-) binding protein (CREB), a member of th
transcription factors, is involved in cytokine gene regulation [45
ATF-1 phosphorylation occurs in BV-2 cells via an MAPK kinase
activator protein-1 (AP-1) is another transcription factor associa
Multiple members of the c-Fos and c-Jun families dimerize to form
$P2X_7$ receptors induced AP-1 DNA binding activity as a result o
treatment also increased the phosphorylation of ERK-1/2 and J
mechanism for these effects (Figure 3).

Figure 3: Schematic depiction of the signal tr
$P2X_7$ receptor activation. Extracellular calcium
receptors leads to activation of calcineurin ar
factor of activated T cells). $P2X_7$ receptor acti
A_2 and D (PLA_2, PLD), as well as tyrosine pl
activated protein kinase (MAPK) pathway p
regulated kinase, ERK). The latter can then in
κB (nuclear factor-κB), CREB (cyclic AMP res
(activator protein-1) which upregulate exp
cyclooxgenase-2 (COX-2) and inducible nitr
receptors also leads to p38 MAPK activatio
CREB. Broken lines indicate multistep pathway

Stimulation of $P2X_7$ receptors increases protein tyrosine phosphory
activation. Many events downstream of $P2X_7$ receptor activation a
44], and activation of MAPK pathways by $P2X_7$ receptors may invo
the calcium-dependent kinase Pyk2, which facilitates Ras activ
treatment with BzATP [48, 50], potentially linking calcium fluxe
receptors. $P2X_7$ receptors also induce the activation of other sm
Rho/p38 pathway may be involved in the shedding of IL-1β
reorganization and membrane blebbing [51, 52], conceivably pro
increased microglial proinflammatory cytokine release.

4. $P2X_7$ Receptors and Neurological/Psychiatric Dise

4.1. Neurodegenerative Disorders

$P2X_7$ receptors may affect neuronal cell death through their ability key mediator in neurodegeneration [53]. Deletion of the $P2X_7$ rec transient or permanent middle cerebral artery occlusion or by exc mouse hippocampal slice cultures were incubated for 3 hours to LF $P2X_7$ receptor agonist. A pronounced activation and apoptotic-like release of IL-1β, together with exacerbated CA3 pyramidal ce glutamatergic agonist α-amino-3-hydroxyl-5-methyl-4-isoxazole p rats subjected to spinal cord injury, areas surrounding the tra sustained pattern of ATP release, and delivery of $P2X_7$ antagon recovery and diminished cell death in the peritraumatic zone inflammatory environments [11], and $P2X_7$ receptor activation of neighboring neuronal cells. $P2X_7$ may be involved in the generati receptor-like immunoreactivity was upregulated around β-amyloi human amyloid precursor protein harboring the Swedish familial localized with activated microglia and astrocytes [37]. Upregulati been observed also after ischemia in the cerebral cortex of r immunoreactivity for the $P2X_7$ receptor on reactive astrocytes in m

Whether $P2X_7$ receptor over-expression is driving microglial activat a consequence of microglial activation is not known. Using cocultu al. [57] have recently shown that ATP and BzATP cause neuro antagonist Brilliant Blue G prevented the deleterious effects of BzA was attenuated by a superoxide dismutase mimetic and by a perc for reactive oxide species [57]. Cocultures composed of wild-type deficient mice failed to exhibit neuronal cell injury in the presenc microglia were derived from genotypically matched normal ($P2X_7^{+/+}$ thus appears necessary for microglial cell‐mediated injury of neur

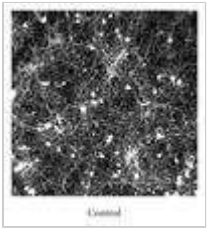

Figure 4: $P2X_7$ receptor activation injures co neurons and microglia were incubated for 3 ATP (BzATP) ± 3 μM Brilliant Blue G (Blue tubulin showed neurons to survive well and with unstimulated microglia (a), whereas degeneration (b) that the $P2X_7$ receptor antag from Skaper et al. [57], with permission from

A marked decline of intracellular ATP levels with a concomitant eff rat brain during the first few minutes after oxygen depletion in viv chemoattractant for microglia [60], directing them to a site of inju microglia [61], and microglial cells could encounter high levels observations indicate that ATP and ATP analogues do act via the health and that the $P2X_7$ receptor can serve as an important com (a)). Receptor antagonists of the $P2X_7$ receptor could have thera

ischemia and neuroinflammatory conditions by regulating patholog

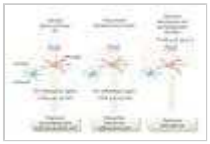

Figure 5: Schematic representation of the co activation in the nervous (a) and cardiovascul injury, infection, and autoimmune disorders, a levels of ATP and/or proinflammatory cyt neighboring cells by paracrine and autocrine p X_7 receptor may allow cells to sense and r environment, modulate the transcription of g and thus regulate cytokine responses. The P2X to spread the ATP wave as its activation trigg release, culminating in pathology. These chara X_7 receptors encourage the therapeutic exploit

4.2. Pain

ATP is recognized as one of the keys for the relay of sensory infor also one of several important mediators involved in immune-neur cells inside and outside of the CNS release ATP to affect surrou gathering body of literature linking activated microglia and astro and maintenance of neuropathic pain [65–67]. Both the localizati the fact that ATP acting at P2X_7 receptors serves as an efficient se IL-1β from proinflammatory cells [68] have implicated a role for P 5(a)).

Labasi et al. [35] observed a lower incidence and severity of receptor knockout mice compared with wild-type, suggesting a p /immune-mediated disease. Deletion of the *P2X*$_7$ gene abolished macrophages isolated from these mice [34]. Local administration effects in the complete Freund' s adjuvant-induced mechanical recently, Chessell et al. [36] demonstrated that in mice lacking hypersensitivity is completely absent to both mechanical and ther preserved. In these knockout animals, systemic cytokine analysis IL-1β, IL-6, IL-10, and macrophage chemoattractant protein-1. M dorsal root ganglia and injured nerves obtained from chronic neur are increased in the nervous system in response to trauma assoc and hyperexcitability [70]. At the level of the spinal cord, blockage animal models of inflammation and nerve injury-induced pain [71,

Much recent research has focused on the development of novel, se P2X_7 receptor [73–77]. A-740003 and A-438079 are structura therapeutic efficacy on neuropathy-induced mechanical allodynia [in the carrageenan- and adjuvant-induced thermal hyperalgesia consistent with a study of an adamantane P2X_7 antagonist (AACB A-740003 and A-438079, which showed dose-dependent antinoc preclinical testing of P2X_7 antagonists strongly suggests therapeuti

4.3. Depression

Intriguingly, cytokines like IL-1β are suggested to be involv

neuropsychiatric disorder is recognized as having high prevalen
autoimmune, and neurodegenerative disorders, conditions associa
proposed that excessive secretion of macrophage cytokines, fo
potential causative factor [81]. Central and systemic administratio
to animals induces what has been described as “sickness be
physiological and behavioral changes associated with depression [
symptoms of sickness behavior in animals and those of depressio
cytokines can induce neuroendocrine and neurochemical changes a
of cytokines (e.g., IFN-α) produces depressive-like symptoms tha
[85]. Not only do patients suffering from major depression, w
significant elevations in the density of microglia [86] and elevat
[87–89] but also mice lacking functional type 1 or type 2 TNF-α r
Cytokines may thus be involved in the etiopathogenesis of depress

Linkage studies have shown that the $P2X_7$ gene may be involv
analysis of a French population indicated a Gln640Arg single nucle
potential susceptibility gene for bipolar effective disorder [91]
polymorphism is located at the C-terminal domain of the $P2X_7$ re
Identified polymorphisms in the $P2X_7$ receptor of lymphocytes ar
trafficking of the receptor to the membrane surface, thus decrea
consequences for cytokine release of polymorphisms in the $P2X_7$
which result in reduction in TNF-α release from LPS stimulated le
[96] have recently described the behavioral profile of $P2X_7$ re
depression and anxiety, and found an antidepressant-like phenc
subefficacious dose of the antidepressant imipramine. Further re
mechanism(s) underlying the antidepressant-like characteristics
inactivation of the *P2* X_7 gene is physiologically translated into the

Activation of the inflammatory response in the etiology of depres
drugs display negative immunoregulatory effects [97]. Indeed,
mechanisms of action, at therapeutically effective concentrations,
in vitro [98] and in vivo [99, 100]. In addition, antidepressants at
elicited by immunostimulation and cytokine administration to h
increased production of proinflammatory cytokines seen in dep
receptors may thus constitute a novel target for the treatment of d

5. $P2X_7$ Receptors and Cardiovascular Disease

ATP is an important neurotransmitter being released with nora
sympathetic nerves; it acts at postjunctional P2X receptors to evok
contributions of ATP and noradrenaline as functional cotransmitte
vessel, the tone/pressure of the blood vessel, and in disease [10
signaling events are associated with the control of blood vesse
perivascular nerves, smooth muscle, and endothelial cells [102,
immunoreactivity was detected in all arteries, with the exceptio
receptor-specific immunoreactivity was seen in the outer adventiti
In the large coronary and cerebral arteries, weak diffuse $P2X_7$ re
smooth muscle layer [104]. $P2X_7$ receptors are involved in sym
arteries of the rat hepatic mesentery [105]. Smooth muscle laye

functional $P2X_7$ receptors [106], suggesting their participation in t
is novel, since the umbilical cord lacks sympathetic innervation [1
is capable of increasing contractile tension in cardiac tissue via P
was not identified. While ATP can also induce vasodilation in isolat
receptor site responsible was not characterized [109 – 111].

Apoptotic cell death is recognized to occur in a number of vascular
hypertension [112, 113]. Vascular endothelial cells are continuo
shear stress that occurs during changes in blood flow causes a sub
which might mediate alterations in the balance between prolif
receptors leads to the production of proinflammatory cytokines, ar
activation of caspase 3 [113] which, conceivably, play a role
Stimulation of $P2X_7$ receptors on human dendritic cells induces
[117], which may have implications for triggering and propagati
vessels. $P2X_7$ receptor activation reportedly amplifies LPS-induced
endothelial cells, in turn inducing downstream nitric oxide produ
important regulator for vascular hypotensive responses in inflan
(b)). Intriguingly, evidence suggests that ambulatory blood pressu
X_7 receptor gene [119].

In cutaneous vessels where purinergic neurotransmission is
physiological and pathological roles of nerve-released ATP have b
human saphenous vein myocytes contribute to the contractile ef
conditions allowing $P2X_7$ receptor activation to cause lysis of ven
and inflammation, or membrane damage, conditions found in the
generated by reduced ecto-ATPase activity [123], may lead
disorganization and loss of contractile myocytes in the muscle la
disease.

It is well established that both ATP and noradrenaline are corel
Although in a range of muscular arteries both neurotransmitters c
is the predominant sympathetic neurotransmitter in rat mesenteri
increased responses produced by ATP at higher pressures coulc
observed in hypertension.

Fibroblasts are a key structural element of the arterial wall, majc
source of inflammatory mediators [127, 128]. In human patholc
degenerative diseases such as atherosclerosis and diabetic angiop
are a source of mediators that stimulate endothelial cells and prc
damage of the arterial intima and media [127]. In diabetes, the
changes [130], the pathogenesis of which is incompletely unde
modifications of fibroblast reactivity. In diabetic patients, fibrobla
thus rendering these cells sensitive to inflammatory factors release
ATP is released at the site of atherosclerotic lesions or during
interesting to note a recent study demonstrating that fibroblasts fr
hyperactive purinergic loop based either on a higher level of ATF
together with an increased pericellular concentration of ATP, anc
spontaneous rate of apoptosis at least in part dependent on autoc
[133] (Figure 5(b)). Accumulation of fibronectin in the interstitial
play a major role in the pathogenesis of diabetic tissue damage [
diabetic rabbits led to a marked reduction in retinal blood velocity a

6. Concluding Remarks

It is now generally accepted that high levels of extracellular r pathological conditions such as inflammation, trauma, and stres conditions exhibit enhanced $P2X_7$ receptor expression in the neur coexisting feature. Recent findings suggest that increased $P2X_7$ re than $P2X_7$ receptor over-expression being a consequence of micro may thus allow cells to sense and respond to events occurring transcription of genes involved in cellular inflammatory processes, distribution of $P2X_7$ receptors and the fact that high concentration P2X receptor may be viewed as a ‘danger’ sensor. The therapeu because of their potential role, not only in such disorders as AD, but also in multiple sclerosis [138], inflammatory neuropathic depressive illness. The discovery of $P2X_7$ receptor-selective anta acute blockage of $P2X_7$ receptors significantly reduces nociceptio inflammatory pain, while there is growing appreciation for the role 1β processing [139], the analgesic activity of $P2X_7$ receptor anta receptors in neuronal-glial cell interactions associated with ongo some selectivity on different types of cells in the cardiovascular s may have promise as clinical antihypertensive and antithromboti may be viewed as a key point of communication between the nerv investigation of the $P2X_7$ receptor with receptor subselective anta specific clinical trials will help to evaluate this target’s potential th

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