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Review article

# P2X7 receptor as a double-edged sword: Neurotrophic and neurotoxic effects

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ABSTRACT

Strong activation of the P2X7 receptor (P2X7R) by extracellular ATP is excitotoxic to neurons during brain ischemia or in spinal cord injury. In addition, activation of P2X7R in microglia is known to cause neuroinflammation and consequently neurodegeneration. This review focuses mainly on the direct effects of activation of P2X7R in neurons. P2X7R is an ATP-gated, nonselective ion channel that provides an influx pathway for $Na^+$ and $Ca^{2+}$, and upon sustained ATP stimulation, dilates into a pore permeable to molecules up to 900 Da. Mechanisms governing P2X7R-mediated cell death due to $Ca^{2+}$ overload in the cytosol and possible involvement of perturbation of $Ca^{2+}$ homeostasis in the endoplasmic reticulum and mitochondria are also discussed. In contrast to strong P2X7R activation, basal and mild activation of the P2X7R have been known to exert both antiapoptotic and proliferative effects in cancer cells, glial cells, and some neuroblastomas. How these effects are related to endoplasmic reticulum and mitochondrial $Ca^{2+}$ homeostasis are described. In addition, the putative role that mild P2X7R activation plays as a neurotrophic signal is discussed.



## 1. Introduction

Extracellular ATP not only functions as a neuromodulator or cotransmitter in cholinergic, gamma-aminobutyric acid (GABA)-ergic, adrenergic, and glutamatergic nerve terminals, but also acts as a fast neurotransmitter in its own right in the central as well as the peripheral nervous system [1–3]. The storage of ATP in synaptic vesicles, $Ca^{2+}$-triggered release, extracellular degradation by ecto-ATPases, and versatile signaling through pre- or postjunctional membrane receptors all indicate that this simple molecule is a neurotransmitter [3,4].

In addition to its physiological roles, a number of pathophysiological effects have been attributed to ATP signaling (for reviews, see [3,4]). Among these, ATP has been shown to be involved in excitotoxicity in neural tissues. In brain ischemia and in stroke, excitotoxicity occurs when a hyperactivation of glutamate receptors leads to cytosolic $Ca^{2+}$ overload and neuronal cell death. What complicates the situation is that during brain ischemia/hypoxia, extracellular ATP levels also increase [5]. Pathologically high levels of ATP can lead to or worsen excitotoxicity [5,6]. Extracellular ATP activates neuronal and glial cell ATP receptors, such as metabotrophic P2Y and ionotrophic P2X receptors. P2X receptors have been known to play important physiological roles in neurotransmission, and are classified into P2X1–P2X7 [7]. Excessive amounts of extracellular ATP in pathological situations cause strong and chronic activation of certain P2X receptors, eventually leading to neurotoxicity.

The P2X7 receptor (P2X7R) in particular has attracted recent attention. Activation of P2X7R, a cation channel, elicits

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substantial $Ca^{2+}$ influx and exacerbates excitotoxicity. The P2X7R has traditionally been regarded as a cytotoxic receptor or a "cell death receptor." For instance, P2X7R stimulation *in vivo* is lethal to rat retinal ganglion neurons, especially in hypoxic conditions [8,9]. Activation of the P2X7R, together with nerve growth factor, aggravates hypoglycemia-induced cell death in cerebellar granule neurons [10]. P2X7R stimulation also causes necrotic death in SN4741 dopaminergic neurons derived from the substantia nigra of transgenic mouse embryos [11] and accounts for neurotoxicity in spinal cord injury [12,13]. P2X7R stimulation is also cytotoxic to neural progenitor cells, thereby preventing successful implantation [14]. Interestingly, it has been shown that activation of P2X7R induces death of retinal cholinergic neurons during normal development, thus regulating the optimal density of these neurons [15]. P2X7R stimulation is detrimental not only to neurons, but also to glial cells. For instance, P2X7R stimulation is cytotoxic to microglial cells [16] and causes damage to oligodendrocytes [17,18]. What worsens the situation is that, during cerebral ischemia, P2X7R expression has been shown to be upregulated [19]. Furthermore, *in vitro* ischemia has also been shown to enhance the sensitivity of P2X7R to ATP [20].

It is conceivable that inhibition of P2X7R stimulation would offer neuroprotection. Thus, downregulation of P2X7R expression by retinoic acid might suppress cell death induced by 2′,3′-O-(4-benzoylbenzoyl)-ATP (BzATP, a selective P2X7R agonist) in human SH-SY5Y neuroblastoma cells [21]. Substantial ATP release and the subsequent activation of P2X7R have been shown to account in part for the neurotoxicity after spinal cord injury, and there is evidence that significant improvement in spinal cord function can be achieved following pharmacological blockade of P2X7R [12,13].

## 2. The mechanism of P2X7R-mediated cytotoxicity

P2X7 receptors are distributed throughout the nervous system. These receptors are present in glial cells (astrocytes, microglia, and Schwann cells) as well as in sensory neurons, neurons in the brainstem, spinal cord, cerebral cortex, hippocampus, amygdala, cerebellum, thalamus, and several neuroblastoma cell lines [22]. One of the causes of P2X7R-mediated neurotoxicity is via activation of these receptors in microglial cells, which causes neuroinflammation (e.g., release of interleukin-1) and subsequent neurodegeneration. Therefore, pharmacological targeting of the P2X7R signaling pathway offers potential therapeutic opportunities for treating neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (for recent reviews, see [23,24]). This mechanism is not discussed in the present review article, but readers can consult recent reviews on this topic [23,24]. The other cause of P2X7R-mediated lethality is the direct death signal to the glia or neurons expressing P2X7R upon activation [22]. This review focuses mainly on the direct effect of P2X7R activation on neurons.

The P2X7 receptor is a nonselective cation channel pore that allows the influx of $Na^+$ and $Ca^{2+}$. It is a homotrimer that becomes activated upon the binding of three ATP molecules [25]. Each subunit has two transmembrane domains (TM1 and TM2), intracellular C- and N-termini and a large chunk of extracellular domain; the latter from each of the three subunits intertwine to surround a vertical cavity at the center.

P2X7R opens as a cation channel in response to high micromolar levels of ATP [25]. Opening of the channel allows for the influx of $Ca^{2+}$ and $Na^+$, and the resulting depolarization causes the opening of voltage-gated $Ca^{2+}$ channels, which eventually leads to $Ca^{2+}$ overload inside the cell. The high intracellular concentration of $Ca^{2+}$ causes activation of nucleases and proteases (e.g., calpains), which results in cell death [26]. $Ca^{2+}$ overload also leads to mitochondrial uptake of $Ca^{2+}$ and the collapse of mitochondrial membrane potential, which eventually culminates in caspase activation and apoptosis [27]. Upon sustained exposure to millimolar concentrations of ATP, the P2X7R, instead of being desensitized, further "dilates" to a nonselective pore permeable to much larger ions such as *N*-methyl-D-glucamine; in fact, the dilated pore allows for the passage of hydrophilic molecules of up to 900 Da [7]. The mechanism for such pore dilation is not yet fully understood, but may involve rotation and separation of the transmembrane helices in the presence of continued ATP binding [25]. The consequent efflux of small and essential cellular constituents through the dilated pore inevitably aggravates cellular toxicity.

Another consequence of excitotoxicity is the perturbation of intracellular organelles that are responsible for handling $Ca^{2+}$, such as endoplasmic reticulum (ER) and mitochondria. Interestingly, a moderately augmented filling of the ER and mitochondria provides a pathway for P2X7R-triggered cell proliferation (see the section on basal or mild P2X7R stimulation as a neurotrophic signal).

## 3. Perturbation of ER and mitochondrial $Ca^{2+}$ homeostasis

The ER performs several essential functions, namely, synthesis of proteins, post-translational modification and folding of proteins, degradation of malfolded proteins, and also intracellular $Ca^{2+}$ storage. Many hormones or neurotransmitters, by activating G-protein-coupled receptors that are associated with phospholipase C, generate inositol-1,4,5-trisphosphate ($IP_3$) and diacylglycerol from phosphatidyl-4,5-bisphosphate ($PIP_2$) cleavage. $IP_3$ binds to its receptor (IP3R, a $Ca^{2+}$-release channel) in the ER and mobilizes $Ca^{2+}$ from intracellular $Ca^{2+}$ stores, while diacylglycerol activates protein kinase C (see [28] for a review). This bifurcating signaling pathway is responsible for the physiological versatility of many neurotransmitters and hormones.

After $Ca^{2+}$ mobilization from the store by $IP_3$, the emptiness of the $Ca^{2+}$ store triggers the opening of a store-operated $Ca^{2+}$ channel at the plasma membrane; this channel is now believed to be composed of the proteins stromal interaction molecule (as a sensor of the $Ca^{2+}$ content in the store) and Orai (the channel protein molecule at the plasma membrane; Orai is tethered to the stromal interaction molecule) [29]. Besides the $IP_3$-sensitive $Ca^{2+}$ pool, there is also the ryanodine-sensitive pool; millimolar levels of caffeine or low micromolar concentrations of ryanodine bind to the ryanodine

receptor (RYR, a $Ca^{2+}$-release channel), which results in the release of intracellular $Ca^{2+}$. The physiological agonist of RYR has been proposed to be cADP-ribose (for a review, see [30]). Interestingly, cytosolic $Ca^{2+}$ acts as a co-agonist of IP3R and RYR. Therefore, high cytosolic $Ca^{2+}$ levels could result in a $Ca^{2+}$-induced $Ca^{2+}$ release (CICR) phenomenon [28,30].

Stress to the ER can be caused by hypoxia, toxins, protein synthesis overload, mutations causing protein malfolding, and perturbations of ER $Ca^{2+}$ stores [31]. Sustained reduction in $Ca^{2+}$ content inside the ER is a strong ER stress signal. For example, cyclopiazonic acid, which acts as a $Ca^{2+}$ store depletor by inhibiting the sarcoplasmic/ER $Ca^{2+}$ ATPase, can induce ER stress by emptying the ER of its store of $Ca^{2+}$. It should be noted that $Ca^{2+}$ overload could potentially, via the CICR mechanism mentioned above, aggravate neuronal excitotoxicity by releasing more stored $Ca^{2+}$ into the cytosol and by causing more depletion of the ER $Ca^{2+}$ pool [32], presumably causing more ER stress.

Whether, and to what extent, ER stress contributes to excitotoxicity in neurons is not fully understood. For instance, whether glutamate-mediated neuronal excitotoxicity involves ER stress still remains controversial. Kainic acid, a glutamate receptor agonist, causes hippocampal neuronal cell death, disintegration of the ER membrane, and appearance of ER stress proteins such as Bip, C/EBP homologous protein, and caspase-12 [33]. N-methyl-D-aspartate (NMDA), an agonist of another glutamate receptor subtype, has been shown to induce ER stress in rat retinal ganglion RGC-5 cells [34]. Conversely, it has been demonstrated *in vitro* and *in vivo* that NMDA receptor-mediated excitotoxic apoptosis of neurons in rat cerebellum, cortex, and hippocampus occurs without any indication of ER stress [35]. ATP-mediated (through P2X7R) neuronal excitotoxicity has been recognized and is known as one of the multiple factors that cause excitotoxicity [5,17]. However, no published information is hitherto available about whether P2X7R-mediated neurotoxicity involves ER stress. We have found that exposure of differentiated neuronal NG108-15 cells to 100 μM BzATP leads to P2X7R activation and the subsequent depletion of $Ca^{2+}$ stores, ER stress, and eventually cell death (unpublished observation). Further research is needed to investigate how $Ca^{2+}$ stores are depleted and whether the depletion involves the CICR mechanism.

$Ca^{2+}$ overload in neurons may also lead to an increase in mitochondrial $Ca^{2+}$ levels via $Ca^{2+}$ transfer from the ER to the mitochondria [36]. $Ca^{2+}$ release via the IP3R creates a very high $Ca^{2+}$ concentration in the ER-mitochondria cleft, which allows $Ca^{2+}$ to enter the mitochondria via a complex formed by the IP3R and voltage-dependent anion channel (VDAC, located in the outer mitochondrial membrane). $Ca^{2+}$ subsequently enters the matrix, presumably via the $Ca^{2+}$ uniporter in the inner mitochondrial membrane [36]. When the mitochondrial matrix $Ca^{2+}$ level reaches a toxic threshold, the permeability transition pore opens and leads to loss of ion and solutes to the cytosol, collapse of mitochondrial membrane potential, and activation of the apoptotic cascade [36]. It would be interesting to evaluate whether strong P2X7R activation in neurons leads to a $Ca^{2+}$ transfer from ER to mitochondria, and if that is the case, how it occurs. Does it occur via the IP3R–VDAC complex? Further investigations are needed to answer such questions.

## 4. Basal or mild P2X7R stimulation as a neurotrophic signal?

Although high (i.e., millimolar) levels of ATP have been shown to be cytotoxic, studies by Di Virgilio and colleagues in the past 10 years have revealed that the basal activities of the P2X7R cause antipoptotic as well as proliferative effects. For example, transfection of P2X7R-deficient lymphoid cells with P2X7R was shown to lead to cell proliferation in the absence of serum [37]. This initially surprising finding was subsequently confirmed by studies showing that several tumor cells had high levels of P2X7R expression [38–40]. The presence of P2X7R (by transfection of P2X7R in HEK293 cells) allows a tonic, albeit mild, stimulation resulting in raised membrane potential and $Ca^{2+}$ levels in the mitochondria, and higher intracellular ATP content, and allows cells to grow in serum-free medium [39]. Such basal stimulation is maintained by the autocrine release of endogenous cellular ATP, since degradation of extracellular ATP by apyrase abolishes cell proliferation. Chelation of extracellular $Ca^{2+}$ by EGTA also abolishes cell growth. It is, therefore, hypothesized that the tonic activation of P2X7R allows for a continuous small flux of $Ca^{2+}$ into the mitochondria, which mildly raises the mitochondrial [$Ca^{2+}$], and leads to increased oxidative phosphorylation and increased mitochondrial potential, and thus increased levels of ATP production. The enhancement in energy production is beneficial for cell growth and survival.

However, if the P2X7R-transfected cells are strongly stimulated by exogenous ATP, cytosolic [$Ca^{2+}$] markedly increases and mitochondria become overloaded with $Ca^{2+}$, leading to a collapse of mitochondrial membrane potential and eventually apoptosis [39]. Interestingly, in the same study, it was found that the P2X7R transfectants and the mock control did not differ in their basal cytosolic [$Ca^{2+}$], suggesting that the weak flux of extracellular $Ca^{2+}$ through the P2X7R could be taken up into the mitochondria, possibly via the ER, without causing any elevation in cytosolic [$Ca^{2+}$]. The above-mentioned proposal that $Ca^{2+}$ passes through the ER to reach the mitochondria is supported by further findings by the same group that P2X7R transfection in HEK293 cells augments $Ca^{2+}$ filling of the ER (i.e., resulting in higher ER $Ca^{2+}$ levels) [41]. $Ca^{2+}$ transfer from ER to mitochondria may occur via the IP3R–VDAC complex (see the previous section). P2X7R transfectants are more resistant to ceramide- and staurosporine-induced apoptosis; they also respond to agonists with larger $Ca^{2+}$ signals in the cytosol and mitochondria, offering these transfectants survival advantages upon stimulation by $Ca^{2+}$-mobilizing agents [41]. Those authors also observed that, in the P2X7R transfectants, there was a stronger activation of nuclear translocation of nuclear factor of activated T cell complex 1 (NFATc1); this activation is considered essential for growth since pharmacological blockade of NFATc1 activation has been shown to abolish the growth effect in P2X7R transfectants.

Does stimulation of P2X7 receptors also enhance cell growth of or protect neuronal cells? Raffaghello et al. [42] have shown that P2X7R stimulation by millimolar levels of ATP or BzATP does not kill but causes $Ca^{2+}$ elevation, plasma membrane depolarization, and enhanced growth of human

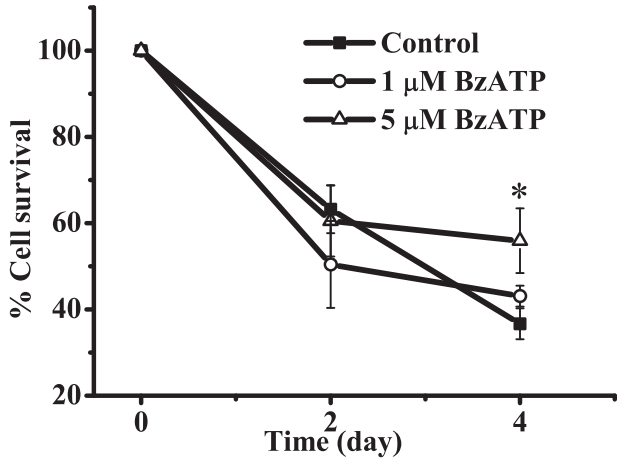


**Fig. 1 – NG108-15 cell death due to incubation in low serum (0.5% fetal bovine serum) was partially reversed by a low concentration of 2′,3′-O-(4-benzoylbenzoyl)-ATP (BzATP). Cells were incubated in medium containing only 0.5% FBS with or without 1 or 5 μM BzATP, and cell viability was determined by a trypan blue exclusion test on different days. Results are mean ± standard error from four separate experiments.**

neuroblastoma cells. It is noteworthy that such stimulation with maximal agonist concentrations only triggers a relatively small rise in cytosolic $Ca^{2+}$ levels, which may not suffice to cause $Ca^{2+}$ overload. The reason for this weak $Ca^{2+}$ signal (by maximal agonist concentration) is unclear. This stimulation does not trigger caspase-3 pathways, but instead causes growth promotion due to release of substance P by nucleotide-activated cells, acting via a autocrine/paracrine pathway [42]. More recently, P2X7R activation was also shown to be important in sustaining mouse N2a neuroblastoma cell viability [43].

We have been investigating whether weak stimulation of P2X7R could be neuroprotective in differentiated neuronal cell lines. In NG108-15 cells induced to differentiate by retinoic acid and forskolin, cells cease to divide and begin to develop long neurites characteristic of neurons. As shown in Fig. 1, differentiated control cells died over time when they were kept in low-serum (0.5% fetal bovine serum)-containing culture medium. Addition of a low concentration (5 μM) of BzATP increased cell survival significantly at day 4. This result suggests that weak P2X7R stimulation could be neuroprotective. We are in the process of delineating the protective mechanisms involved. Does the protection happen via mildly enhancing the filling of ER and mitochondria? It will also be of importance to examine whether similar protection would occur in primary neuron cultures. On the other hand, it would be interesting to examine whether a mild and tonic activation of P2X7R could provide a trophic signal to neural progenitor cells.

Basal P2X7R stimulation can also lead to microglial proliferation. For example, small interfering RNA knockdown of P2X7R expression or pharmacological blockade of P2X7R has been shown to markedly inhibit microglial growth [44]. In addition, it has been reported that overexpression of P2X7R alone (without inflammatory stimuli) suffices to stimulate proliferation of microglia in rat primary hippocampal cultures; this trophic effect has been shown to be abolished by selective P2X7R antagonists [45].

## 5. Conclusion and perspectives

The basal activities, or weak stimulation, of P2X7R appear to be important for the growth of a number of cancer cells, including neuroblastoma cells. Such mild activation may not involve large pore formation, and would allow a small $Ca^{2+}$ influx to enhance the filling of ER and the subsequent raising of mitochondrial $Ca^{2+}$ levels. Whether this mild stimulation of P2X7R is neuroprotective or even beneficial to the growth of neural progenitor cells warrants future in-depth exploration. Basal or weak P2X7R activities appear to promote glial cell activation and proliferation, but may lead to neuroinflammation and eventually neurodegeneration. Strong stimulation of P2X7 receptors, which is likely to involve large and nonselective pore formation, leads to cell death of both neurons and certain glial cells. Therefore, inhibition of P2X7R stimulation would offer dual neuroprotection: prevention of neuronal cell death and suppression of microglial activation. If mild P2X7R stimulation is trophic to neural progenitor cells, caution has to be exercised when P2X7R antagonists are administered as potential neuroprotective drugs.

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