P2X7 Receptors in Astrocytes

Subjects: Neurosciences

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P2X7 receptors (P2X7Rs) in astrocytes play essential roles in PC. Although P2X7Rs trigger inflammatory and toxic responses, PC-induced P2X7Rs in astrocytes function as a switch to protect the brain against ischemia.

Keywords: P2X7 receptor ; ischemic tolerance ; astrocytes

1. Introduction

The brain is one of the most vulnerable organs to ischemia. Therefore, scientists have been pursuing research to save the brain against ischemia, and have also spent a great deal of time and money developing drugs to treat stroke. There have been more than 1000 clinical trials on stroke targeting neurons, but most of them have failed [1]. Dr. Barres believes that a neuron-related strategy is insufficient to save the brain and will not result in effective therapeutic drugs for stroke. He has stated “Glial cells know how to save the brain, but researchers have not known yet” [2]. Despite the difficulties encountered in developing drugs and therapies for stroke, major progress has been made in research on ischemic tolerance. In this phenomenon, organs that experience prior mild non-invasive ischemic preconditioning (PC) acquire tolerance to subsequent invasive ischemic stress. This ischemic tolerance is commonly observed clinically and experimentally. The endogenous neuroprotective effects by PC were originally reported in the heart [3][4], but were also observed in the kidneys [5], liver [6], skeletal muscle [7], and the brain [8][9]. Since the discovery of ischemic tolerance [3], it has received tremendous attention because it shows robust neuroprotective effects. With regard to cerebral ischemic tolerance, there have been a large number of studies about mechanisms of ischemic tolerance [10][11], but almost all studies were performed from the point of view of neurons.

2. Localization and Functions of P2X7Rs

Purinergic signaling was proposed as extracellular signaling molecules in 1972, and recently focus has been put on the therapeutic potential of both P1 (adenosine) and P2 receptors [12]. For example, P2Y12 is a G protein-coupled receptor, and its antagonists inhibit aggregation in platelets and thus are widely used for the treatment of thrombosis and stroke [13]. Among seven subtypes of P2X ion channel receptors, P2X7Rs are a non-selective cation channel gated eATP, and it has been revealed that they play a crucial role in the CNS [14]. Although P2X7Rs are ion channels, they differ from other subtypes of P2X receptors in that P2X7Rs are much less sensitive to eATP, require ~mM eATP to be activated, have a long intracellular C terminus, and form a large pore when activated [15]. Therefore, the activation of P2X7Rs not only increases cation permeability, but also increases the permeability of larger molecules and various C-terminus-mediated intracellular signal cascades. These cascades include phosphatidylinositol 3-kinase/Akt, extracellular signal-regulated kinase, and mitogen-activated protein kinases [16][17]. Therefore, the roles of P2X7Rs are diverse and control various physiological and pathological events. These events include the release of proinflammatory cytokines, such as tumor necrosis factor [18] and interleukin-1β [19], proliferation [20], induction of cell death [21], phagocytosis [22], and inflammatory responses [23].

In the adult brain, P2X7Rs are mainly expressed in microglia. In physiological conditions, P2X7Rs are not active simply because eATP in the healthy brain is insufficient to activate these weakly sensitive P2 receptors [24][25]. Additionally, the findings that P2X7R knockout mice are healthy and have no major phenotype in physiological conditions [26] support the idea that P2X7Rs do not function well in the healthy brain. However, unlike physiological conditions, P2X7Rs are upregulated and activated in various pathological conditions or diseases (**Table 1**). P2X7Rs are associated with the pathological process of neuropathic pain via inflammatory responses, such as the release of tumor necrosis factor-α and interleukin-1β. In spared nerve injury, which is a neuropathic pain model, P2X7Rs are increased in microglia, and a P2X7R antagonist can suppress the development of mechanical hypersensitivity [27].

Table 1. Role of P2X7 receptors in central nervous system diseases.

Roles	Pathology (In Vivo Model)	Findings	Ref.
Protective	Cerebral ischemic tolerance by preconditioning (MCAO)	Cerebral ischemic tolerance is abolished in P2X7R knock-out mice	[28]
	Cerebral ischemic tolerance by postconditioning (BCAO)	Ischemic postconditioning-induced neuroprotective effects are abolished by pretreatment of pannexin 1/P2X7R antagonist mefloquine	[29]
	Multiple sclerosis (EAE)	BBG or oATP ameliorates chronic EAE by reducing demyelination	[30]
	ALS (SOD1-G93A mice)	BBG attenuates motor neuron loss in SOD1-G93A mice	[31]
	Parkinson's disease (6-OHDA)	BBG attenuates the 6-OHDA-induced neurotoxicity	[32]
	Alzheimer's disease (hAPP-J20 mice)	BBG prevents the development of amyloid plaques in hAPP-J20 mice	[33]
Harmful		P2X7R antagonist A-438079 suppresses the development of mechanical hypersensitivity in SNI model	[27]
	Neuropathic pain (SNI, PSL, and SNL)	Development of both thermal and mechanical hypersensitivity after PSL is absent in P2X7R knock-out mice	[34]
		P2X7R antagonist A-740003 reduces SNL-induced mechanical allodynia	[35]
	Status epilepticus (KA)	BBG or P2X7R antagonist A438079 protects against KA-induced neuronal death	[36]
	Huntington's disease (R6/1 mice)	Administration of BBG to R6/1 mice attenuates their motor-coordination deficit	[37]

Abbreviations: P2X7R, P2X7 receptor; MCAO, middle cerebral artery occlusion; BCAO, bilateral carotid artery occlusion; EAE, experimental autoimmune encephalomyelitis; BBG, brilliant blue G (P2X7R antagonist); oATP, oxidized ATP (P2X7R antagonist); ALS, amyotrophic lateral sclerosis; 6-OHDA, 6-hydroxydopamine; SNI, spared nerve injury; PSL, partial sciatic nerve ligation; SNL, spinal nerve ligation; KA, kainic acid.

P2X7Rs are also upregulated in other types of cells, such as neurons. In status epileptics induced by kainic acid, P2X7Rs are increased in dentate granule neurons, and kainic acid-evoked status epileptics are inhibited by P2X7R antagonists, suggesting the causal role of neuronal P2X7Rs in epilepsy [36]. In multiple sclerosis, P2X7Rs are increased in oligodendrocytes, and a P2X7R antagonist can reduce demyelination by chronic experimental autoimmune encephalomyelitis, which is a model of the disorder [30]. In a Huntington's disease mouse model, R6/1 mice, P2X7Rs are upregulated in neurons and microglia, and the administration of a P2X7R antagonist to R6/1 mice attenuates body weight loss and a motor coordination deficit [37]. Therefore, P2X7Rs appear to be associated with pathological events, and function as a "death receptor" or "toxic receptor". Several clinical studies have been performed to test the efficacy of P2X7R inhibitors on pathological events [38].

P2X7Rs also have beneficial roles in some pathological brains. For example, it has been reported that the activation of P2X7R by ATP induced the release of tumor necrosis factor-α from microglia, which protected neurons from *N*-methyl-D-aspartate-induced excitotoxicity in organotypic hippocampal slice cultures [39]. In a cerebellar granule neuron culture, Ortega et al. showed that glutamate-induced cell death was prevented by P2X7R agonist BzATP [40]. They also showed that BzATP elicited the neuroprotection of granule neurons via a phosphorylation of GSK3-mediated mechanism(s) [41]. In CNS diseases, the activation of the pannexin 1/P2X7R complex contributes to the neuroprotective mechanism of ischemic postconditioning [29]. Similarly to this effect, studies have shown that after mild, non-invasive brain ischemic PC, P2X7Rs are upregulated and have a central role in inducing "ischemic tolerance". Interestingly, after PC, P2X7Rs are mainly upregulated in astrocytes [28]. Furthermore, although ischemic tolerance is believed to be caused by cell autonomous mechanisms of neurons, astrocytes play a main role in its induction. Additionally, P2X7Rs play a major role in regulating astrocyte-mediated ischemic tolerance. Therefore, P2X7Rs are not solely toxic or death receptors, but are a double-edged sword to control the pathological brain.

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