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Case Report

The Role of P2y6 Receptor in Disease Occurrence and Progression

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Abstract

The P2Y6 receptor is a sub-type of P2Y receptors belonging to the G protein-coupled receptors family. The receptor is widely distributed and has recently gained attention because of its roles in various physiological processes. Moreover, the receptor has been implicated in the occurrence and development of many diseases. The activation of P2Y6 receptor leads to different biochemical pathways, depending on the disease context and the pathological environment. With the physiological functions, pharmacological features, and clinical value of P2Y6R has been revealed, targeted to P2Y6Ras new drugs make a great significance for a variety of disease prevention and control. This article reviews reorganized the distribution, properties, and diseases associated with P2Y6 receptor. We present evidence that P2Y6 receptor may have a detrimental or beneficial role in different pathological mechanisms and physiological processes, providing a theoretical basis for studies related to P2Y6 receptor.

Keywords: Purine Receptor; P2y6; Distribution; Properties; Role in Disease

Introduction

The theory of purine neurotransmission was first proposed by Burn stock in the year 1972. In this theory, Burn stock argued that the purine nucleotide/ATP utilized by the purine nerve is a neurotransmitter [1]. A few years later, some scholars named the ATP receptor as a purinergic receptor. Purine receptors are divided into P1 and P2, and P2 receptors are further divided into ligand-gated ion channel receptors (P2X) and G protein-coupled receptors (P2Y). The P2Y6 receptor (P2Y6R), one of the eight sub-types belongs to the G protein-coupled receptor family (P2Y), has recently gained attention because it is widely distributed and its roles in various physiological processes [2,3]. Moreover, it has also been implicated in the occurrence and development of many diseases. This article reviews recent advances in the distribution, properties, and diseases associated with P2Y6R, providing a theoretical basis for studies related to P2Y6R.

Properties and Signal Transduction of P2Y6R

P2Y6R is widely distributed in various tissues and organs. The endogenous ligands of the P2Y6R are extracellular nucleotide molecules, which mainly include Adenosine triphosphate (ATP), adenosine diphosphate (ADP), uridine triphosphate (UTP), as well as uridine diphosphate (UDP) and its derivatives. Under physiological conditions, the concentration of extracellular nucleotide molecules is usually significantly lower than the intracellular concentration. Under pathological conditions, such as hypoxia, inflammation, and injury, cells can communicate via autocrine or paracrine mechanisms and release intracellular nucleotides, thus leading to the extracellular activation of the P2Y6R, which produces a biological effect. In recent years, lots of literature has reported that the P2Y6 signaling pathways were revealed via the technology of laser confocal, patch clamp technique, RT-PCR and knockout etc. technology of molecular biology. P2Y6 receptors coupling with Gq/11 can activate signaling pathways of the following: (1) Activation of phospholipase C (PLCβ), intracellular increase of inositol triphosphate and diacylglycerol, endoplasmic reticulum Ca2+ release and enhanced PKC phosphorylation [4]. (2) Promote the trans-activation of epidermal growth factor receptor (EGFR) and the phosphorylation of erK1/2 and participate in DNA repair after cell injury [5]. (3) Promote the phosphorylation of C-Jun N-terminal kinase and myosin and facilitate the phosphorylation of P38MAPK acts on NF-κB to enhance its function [6,7]. (4) Promote the activation of meK1/2-ERK1/2 2-MAPK-API signaling pathway [8]. In addition, when P2Y6R coupled with G 12/13, the small G protein RhoA and its effect or molecule ROCK can be activated [9]. Protein Interacting with Cα kinase 1 (PICK1), can promote the

expression of P2Y6 receptors in cell membranes [10]. UDP and UTP are major endogenous ligands and agonist of P2Y6 receptors, while the former is approximately 100 times more efficient than the latter. ADP, ATP, and their 2-methylthio derivatives are virtually inactive [11,12]. MRS2964, MRS2957 PSB0474 and INS48823 are powerful P2Y6 receptor agonists developed in recent years [4-14]. MRS2578, MRS2567, and MRS2575 are currently the most commonly used antagonists of P2Y6R [13-15].

The Role of P2Y6R in Cardiovascular System

Promote the occurrence of vascular inflammatory lesions

P2Y6R is thought to promote the development of cardiovascular diseases by promoting vascular inflammation, enhancing vascular tone, and by promoting smooth muscle cell contraction and proliferation. The P2Y6R plays crucial roles in various functions of circulating blood cells, as well as in the cells that make up the wall of blood vessels [16,17]. Excessive activation of the P2Y6R can cause severe physiological dysfunction and disease. Under the stimulation of TNF-A or LPS, the expression of P2Y6 receptor on vascular endothelial cells is selectively up-regulated. P2Y6 receptors activate the NF-κB pathway to induce the expression of interleukin-8 (IL-8) and vascular cell adhesion molecule-1(CAM-1), promoting the occurrence of vascular inflammatory response [18]. A previous study has reported that the P2Y6R potentiates the pro-inflammatory responses of macrophages, plays a pro-atherogenic role and accelerates the formation of aneurysm in vascular disease [19], while a deficiency of P2Y6 can limit atherosclerosis and plaque inflammation in mice [19,20].

Mediated VSMC proliferation and contraction

Previous study revealed that P2X1, P2Y2 and P2Y6 are the most expressed purine receptors in vascular smooth muscle cells (VSMC), which may be involved in mediating the contraction and proliferation of smooth muscle cell [21]. Research of Bobbert et al. demonstrated that the cascade stimulation of Ras-Raf-MEK-ERK1/2 caused by activated P2Y6R, contribute to VSMC proliferation [22]. Govindan [23] has carried on the further study which confirmed P2Y6R is one of receptors to promoting VSMC proliferation and contraction. Moreover, nucleotides released by paracrine as a result of P2Y6-like receptor mediation has been shown to induce renal vasoconstriction in mice [24]. In cigarette smoke exposure (CSE) WT mice, the activity of neuronal UDP on the P2Y6R reduces contraction of left descending artery and increases the contraction of basilar artery (BA) [25]. Sub-chronic smoking induces vascular changes in WT mice through activity of P2Y6R and the induction slight variations in the endothelin-1 receptor. Notably, the contractility to UDP also altered in the cerebral and cardiac vascular system in CSE mice [25].

Promote myocardial fibrosis

Stimulation of cardiomyocyte P2Y6R can promote the development of myocardial fibrosis [26]. It has been revealed that the purinergic receptor P2Y6 promotes Ang II-induced hypertension [27-29]. Pressure (such as hypertension) stimulate cardiomyocytes, UDP, ATP and other nucleotide released to the extracellular via Pnx channels, stimulate P2Y6R in cardiomyocytes, regulates the expression of fibrosis factors (such as CTGF and TGF-β) through activated Rho pathway by coupled with G12/13 protein, thereby promoting the expression of downstream Type 1 collagen, and promoting the production of myocardial fibrosis [26]. The release of nucleotides coupled to specific autocrine/paracrine activation of the P2Y6 uracil nucleotide receptor could impair tissue perfusion in cardiovascular diseases [9].

The protective effect of P2Y6R on cardiovascular system

A previous study demonstrated that mouse P2Y6R is a regulator of cardiac development and cardiomyocyte function [30]. The extracellular pyrimidines UTP and UDP may be important inotropic factors in the development of cardiac disease [31]. Clouet and his team found that loss of P2Y6 was related to a large cardia phenotype and enlargement of diseased cardiac hypertrophy. The proliferation and size of cardiomyocytes in newborn without P2Y6 increase, leading to increased cardiac growth after birth. Loss of P2Y6R enhances pathological cardiac hypertrophy following isoproterenol injection. They also identified the inhibitory effect of UDP on isoproterenol-induced cardiomyocyte proliferation and hypertrophy in vitro. Thus, P2Y6R could be used as a therapeutic target to regulate cardiac hypertrophy [30]. However, further research is required to elucidate the mechanism. Therefore, the effect of P2Y6R on cardiovascular diseases has not been fully revealed, and the benefits or risks of this receptor for the process of cardiovascular diseases and treatment cannot be easily concluded in a word.

P2Y6R Involved in the Occurrence and Development of Neurological Diseases

The purinergic receptor P2Y6 is extensively expressed and distributed in nervous system, including sympathetic ganglia, superior cervical ganglia, dorsal root ganglia, and sciatic nerve [32]. Also, it was revealed that P2Y6R are expressed in anterior horn motor neurons, spinal dorsal horn microglia, hippocampal pyramidal neurons and dorsal root ganglion sensory neurons [33-35]. In the CNS, P2Y6R are expressed in the cerebral cortex, cerebellum, hippocampus, substantia nigra, striatum, and spinal cord [32]. This part aims to discuss the various functions of P2Y6R in some nervous system disease.

P2Y6R and Alzheimer's disease

Alzheimer's disease (AD) refers to a common advancing, incurable neurodegenerative disease. It is related to chronic activation of innate immunity within the nervous system [36]. Whether P2Y6R is connected with the pathological mechanism of AD is still under debate. The pathologically features of AD are the occurrence of β-amyloid plaques, amyloid vascular lesions and neurofibrillary tangles [37], accompanied by inflammation,

neuromal nutrition, pathological gliosis as well as nerve loss [27-33]. UDP released by degraded or damaged neurons, can activate P2Y6R, enhance chemotaxis, and then promote its phagocytosis [38]. Activation of P2Y6 enhanced the interstice in amyloid plaques, maintained synaptic plasticity and reversed the memory dependence on the hippocampus in the AD mouse model, indicating that P2Y6R regulated microglial phagocytosis is conducive to the reduction of burden and improved cognitive deficits [39]. P2Y6R in microglia has been shown to control the phagocytosis of nerve debris, thereby minimizing neuroinflammation in AD brain, although the same pathway may promote the phagocytosis of living neurons, leading to neurodegeneration [40]. And the P2Y6 agonist UDP can enhance the activation of microglia cells and the phagocytosis of neurons, thus leading to the death of neurons. Moreover, MRS2578, a P2Y6R antagonist, weakens this effect [41-44]. These findings confirm that changes in P2Y6R function may be associated with the development of Alzheimer's disease.

P2Y6R and Parkinson's disease

Parkinson's disease (PD), also known as tremor paralysis, is one of the commonest chronic advancing neurodegenerative disorder in the elderly, and it is featured with advancing loss of dopamine neurons in the substantia nigra and a reduction of dopamine level in striatum [45,46]. A previous study has indicated that inflammation may be a potential pathogenic mechanism of PD [47]. Yang et al. reported that the expression of P2Y6R together with inflammatory cytokinesis peripheral blood monocytes of PD patients was higher than that of healthy people and patients with multiple system atrophy (MSA), suggesting that P2Y6R may be a potential clinical biomarker of PD [44-48]. Furthermore, oxidative stress and neurodegeneration have been proposed to participate in the pathogenesis of PD. Qian, et al. [49] found that 1-methyl-4-phenylpyridinium (MPP(+)) increased the concentration of UDP/P2Y6RinSH-SY5Y cells, while inhibiting the pharmacological activity of P2Y6R or knockdown P2Y6R could inhibit the reactive oxygen species (ROS) level (induced by MPP(+)), thus playing a protective role, and knockdown P2Y6R also can reverse the loss of cellular vitality [50]. Similarly, apyrase and MRS2578, one of the most commonly used antagonists of P2Y6R, also weaken the role of MPP (+), while UDP amplify the role of MPP (+), indicating that P2Y6R may play a major role in PD pathogenesis. Evidence showed that MRS2578inhibited the death of dopaminergic neurons of rat nigral SH-SY5Y cells damaged by 6-hydroxydopamine (6-OHDA), both in vitro and in vivo. It is proved that antagonism of P2Y6R can lead to neuroprotective effects respectively [51]. However, the exact role of P2Y6R in PD has yet not to be confirmed, and it might as well be a result of neuronal damage or loss, inflammation, or oxidative stress, even a combination of these.

P2y6r In the Repair of Radiation-Induced Injury

Radiation therapy is one of the most effective methods to treat malignant tumor [52]. However, while helpful for the treatment of tumors may cause irreversible damage to healthy tissues [53]. A study reported that P2Y6R has a high expression in the human lung cancer A549 cells, knockout P2Y6R with MRS2578, the survival rate of tumor cell exposed to radiation decreased obviously, which confirmed that the activated P2Y6R accelerate the repair of DNA damage in tumor cell exposed to rays through ERK1/2 pathway [54]. Studies have shown that radiation could trigger microglial phagocytosis no matter in vitro and in vivo [7]. Moreover, UDP/P2Y6R is involved in the pathogenesis of radioactive brain injury, by triggering the activation of microglia phagocytosis, indicating that the P2Y6R plays a critical role in regulating microglial phagocytosis in radioactive brain injury, which may be a potential therapeutic strategy to relieve radioactive brain injury [5].

Regulate Microglia Cell Function

Microglia cells are the major immune and phagocytic cells of the central nervous system (CNS) and are involved in the monitoring and response of the central system microenvironment. Stimulate the microglia P2Y6 by physical markedly enhance the phagocytosis of damage neurons [9], inhibition of UDP/P2Y6 signaling pathways can prevent the phagocytosis of microglia cells in vivo and in vitro, effectively prevent neuron loss and death [10]. ATP and other nucleotides activate microglia through the up-regulation of P2Y6Rafter nerve injury and are involved in the occurrence of neuropathic pain [13,14]. Researchers have found that the use of the P2Y6R antagonist could suppress microglial polarization and IL-6 production, conducing to the decrease of neuropathic pain (NP) in chronic contractive injury (CCI)rats [55]. Kobayashi et al. found that the expression of P2Y6R in spinal microglia cells without nerve injury was significantly increased, which lasted for at least a couple of weeks after injury [56,57]. P2Y6 exists in spinal cord microglia, also exists in the spinal cord, the receptors in spinal cord injury rats are up-regulated, P2Y6R in spinal cord is involved in maintenance of neuropathic pain [32]. Therefore, P2Y6R inhibition may become a potential target of NP therapy in the future. However, some scholars have found that systemic and intrathecal administration of MRS2578 could not affect the neuropathic pain behavior caused by injury, which means that P2Y6R plays a minor role in neuropathic pain induced by nerve injury [58]. In summary, it is difficult to identify whether P2Y6R plays a role in the pathological process of neuropathic pain. In addition, P2Y6R is principally involved in the activation and phagocytosis of microglia activation [59]. It has been reported that P2Y6R-mediated microglial phagocytosis contributed to debris clearance and functional recovery after ischemic stroke [60]. The results show that microglial phagocytosis mediated by P2Y6R plays a protective role in the acute stage of ischemic stroke and may be a therapeutic target for ischemic stroke.

P2Y6 in Respiratory System

The role of P2Y6R in respiratory system is controversial. Some scholars believe that P2Y6 can play an active therapeutic role in respiratory diseases, and they found that GC021109 (pro-drug of P2Y6R) could inhibit the changes in lung function, reduce

inflammation and smooth muscle mass [61]. Besides, Schreiber and Kunzelmann reported that activation of the epithelial P2Y6R of the airway cavity could promote the secretion and transport of electrolytes [62]. P2Y6R signaling can prevent inappropriate allergic type 2 immune reactions when respiratory allergens are exposed. Targeted P2Y6 signal transduction may be a potential additional therapeutic strategy for the treatment of allergies [63]. The P2Y6R may be a novel therapeutic target for inhibiting excessive host response mediated by white blood cells in inflammatory lung diseases [64]. To sum up, they believed that the activation of P2Y6R could provide an effective strategy for the treatment of respiratory illness. On the contrary, some researchers reported that during airway inflammation, activation of the P2Y6R induces the production of pro-inflammatory factors, such as IL-6 and IL-8, in human bronchial epithelium and mouse macrophages in the process of airway inflammatory, thus promoting the occurrence of airway inflammation disease [65]. In airway epithelial cells, P2Y6 induces the expression of the C-C Motif Chemokine Ligand 20 (CCL20), promote the occurrence and maintenance of airway inflammation, and this effect can be significantly blocked by P38 inhibitors. Therefore, P2Y6 receptor is believed to induce the expression of CCL20 by activating the mitogen-activated protein kinase (MAPK) / P38 pathway [66] [13]. In the process of airway inflammation, the activation of P2Y6 induces the production of at least two kinds of pro-inflammatory factor (IL - 6 and IL - 8). This process is a Ca2+ dependent, the secretion of the inflammatory factors and the formation of the inflammatory network plays an important role in maintaining airway inflammatory disease [62]. The release of the cytokine IL-4, mast cell invasion, and airway remodeling phenotype were more severe in asthmatic mice treated with UDP. They held that P2Y6 and UDP were over-expressed in lung tissue of asthmatic mice induced by ovalbumin, and P2Y6 promotes inflammation and remodeling of allergic airways by enhancing the role of mast cells by activating the AKT signaling pathway [67]. Blocking P2Y6 can relieve inflammation without affecting the antibacterial properties of human neutrophilic peptide (HNP) [64]. Therefore, it is still under debate that whether the activation of P2Y6R provides an effective therapeutic or deleterious response in respiratory illness.

Regulating Bladder Function

Stimulate P2Y6 receptor in bladder smooth muscle can regulate its contraction through PLC/IP3 signal pathways [68]. In anesthetized mice, bladder epithelial cells activate P2Y6R by releasing of ATP, promotethe frequencies of bladder emptying [69]. Bladder epithelium activated P2Y6R to increase the frequencies of bladder contraction by pannexin-1 release ATP. Firouzmand et al. revealed that compared with wild-type mice, mice without P2Y6 urinate more frequently and have a smaller bladder volume, and in vivo bladder contractile analysis, the bladder contractile time of P2Y6 deficient mice was significantly shortened, but there was no difference in peak contractile pressure [70]. In vitro experiments showed that P2Y6 didn't involve in the contraction and relaxation of bladder muscle strips, nor does it participate in the release of ATP by mechanical stimulation of primary cultured urinary epithelial cells [71]. The P2Y6R in the central nervous system is involved in the inhibition of bladder incoming signals or the sensitivity of pons micturition centre, and P2Y6R in the detrusor may be involved in the process of promoting and maintaining bladder contractility. Relaxation of purine bladder signals may lead to persistent detrusor hyperactivity in patients with bladder outlet obstruction. Activation of uridine diphosphate sensitive P2Y6R indirectly increases the frequency of urinates in rats by releasing adenosine triphosphate from the urinary cortex [72]. In patients with benign prostatic hypertrophy (BPH), activation of P2Y6R amplifies the release of adenosine triphosphate in the sub-bladder mucosa, although UDP sensitive P2Y6R is highly expressed in epithelial cells and in the urothelium subcutaneous myofibroblasts [73]. Exogenous neural circuits are required for P2Y6R-mediated effects in the urinary tract epithelium, and the agonist of P2Y6R increased ATP level in the drainage by 3 times [69]. The activation of P2Y6R indirectly increases the urination frequency by releasing ATP through the urotheliumon sub-urothelial nerve afferents. Bladder dysfunction characterized by abnormal bladder smooth muscle (BSM) contractions is a key process in bladder hyperactivity, urge incontinence. P2Y6 activation can increase ATP-mediated BSM contractile by 45% [68]. Interference with purinergic signals in vivo results in changes in P2Y6 activity and bladder contractility. Therefore, P2Y6R may play an important role in dysuria characterized by abnormal bladder movement.

P2Y6R and Insulin Secretion

The P2Y6R accelerates the metabolism of glucose in peripheral tissues, and its agonists, including UDP, stimulate secretion of glucose-dependent insulin and protect pancreatic islet cells from apoptosis [74,75]. As an agonist, UDP has recently been shown to regulate agouti-related protein (AgRP) neurons. Besides, obesity-related hyperlipidemia and the onset of systemic insulin resistance are characterized by P2Y6 signaling in AgRP neurons [76,77]. Uptake of glucose by peripheral tissues such as skeletal muscles and adipocytes is an essential factor in maintaining glucose homeostasis. Activating P2Y6R by MRS2957 or UDP can stimulate the glucose uptake of primary adipose cells in wide-type mice, and MRS2578 antagonizes P2Y6R effect [75]. However, in adipocytes of P2Y6R knockout mice, P2Y6R agonist had no effect on glucose uptake, so did insulin. Extracellular UDP activates P2Y6R of pancreatic β-cells to release insulin and reduces cell apoptosis, which is beneficial to diabetes. Tsuchiya and his partners studied the function of P2Y6R in AMPK activation and insulin secretion of pancreatic β-cells in MIN6 mice, and they found that P2Y6R agonist could induce insulin secretion in the hyperglycaemic state [78]. Therefore, P2Y6R plays a crucial role in β-cell function, indicating that it may be a therapeutic target for diabetes.

Conclusion

Excessive activation of P2Y6R may cause serious physical dysfunction disease. P2Y6 involved in cardiovascular disease via

promoting vascular inflammation, improving vascular tension, facilitating the contraction of smooth muscle cells and proliferation. Therefore, research on regulation P2Y6 receptors may become a hotpot in the field of drug research for cardiovascular disease in the near future. P2Y6R expression or dysfunction can lead to damage neurons and glial cells, and CNS injury and the nervous system degenerative change can also lead to increased extracellular ATP release, and P2Y6R expression and function change further aggravate the CNS injury. And the role of P2Y6R in inflammation is twofold: the role of P2Y6R (activated) and other nucleotide ATP in against the invading pathogens or tumor is of vital importance to the correct inflammatory reaction, but P2Y6 in conditions such as asthma, chronic lung disease or enteritis etc. can cause the occurrence and the sustaining of chronic inflammation. At the same time, the activation of the P2Y6R stimulates the secretion of insulin, which means that its corresponding receptor agonists and antagonists could be potential anti-diabetic treatments. Therefore, studying the biological effects of P2Y6 receptors has crucial theoretical and application value. These studies above have sufficiently demonstrated that P2Y6R exist extensively in the nervous system and peripheral tissues and perform a variety of physiological functions: pain generation and modulation, nervous system development and regeneration, vasodilation, gland secretion regulation, neuronal and microglia function regulation, inflammatory response, memory function regulation, etc. Therefore, studying the biological effects of P2Y6R is of significant theoretical and practical value, particularly for treatment and prevention of cardiovascular, neurological, and respiratory etc. diseases. With the development of various new technologies, we human research for P2Y6 receptor signal transduction pathways have made great progress. All these researches suggested that P2Y6 receptor occupied a significant position in the process of regulating the organism physiological function and P2Y6 were involved in the occurrence and development of the disease. With the physiological functions, pharmacological features, and clinical value of P2Y6R has been revealed, targeted to P2Y6Ras new drugs make a great significance for a variety of disease prevention and control. In a word, P2Y6R is a multifaceted receptor that participates in many physiological and pathological conditions. P2Y6R may have distinct and conflicting results in different diseases, just like a double-edged sword. The activation of P2Y6R may create both protective and deleterious responses. And its role depends largely on its activation level, the type of cell becoming investigated, and the nature and the course of the disease. Under what circumstances can its blade be used against diseases, or will it hurt us? This is still an unsolved problem.

Declarations

Ethics approval and consent to participate: This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

Consent for publication

Not applicable.

Availability of Data and Materials

This article is based on previously conducted studies.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

HL and ZZ conceived the review. YR conducted the literature search and drafted the manuscript; HL finalized the paper and provided suggestions to improve it.

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