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Review

P2 receptors - promising targets for future drugs

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ABSTRACT

P2 receptors, where ATP is the main endogenous agonist, are widely distributed in human tissues and deserve significant interest as potential drug targets. Based primarily on our own results, in this review we discuss some possible directions for such drug development. We have suggested that P2 receptors are upregulated in human uterus during pregnancy and involved in physiological labor, while low concentration of ATP can potentiate the uterotonic activity of prostaglandins in labor. Cardiodepressant activity of ATP is more pronounced at low temperature, which draws attention to drug action (and interaction) during hypothermic cardiac surgery. P2 receptor-mediated vasoconstrictive effect is decreased in varicose veins, which opens up a promising field for development of new venotonic drugs.

KEYWORDS: P2 receptors, agonists, antagonists, ATP, novel drugs

INTRODUCTION

Intracellular purine nucleotides play an important role in the synthesis of nucleic acids and accumulation of energy, functioning of enzymes and ion channels. However, it is obvious now that adenosine -5'-triphosphate (ATP) as well as some other nucleotides can be released from nerve endings and secreting cells into the extracellular space and play the role of a neurotransmitter or neuromodulator in peripheral tissues, autonomic ganglia, peripheral and central nervous systems [1-6]. It was established that the physiological effects of extracellular ATP are implemented through specific receptors, which were initially named P_2-purinoceptors [7], and currently are named P2 receptors [4, 6], since not only purine, but also pyrimidine, nucleotides can be agonists of these receptors. Many laboratories and research centers are currently involved in the study of P2 receptors, and several pharmaceutical companies are doing in-depth research in developing new purinergic drugs. The real breakthrough in this field was the introduction of highly effective antiplatelet drugs - antagonists of platelet PY_{12}-receptors [8].

Classification of purinoceptors

Purinoceptors underwent numerous changes to their classification [7, 9, 10]. According to the current classification [11], purinoceptors are divided into two major classes - adenosine (or P1) receptors, and P2 receptors.

In addition, there is evidence showing the existence of "relative" receptors, which can be specifically activated by adenine [12], guanyl nucleotides [13], and dinucleoside-polyphosphates [14]. However, further research is required to confirm their structural and functional differences from the subtypes of adenosine and P2 receptors.

There is a number of publications, including detailed reviews, devoted to characteristics of adenosine receptors [15-18]; in this review we will mainly focus on P2 receptors and the perspectives for development of new drugs acting via these receptors.

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P2 receptors

P2 receptors are divided into two large families - P2X and P2Y. Each family consists of several receptor subtypes, indexed by corresponding numbers. These numbers are assigned only after the molecular structure of the receptor has been established and the receptor has been cloned. At present, seven subtypes of P2X and eight subtypes of P2Y receptors have been identified [6, 11].

According to the mechanism of action, P2X receptors belong to the family of ligand-gated ion channels that regulate the entry of sodium, potassium, and calcium ions into the cells. The major part of the receptor molecule is located extracellularly, forming a loop with the ligand-binding site. There are also two hydrophobic transmembrane regions and two terminal fragments that are located inside the cell. Distinction of receptor subtypes is mainly reflected in the length of the C-terminal fragment of the protein molecule [19-22].

Under physiological conditions, ion transport is provided by three P2X receptor subunits (multimers), which together form an ion channel. These ion channels can be homomultimers, i.e. complexes formed by subunits of only one subtype of P2X receptors, and heteromultimers when the formation of ion channels involves subunits of two different P2X receptor subtypes [22].

P2X receptors are widely represented in excitable tissues (nerve cells and smooth muscle cells), but are also present in immune system, blood and epithelial cells [23]. Important is the fact that P2X receptors are involved in establishing contacts with other stimulating and inhibiting receptors and ion channels ("cross-talk"), which explains the wide variety of effects of the agonists and antagonists of P2X receptors [24].

P2Y receptors by the mechanism of action are typical G-protein-coupled receptors. The receptor protein has 7 transmembrane fragments and forms three pairs of intracellular and extracellular loops. The differences between subtypes are mainly in the structure of the transmembrane fragments of the molecule [25]. In most cases inositol triphosphate serves as the secondary messenger, which is formed as a result of phospholipase C activation ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$), however in some cases signal mediation is conducted by modulation of cAMP levels ($P2Y_{12-14}$ receptors) [26].

P2 receptors are widely distributed in animal and human organs and tissues - Table 1 shows only

Table 1. Localization of subtypes of P2X and P2Y receptors (modified from [6]).

Subtype	Localization
$P2X_1$	Smooth muscles, platelets, cerebellum, posterior roots of spinal cord
$P2X_2$	Smooth muscles, central nervous system, autonomic and sensory ganglia
$P2X_3$	Sensory and sympathetic neurons
$P2X_4$	Central nervous system, testicles, colon
$P2X_5$	Proliferating cells of the skin, intestine, urinary bladder, spinal cord
$P2X_6$	Central nervous system, motoneurons of the spinal cord
$P2X_7$	Apoptotic cells, for example in the immune system, skin, pancreas
$P2Y_1$	Epithelial and endothelial cells, platelets, immune cells, osteoclasts
$P2Y_2$	Immune cells, epithelial and endothelial cells, renal tubules, osteoclasts
$P2Y_4$	Endothelial cells
$P2Y_6$	Some epithelial cells, placenta, T-cells, thymus
$P2Y_{11}$	Spleen, intestine, granulocytes
$P2Y_{12}$	Platelets, glial cells
$P2Y_{13}$	Spleen, cerebrum, lymphatic nodes, bone marrow
$P2Y_{14}$	Placenta, adipose tissue, stomach, intestine

some of their location sites. It has been shown that P2 receptors are involved in maintaining the vascular tone, in modulating neural transmission, in regulation of homeostasis and functions of many organs [27].

PPADS is an effective antagonist of P2 receptors

For a long time one of the most challenging problems with P2 receptor was the lack of effective and selective antagonists of these receptors. Arylazido aminopropionyl-ATP, α,β-methylene-ATP, reactive blue 2, suramin, trypan blue, and some other compounds were described as P2 receptor antagonists, however due to either low efficiency, or antagonistic non-selectivity they could not fully satisfy researchers [28].

A real breakthrough in this field was the emergence of a novel antagonist of P2 receptors, PPADS - pyridoxal-phosphate-6-azophenyl-2',4'-disulfonic acid, a compound, which is currently used as one of the reference analyzers. This compound was originally synthesized and studied in the University of Frankfurt [29], and then more detailed studies were conducted at the University College London. After analyzing the action of PPADS on several animal tissues, we established good antagonistic properties of PPADS in relation to P2X receptor-mediated processes.

We showed that on the rabbit isolated urinary bladder preparations PPADS causes concentration-dependent inhibition of P2X receptor-mediated contractions evoked by both α,β-methylene-ATP, a P2X receptor agonist, and by electric field stimulation in the presence of cholinergic and adrenergic receptor blockers [30]. Similar results were obtained in experiments on the rabbit central ear artery and femoral artery, where PPADS also inhibited P2X receptor-mediated contractions, caused by both an exogenous agonist and by purinergic nerve stimulation, in a concentration-dependant manner. At the same time, we established that at a working concentration (10 μM) PPADS did not significantly affect the P2Y receptor-mediated relaxation of rabbit aorta, nor did it affect the contractile responses of the rabbit arteries induced by noradrenaline or histamine [31]. Later, however, we also showed that at high concentrations (30 μM and higher) PPADS inhibits the relaxation of the guinea pig tenia coli mediated via P2Y receptors [32].

Overall, we established that PPADS is an effective antagonist of P2 receptors, exhibiting good selectivity to P2X receptors at concentrations no higher than 10 μM. Currently PPADS is widely used as an effective antagonist of P2 receptors, and is synthesized on a commercial basis by large chemical companies such as Sigma-Aldrich, RBI, Tocris Cookson.

P2 receptors in female reproductive system

ATP as a drug was introduced into clinical practice more than 50 years ago [33]. It was used in coronary artery disease, in peripheral vascular disease, and also to facilitate delivery, although the effect of the drug was not very stable. At that time most practicing physicians believed that the therapeutic effects of ATP resulted from the increase in the cell energy potential due to additional energy brought by ATP. However, biochemists and pharmacologists were confident that ATP as a highly polarized (charged) molecule cannot cross the cell membrane and cannot bring any energy inside the cells. So how does it work? By the end of 20th century the answer to this question was becoming increasingly evident - via P2 receptors, but this hypothesis needed strong evidence to prove it.

When we initiated our studies in this area, there was already evidence showing the presence of P2 receptors in the uterus of several experimental animals [23], but nothing was known about the presence of P2 receptors in the human uterus. For our study we used samples of human myometrium, which were obtained during elective Cesarean sections or hysterectomies for various indications. We found that isolated strips of pregnant human uterus produce phasic concentration-dependent contractions in response to ATP while the non-pregnant uterine muscle preparations showed no contractile responses to ATP [34]. Further, we found that other agonists of P2 receptor, similarly to ATP, also cause contractions of pregnant human myometrium. Incubation of the tissue with PPADS, a P2 receptor antagonist, significantly reduced the contractile responses of the pregnant uterus preparations caused by agonists of P2 receptors [35]. Based on these findings we made a

suggestion that P2 receptors are absent in the non-pregnant human uterus, but appear in the myometrium on the late stages of pregnancy.

In the next series of experiments we tried to establish a relationship between the expression of P2 receptors in the uterus and the gestational age. Considering understandable ethical constraints, we were able to show that starting from the 26^{th} week of pregnancy contractile responses to agonists of P2 receptors can be detected in the human myometrium and the strength of these responses increases with gestation age, becoming maximal at delivery [36]. We suggested that this phenomenon has a physiological meaning - P2 receptors appear on the late stages of pregnancy to enhance the contractile activity of the uterus during childbirth.

Analysis of the possible mechanisms of stimulation of the contractile activity of the pregnant myometrium by ATP showed that these contractions are at least partially mediated by prostaglandins, since indomethacin, an inhibitor of prostaglandin synthesis, significantly inhibited the amplitude of the contractile responses induced by ATP. On the other hand, L-NAME, an NO-synthase inhibitor, significantly increased the amplitude of contraction, providing evidence for the involvement of NO-dependent processes as well. We suggest that ATP, as a universal agonist of P2 receptors, evokes contractions mediated via P2X receptors, and at the same time also induces relaxative responses via P2Y receptor-mediated activation of NO-dependent processes. The latter is usually hardly noticeable, but becomes apparent when synthesis of NO is blocked [37].

Recently, a study was initiated to answer another important question - how female sex hormones influence the P2 receptor-mediated processes in the human uterus. These studies are currently ongoing, but we already have the first results: the synthetic analogue of estrogen - hexestrol - has a certain inhibitory effect on the contractile responses of isolated pregnant myometrium to ATP [38]. These findings open up a whole new field of the potential clinical significance of the interaction of hormones and P2 receptor agonists and antagonists.

In the next series of experiments, we analyzed the relationship of ATP with some compounds that stimulate the contractile activity of the uterus. We found that low concentrations of ATP (0.1-1 μM), which by themselves do not cause any contractile responses of the myometrium, significantly potentiate the contractions evoked by prostaglandin $F_{2\alpha}$ [39].

With permission of the local ethic committee, we conducted a pilot study of the interaction of ATP and prostaglandin $F_{2\alpha}$ in a clinical setting during childbirth. We found that continuous intravenous administration of ATP significantly enhances the effectiveness of prostaglandin stimulation of uterine contractions and accelerates the preparation of the birth canal [39, 40].

Human fallopian tubes were our next focus of research. The fallopian tubes were obtained during elective gynecological operations. We showed that isolated human fallopian tubes increase their spontaneous mechanical activity in the presence of ATP and other P2 receptor agonists [41]. Furthermore, it was found that the fallopian tubes of elder women have significantly greater sensitivity to ATP than the fallopian tubes of younger females. Increased contractile activity in response to ATP was also seen in the fallopian tubes with acute inflammatory processes in them (salpingitis) compared to those without inflammation [42].

Such changes in the functioning of the P2 receptors seem to be one of their specific features: in many tissues the activity of P2 receptors under physiological conditions is minimal, however it increases dramatically during pathological processes [27] and ageing [43].

It is well known that the spermatozoid meets the egg cell in the fallopian tubes where fertilization occurs. Therefore, increased mechanical activity of the fallopian tubes during inflammation may be the underlying cause of infertility in such women. From this perspective, the blockade of P2 receptors of the fallopian tubes by specific antagonists may be an important component of integrated treatment of female infertility.

P2 receptors in the human cardiovascular system

P2 receptors have been found in the heart, blood vessels and blood cells of many experimental

animals [23], however, the role of P2 receptors in the human cardiovascular system has not been studied enough. It has been shown that ATP has an antiarrhythmic effect when used in clinical settings, it also reduces blood pressure, improves peripheral circulation [44], but the presence and functional activity of P2 receptors in the human tissues of the cardiovascular system have not been studied.

We used myocardium preparations from right atrial appendages as material for these studies. Tissue samples were obtained from patients undergoing elective cardiac surgery for valve replacement or congenital heart defects. We found that ATP inhibits the amplitude of contractile responses of atrial preparations, while the P2 receptor antagonist, PPADS, significantly counteracts this effect. Interestingly, the inhibitory effect of ATP was more pronounced at hypothermic conditions than at normal temperature [45].

Unique sensitization of P2 receptors by low temperature was shown previously in animal smooth and skeletal muscles. We found that in the guinea pig smooth muscle tissues lowering the temperature causes an increase in P2 receptor-mediated contractions, compared to normal temperature, whereas the increase in the temperature has the opposite effect [46-48]. Subsequently we found a similar low-temperature sensitization in frog skeletal muscle tissue [49].

This finding could be of very high importance for anesthesiologists and cardiac surgeons, who use hypothermia as a means of brain protection during complex surgical procedures. We suggest that drugs, which act via P2 receptors could find significant application in such circumstances, since the P2 receptor activity increases with the decrease of temperature, while most of the other receptor systems possess an opposite property.

Human blood vessels were the other object of our studies. We used blood vessels that were either surgically removed, or were left unused after aortocoronary bypass surgery.

We compared the contractile responses of the isolated human great saphenous vein in response to agonists of P2 receptors from patients with and without varicose disease of the lower extremities. We found that P2X receptor-mediated responses of the veins obtained from patients with varicose disease were significantly less pronounced compared to the responses of the veins taken from patients without such pathology [50, 51]. We believe that the decrease of the venotonic action of agonists of P2 receptors may reflect certain disturbances in the receptor system of varicose veins. Probably this is of some importance in the development of varicose disease, and hence P2 receptors of the veins may be considered as potential drug targets.

Of the arterial blood vessels we used the gallbladder artery, which we obtained from patients undergoing elective cholecystectomy. In this artery we identified clear concentration-dependent contractions in response to agonists of P2 receptors, which were effectively inhibited by the P2 receptor antagonist PPADS [52].

Thus, our experiments have shown the presence of P2 receptor-mediated responses in the tissues of the human cardiovascular system. However, the features and intensity of the responses varied. In the atrial myocardium we revealed inhibitory effects, whereas in the studied blood vessels the effects were mostly stimulative.

CONCLUSION

At present, the study of P2 receptors no longer possesses a purely fundamental interest, but has acquired distinct clinical application features. The real achievement of pharmacology and pharmacy in the P2 receptor field in recent years has been the introduction for extensive clinical use of a new group of antiplatelet drugs, acting through the blockade of platelet $P2Y_{12}$ receptors [53-55]. In the very near future we are expecting to see a new drug on the market for the treatment of cystic fibrosis, which is a selective agonist of $P2Y_2$ receptors [56]. There is a serious potential for the development of new antihypertensive, anti-cancer, anti-inflammatory, antidiabetic, analgesic drugs acting via certain subtypes of P2 receptors [27, 57]. Due to growing interest to this area of many pharmaceutical companies we can expect to see in the near future selective agonists and antagonists of P2 receptors that will be clinically effective. It is obvious that this field is very promising for novel drug development.

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