Chapter

Temperature-Dependent Effects of ATP on Smooth and Skeletal Muscles

Ayrat U. Ziganshin and Sergey N. Grishin

Abstract

ATP acting via different subtypes of P2X and P2Y receptors induces contractions or relaxation of mammalian smooth muscles, while in skeletal muscles, ATP can pre- and postsynaptically modulate effect of acetylcholine. It was shown that effects of ATP on both types of the muscle are significantly changed when the temperature shifts from physiological condition. For example, contractile responses of rodent urinary bladder and vas deferens mediated by P2X receptors are markedly increased with the decrease of the temperature. Similarly, in frog skeletal muscles, ATP-induced inhibition of acetylcholine release became more pronounced at low temperatures. In case of mammalian skeletal muscle, effect of temperature on ATP-induced responses depends on the type of muscle—slow and fast. In this chapter, we will discuss temperature-dependent effects of ATP on different muscle contractility and their possible mechanisms.

Keywords: ATP, P2 receptors, temperature, hypothermia, smooth muscles, skeletal muscles, contractility, neuromuscular synapse

1. Introduction

It is widely accepted now that ATP, except well-known role as an intracellular source of energy, can regulate many important cell functions acting via specific extracellular receptors, namely P2 receptors [1]. P2 receptors are divided into two families, P2X and P2Y receptors, P2X receptors being a ligand-gated ion channel, while P2Y receptors are G protein-coupled. Seven subtypes of P2X and eight subtypes of P2Y receptors are well identified and put into current classification of receptors [2, 3].

P2X and P2Y receptors are widely distributed in animal and human tissues including smooth and skeletal muscles. In smooth muscles, stimulation of P2X receptors causes contractile responses, while stimulation of P2Y receptors usually leads to relaxant effects [4]. In contrast, in adult skeletal muscles, it has been established that, while stimulation of P2 receptors does not cause either contraction or relaxation, it significantly inhibits transmitter release at the neuromuscular junction [5, 6].

Although most experiments on P2 receptors were carried out on normal temperature conditions, we have shown in our publications that in several animal smooth and skeletal muscles, the responses mediated by both P2X and P2Y receptors are

significantly affected by changing the temperature conditions. In this chapter, we will review our earlier and recent studies as well as those findings done in other laboratories.

2. Guinea pig smooth muscle tissues

Our first publication on temperature dependency of the P2 receptor-mediated processes was about guinea pig smooth muscle tissue [7]. We registered responses of isolated guinea pig urinary bladder and vas deferens (P2X receptors) and taenia caeci (P2Y receptors) at the three temperature conditions of 30, 37, and 42°C. We found that the contractile responses of both urinary bladder and vas deferens to a P2X receptor agonist α,β-methylene ATP (α,β-meATP) and to electrical field stimulation in the presence of atropine and phentolamine were markedly more prominent at a temperature of 30°C than at 37 or 42°C. Similarly, relaxation of carbachol-precontracted taenia caeci caused by electrical field stimulation temperature dependently increased with decrease of temperature, while relaxation of this tissue by exogenous ATP was not affected by the temperature. A P2 receptor antagonist pyridoxalphosphate-6-azophenyl-2′,4′-disulphonic acid (PPADS) at all three temperature conditions concentration-dependently antagonized contractile responses to α,β-meATP and electrical field stimulation in both urinary bladder and vas deferens. PPADS, even at the highest concentration tested, had no effect on the relaxant responses of the taenia caeci either to electrical field stimulation or ATP, and its action was not affected by the change of temperature. It was concluded that the effectiveness of P2 receptor-mediated responses in guinea pig urinary bladder, vas deferens, and taenia caeci increases by the decrease of temperature.

Temperature dependency for some receptor-mediated responses has been tested earlier on several animal and human tissues. Using guinea pig ileum and trachea and rat vas deferens and atria preparations, hypothermia-induced supersensitivity to adenosine has been established for responses mediated via adenosine A1, but not adenosine A2, receptors [8]. It has been shown that in the rabbit central ear artery, but not femoral artery, cooling to 24°C reduces contraction, increases the relaxation caused by histamine [9], and enhances the relaxation caused by cholinoceptor stimulation [10]. Later in the study from the same laboratory, it was shown that in rabbit central ear artery at 30°C α1-adrenoceptor-mediated response is reduced and the P2 receptor-mediated component becomes more prominent [11]. On the other hand, it was found that the release of ATP from rabbit pulmonary artery induced by methoxamine, an α1-adrenoceptor agonist, being observed at 37°C, was completely eliminated at a temperature of 27°C [12].

The increase of bladder contractility at low temperature might be due to activation of cold receptors in the bladder, the presence of which has been shown both in animal and human urinary bladder [13, 14]. However, it is unlikely that cold receptors are involved in the effects which we registered in the present study since the threshold temperature to stimulate these receptors was found to be less than 30°C, and the maximum effect was registered at around 20°C [13].

It is generally accepted that in the presence of adreno- and cholinoceptor blockers, the contractions of guinea pig vas deferens and urinary bladder are mediated by P2X receptors, while in guinea pig taenia caeci, low-frequency electrical field stimulation evokes the relaxation via P2Y receptors [15–17]. We have found that both P2X and P2Y receptor-mediated responses elicited by electrical field stimulation are increased at low temperature. It could be suggested that this effect occurs due to the decrease of activity of the transmitter-metabolizing enzymes, namely, ecto-ATPase and ectonucleotidases during cooling, since it is generally accepted that

ecto-ATPase activity is temperature-dependent, with the optimum temperature of 37°C for warm-blood temperature animals [18]. However, this cannot explain results with the enzymatically stable P2X receptor agonist α,β-meATP, the effects of which are not affected by ecto-ATPases. Moreover, in taenia caeci when we used ATP, which is readily degraded by ecto-ATPases, we did not find any temperature dependency in agonist activity. Thus, it seems that supersensitivity of P2 receptors at a low temperature is a feature of receptor itself and is not dependent on ecto-ATPase activity.

It was believed initially that PPADS was a selective P2X receptor antagonist [19, 20] although later antagonism of recombinant P2Y receptors by PPADS was reported [21]. In our earlier study, we established that in the guinea pig taenia caeci, substantial antagonism against P2Y receptor-mediated relaxation was obtained only at a concentration of 100 μM of PPADS [22]. Similarly, in these experiments we did not find any antagonism at P2Y receptors of PPADS at concentrations up to 30 μM on taenia caeci. Thus, it supports the view that at least in the pharmacological organ bath experiments, PPADS shows relatively good selectivity to P2X receptors.

It was an interesting finding that in taenia caeci responses to electrical field stimulation were clearly temperature-dependent, while the relaxation caused by exogenous ATP was statistically identical at different temperature conditions. Since it has been clearly shown that ATP is a transmitter which is released during electrical field stimulation of guinea pig taenia caeci to act on P2Y receptors, it seems that in this tissue only prejunctional mechanisms of transduction are sensitive to the shifts of the temperature while postjunctional processes are not.

3. Frog skeletal muscle

Next, we decided to test the P2 receptor-mediated effects in tissues of cold-blooded animals. For that the contractile responses of isolated *Rana ridibunda* frog sartorius muscle contractions evoked by electrical field stimulation (EFS) were studied at three temperature conditions of 17, 22, and 27°C [23]. ATP concentration dependently inhibited the electrical field stimulation-evoked contractions of sartorius muscle at all three temperatures; this effect was significantly more prominent at a temperature of 17°C than at the other two temperatures. Adenosine also caused inhibition of electrical field stimulation-evoked contractions which was statistically identical at all three temperature conditions tested. A P2 receptor antagonist, PPADS, reduced the inhibitory effect of ATP at all three temperatures but did not affect inhibitory action of adenosine. In contrast, 8-(p-sulfophenyl)theophylline (8-SPT), a nonselective P1 receptor antagonist, abolished inhibitory effects of adenosine at all three temperature conditions but did not antagonize inhibition caused by ATP. In electrophysiological experiments, ATP and adenosine temperature dependently reduced end-plate currents recorded in sartorius neuromuscular junction by voltage clamp technique. The inhibitory effects of both agonists were enhanced with the decrease of temperature. 8-SPT abolished the inhibitory effect of adenosine but not ATP on end-plate currents. Suramin, a nonselective P2 receptor antagonist, inhibited the action of ATP but not adenosine, while PPADS had no influence on the effects of either ATP or adenosine. It was concluded from this study that the effectiveness of P2 receptor-mediated inhibition of frog skeletal muscle contraction in contrast to that of adenosine is dependent on the temperature conditions.

Thus, we had demonstrated that presynaptic P2 receptor-mediated inhibition of the frog skeletal muscle contractions produced by nerve stimulation has a clear temperature-dependent feature—lowering the temperature leads to the increase of

P2 receptor-mediated inhibition. The depressant effect of exogenous ATP on neuromuscular transmission was demonstrated for the first time more than 40 years ago [24], although for a long time, it was believed that inhibitory action of ATP is indirect and depends on degradation to adenosine [25, 26]. In mammalian tissues, the existence of presynaptic P2 receptors at neuromuscular junction was suggested by immunohistochemical analysis [27], and electrophysiologically, it was established that ATP but not adenosine inhibited nonquantal release of acetylcholine [5]. At frog neuromuscular junction, it was shown that ATP inhibited transmitter release via presynaptic P2 receptors [6], and it was proposed that ATP produces its effect via P2Y2-like receptors coupled to multiple intracellular cascades [28].

Temperature dependency of skeletal muscle contractility is a known phenomenon. It has been shown that this phenomenon has an endothermic nature, and raising the temperature increases the force and the strain of the myosin heads attached in the isometric contraction [29]. The decrease of contractile force at lower temperature could be due to the attenuation of metabolic enzyme activities [30, 31] or processes of energy production and transfer [32, 33].

In contrast to adenosine, we have found that the effect of ATP on neuromuscular transmission was temperature-dependent in functional experiments. Lowering the temperature caused the increase of ATP-induced inhibition of electrical field stimulation-evoked contractions, and this effect was highly sensitive to P2 receptor antagonist PPADS and not sensitive to 8-SPT, a P1 antagonist. These differences between two purines are thought to be coupled at their action mechanism. Both ATP and adenosine reduce quantal release of acetylcholine [6], thereby decreasing amplitude of postsynaptic end-plate currents. However, the temperature-mediated effect of ATP is more prominent and can achieve corresponding to amplitude of end-plate current reduction of the muscle contraction.

To find the nature of receptors involved, we used PPADS, a P2 receptor antagonist with a preferential effect on P2X receptors in functional whole tissue experiments [19, 20], and found that ATP-evoked inhibition of muscle contraction was highly sensitive to this antagonist, while in electrophysiological study, it failed to affect responses to ATP. However, another nonselective P2 receptor antagonist suramin [15] significantly reduced ATP-induced inhibition. Although both PPADS and suramin are considered as nonselective P2 receptor antagonists, it has been shown that suramin, compared to PPADS, has a more broad P2 receptor antagonist activity, affecting most of P2X and P2Y receptor subtypes [34]. For instance, it has been shown that recombinant P2Y2 receptors are sensitive to antagonistic effect of suramin but not of PPADS [35]. In addition, in organ bath pharmacological experiments, PPADS tends to antagonize mostly P2X receptor subtypes [16, 19, 20], blocking P2Y receptor-mediated processes only at higher concentrations [22]. Neither PPADS nor suramin affects inhibition caused by adenosine. These results support the view that ATP inhibited the electrical field stimulation-evoked contractions of frog skeletal muscle by acting on presynaptic P2 receptors. It is most likely that these receptors belong to P2Y family, but involving some subtypes of P2X receptors cannot be ruled out at present.

It has been proposed that purine nucleotides and nucleosides were among the first neurotransmitters in the evolution and development of the living cells [36, 37]. Thus, it is possible that, in phylogenetically older animals, in which organism is functioning in low-temperature conditions, the transmitter role of purine nucleosides and nucleotides in cell-to-cell communications is as important as well-known intracellular metabolic actions of purines (production of energy, involvement in synthesis of nucleic acids). Thus, we suggest that supersensitivity of P2 receptor-mediated responses at lower temperature, which we have demonstrated in mammal

[7] and amphibian tissues [23], is a fundamental feature of these receptors which could be a reflection of their past role in the early stage of evolution.

4. Rodent skeletal muscles

When we found that, similar to that in guinea pig smooth muscle tissues, P2 receptor-mediating processes in amphibian skeletal muscles are markedly more pronounced in low-temperature condition, we did the next study using rodent skeletal muscles, namely rat soleus muscle [38].

We registered carbachol- and electric field stimulation-induced contractions of rat soleus muscle in norm and in the presence of ATP under different temperature conditions—37 and 14°C. We found that with decreasing temperature, both the force and the time of contractions are increased. ATP inhibited the amplitude of contraction caused by indirect stimulation by an electric field; in this case, the combined pre- and postsynaptic modulation effect of this purine was observed. To separate these effects, we investigated the effect of ATP on carbachol-induced contraction. In this mode, ATP increased the contraction of the "slow" muscle. With a decrease in temperature, both pre- and postsynaptic effects of ATP are enhanced, but not equivalent. The increasing potentiating effect of ATP with the use of postsynaptic P2 receptors overlaps and masks an increased, but to a lesser extent, inhibitory presynaptic effect [38].

Maintaining the body temperature in certain range provides for warm-blooded animals the ability to move and perform motor activity in a wide range of temperature differences of the environment [39].

It is known that in the absence of significant fluctuations in the temperature of the internal organs of mammals, the peripheral parts of their body can experience significant changes in temperature, for example, up to 15°C decrease in humans [40, 41]. Thus, the peripheral skeletal muscles of warm-blooded animals retain the ability to contractile activity even with a significant decrease in their temperature.

According to modern ideas, the strength, speed of contraction, and relaxation of skeletal muscles of warm-blooded animals as a rule increase with increasing temperature [42, 43]. This was observed, for example, during physical exercises when the temperature of skeletal muscles on the periphery of the human body increased by several degrees Celsius [44–46].

At the same time, the above studies did not attach special importance to the types of skeletal muscle examined. It is known that several types of phase skeletal muscle fibers are distinguished from which "slow" and "fast" are distinguished in all classifications [47, 48]. It is understandable that these muscles differing in their very function—maintaining pose ("slow" muscles) and performing subtle movements ("fast")—are made to react differently to temperature changes which is observed in practice [49–51].

Molecular non-quantum secretion of the mediator still has not given a fundamental importance due to the lack of a generalized action. Indeed, despite its large value, non-quantum secretion only depolarizes the end-plate region by ~5 mV which can be determined by hyperpolarization in the presence of postsynaptic receptor blockers—the "H effect" [52–54]. However, non-quantum secretion is extremely important and is crucial for the functioning of the synapse. It should be noted that the evaluation of non-quantum secretion of the myoneural synapse in the cold-blooded is difficult because of the small value of the registered H effect [54, 55].

The temperature dependence of the magnitude of non-quantum secretion in neuromuscular preparations of rodents is complex. It was found that in the range

from 10 to 35°C, the size of non-quantum secretion has two relative peaks at 20 and 35°C and two minima at 25 and 10°C (in the latter case, the H effect is not expressed at all) [54–56].

The frequency of spontaneous single-quantum responses in synapses of warm-blooded animals increases as the temperature increases [56–58] without changing the amplitude of these responses [59]. Thus, two processes of acetylcholine release, namely quantum and non-quantum, have a different temperature dependence, which indicates the presence of independent mechanisms [55, 58].

The analysis of the published data leads to an unequivocal conclusion about the rise of the synaptic delay of postsynaptic responses with decreasing temperature on rodent preparations [60, 61]—the same as in cold-blooded.

It is known that in the neuromuscular synaptic cleft, there is an acetylcholinesterase which rapidly cleaves the neurotransmitter acetylcholine [62]. It was shown that when the temperature of the rat diaphragm preparation was reduced from 37 to 17°C, the activity of acetylcholinesterase decreased by 34% [63]. A similar pattern was observed in experiments with the preparation of the frog sartorius muscle which led to a suggestion that a decrease in the activity of acetylcholinesterase is responsible for an increase of the time course of the end-plate current at hypothermia [64].

To study the state of postsynaptic cholinergic receptors, cholinomimetics (primarily the slowly decaying cholinomimetic agent—carbachol) and cholinolytics are used. In experiments with slow muscle preparations such as rat m. soleus, the amplitude of the miniature potentials of the terminal plate did not change after application of carbachol at a temperature range from 18 to 38°C. On the other hand, at temperatures 37–38°C, there was a 40% decrease in the incidence of spontaneous postsynaptic responses in the presence of this cholinomimetic (in which combination indicates presynaptic nature of the effect) [65].

There are several studies on the temperature dependence of the contractile apparatus of "slow" skeletal muscles with conflicting data on the muscles of the same animals [66–70]. Thus, according to some sources, the temperature dependence of the "slow" muscle fibers of the rat is much more pronounced than the "fast" ones [42, 71–79], while others found that the temperature sensitivity of the myosin of the "slow" muscle fibers of the rat does not differ from the "fast ones" [80, 81].

In experiments on demembranized muscle fibers, where the temperature effects of electromechanical coupling are not relevant and only the modulation of the mechanical function itself plays a role, it was clarified that the dependence of the reduction force of "slow" and "fast" fibers on temperature is similar [80]. With an increase of temperature from 10 to 35°C, the force of contraction of "slow" fibers increased threefold and the "fast" ones by three and a half. The situation is different with the rate of contraction. Thus, the rate of reduction of "fast" fibers increased with increasing temperature from 10 to 35°C, while for "slow" fibers this parameter changed insignificantly [80].

We found that as the temperature is lowered, the force of contractions of the slow skeletal muscle of the rat increases [38], while the fast one decreases. With carbachol-induced contraction (when only receptors of the postsynaptic membrane are stimulated), as the temperature decreases, the amplitude of contractions of the slow muscle of the rat also increases [38].

It is known that a decrease in Ca^{2+} concentration, which provides exocytosis of the neurotransmitter quanta [82–84], reduces the strength of the contraction of the skeletal muscle over time—in contrast to the rapid effect on cardiomyocytes [85]. This action is temperature-dependent; in rat fast muscle fibers, the contraction force increased with increasing concentration of calcium ions; the lower the temperature, the more is the effect. A rat slow muscle did not produce similar effect [86].

5. Conclusion

Despite a large number of studies, the direct mechanisms of temperature effects on the functioning of the muscle remain unsolved [87, 88]. Moreover, if the muscle is stimulated directly, then the temperature change no longer has such an effect. That is, the reason for the phenomenon being discussed is synaptic.

It was believed that changes in motor units at low temperature are due to depletion of the activity of metabolic enzyme systems [30, 31] or energy synthesis and transfer processes [89, 90]. However, it was clear that the contribution of the temperature sensitivity of the muscle biochemical processes cannot justify such dramatic changes in the nature of the contraction of the whole muscular organ with a change in temperature [91]. We suggest that the temperature-sensitive tonic effects of endogenous ATP during the contraction can underlie the phenomenology of changes in muscle responses with decreasing temperature.

In conclusion, we believe that studying the effects of hypothermic conditions has not only theoretical significance but also potentially important clinical implications since hypothermia is widely used in clinical practice for cerebral protection during surgical interventions or resuscitation of critically ill patients [92–96]. This underlines the importance of studying the reaction of other organs and tissues to hypothermia and especially the effect that low temperatures have on receptor-based interactions. Such studies add important information regarding the activity of P2 receptors under hypothermic conditions in mammalian muscles. Although these results cannot be directly transferred to human muscle tissues, they provide important insight into how activation of human P2 receptors might behave under hypothermia and predict how effects of certain drugs might be altered by this nonphysiologic state.

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Conflict of interest

The authors declare the absence of conflict of interest.

Author details

Ayrat U. Ziganshin* and Sergey N. Grishin
Kazan State Medical University, Kazan, Russia

*Address all correspondence to: auziganshin@gmail.com

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