Purinergic receptors in skeletal muscles in health and in muscular dystrophy

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ABSTRACT

The P2 purinergic (nucleotide) receptor super-family comprises of two families of protein. The P2X, which are channel-forming ionotropic receptors and the P2Y metabotropic receptors activating G protein-mediated signalling pathways. Members of both groups have been identified in skeletal muscle cells at different stages of differentiation. It is well documented that sequential expression and down-regulation of particular P2 receptors on the surface of sarcolemma is closely associated with muscle maturation during embryogenesis and postnatal growth. P2 receptors are also involved in muscle regeneration following injury. Moreover, enhanced expression of specific purinergic receptors together with increased availability of extracellular ATP in dystrophic muscles are important elements of the dystrophic pathophysiology considerably increasing severity.

INTRODUCTION

Skeletal muscles (SM) are the most abundant type of muscle and considered the largest human organ as they account for at least 40% of body mass. However, despite morphological and functional similarities, specific muscle groups can differ significantly in their developmental origins and susceptibility to diseases (for review see: [1]). Indeed, muscle is a heterogeneous and metabolically dynamic structure, made of several kinds of tissues. Its main function, the body movement, can be controlled voluntarily. Due to specific properties including excitability, conductivity, extensibility and elasticity muscles are susceptible to excitation, signal transduction and propagation and fully reversible contraction. Skeletal muscles are not only responsible for movements but also allow maintaining and stabilizing the posture and strengthening the joints of the skeleton. SM can also generate heat. Moreover, SM play an important metabolic role, particularly in the insulin-dependent regulation of glycaemia and glycogen storage and in fatty acid metabolism.

Fully differentiated muscle cells are multinucleated large fibres surrounded by a specialised cell membrane called sarcolemma and contain a very orderly arrangement of myofibrilar proteins responsible for muscle contraction, large sarcoplasmic reticulum and multiple mitochondria clustered in the subsarcolemmal and intermyofibrillar spaces.

All muscle functions occur at the expense of ATP produced in muscle cells but fibres differ in their preference for energy sources. Oxidative phosphorylation is a major source of ATP in the so called slow twitch or "red" muscle fibres while metabolism of the fast twitch ("white") muscle relies on an anaerobic glycolysis. The proportion between fast and slow fibres decides about the energy metabolism and physiological properties (fast or slow twitching) of particular muscles.

Molecular and metabolic differences determining muscle locus and metabolic properties appear during their differentiation, which is a multistep process originating from muscle progenitors called satellite cells (SC). SC reside underneath the basal lamina of muscle fibres and originate from somites — spheres of paraxial mesoderm [1,2]. These mononuclear cells, when activated during either development or postnatal growth, divide in an asymmetrical fashion resulting in generation of another SC and a second cell subsequently differentiating into a myoblast. Myoblasts, when stimulated to differentiate, may fuse with a preexisting muscle fibre thus increasing its size and force of contraction or they may fuse with each other leading to formation of new muscle fibres. These processes are regulated by specific transcription factors, which expressions change in an orchestrated fashion with progression of differentiation in developing but also in a growing, adult SM.

If muscle fibers become damaged, either due to injury or as a consequence of muscle diseases, adult SM also have the ability to regenerate. Thus, satellite cells are activated not only during physiological growth of muscle fibres but also under pathological conditions. They start to proliferate, migrate and fuse with pre-existing fibres and with each another while undergoing differentiation to replace damaged fibres. The entire process can be accomplished within just a few days [3]. Fully differentiated myofibres are not capable of further division and remain in the G_0 phase of the cell cycle.

Differentiation and maturation to myoblasts, myotubes and finally mature muscle fibres need numerous extracellular stimuli to be induced. Amongst these, it has been shown that differentiation is accompanied by quantitative and qualitative changes of nucleotide receptors. These involve both ionotropic (P2X) and metabotropic (P2Y) receptors and specific nucleotides, acting at these receptors, are important stimuli, which contribute to muscle cell differentiation (see below) [4,5].

PURINERGIC SIGNALLING IN SKELETAL MUSCLES

Nucleotides acting in autocrine or paracrine manner mediate cellular responses *via* purinergic P2 receptors located on the cell surface. These receptors belong to one of the two main families distributed in almost all mammalian tissues: the ionotropic receptors $P2X_{(1-7)}$, which are a heterogeneous group of ligand-gated, oligomeric ion channels, with seven subtypes identified so far [6,7] and the metabotropic (P2Y) G protein-coupled receptors family [8].

While the only natural agonist of P2X receptors is ATP, P2Y receptors are selectively sensitive to different purine and pyrimidine nucleotides. And so: $P2Y_1$ is sensitive to ADP >ATP; $P2Y_2$ to UTP ≥ ATP; $P2Y_4$ to UTP ≥ ATP (rat) > CTP, ITP; $P2Y_6$ to UDP > UTP >> ATP; $P2Y_{11}$ to ATP; $P2Y_{12}$ to ADP; $P2Y_{13}$ to ADP > ATP and $P2Y_{14}$ to UDP UDPglucose > UDP-galactose [for review see 8]. More details are also available in article by Barańska in this issue of Postępy Biochemii.

The role of purinergic receptors in muscle cells has been investigated for about 30 years, so the main principle of their action there seems to be understood. However, surprisingly many aspects of nucleotide-evoked stimulation of SM, particularly under pathological conditions, still need to be clarified.

Susceptible to stimulation with extracellular nucleotides specific purinergic receptors participate in muscle cell differentiation during embryogenesis, postnatal muscle formation and regeneration [9]. Intensity of cellular response to extracellular nucleotides depends on both the expression of particular receptor on the cell surface (which changes during muscle maturation) and the presence of appropriate nucleotides in the inter-cellular space. At the resting state, skeletal muscle has a rather low metabolic rate, with the cytosolic ATP concentration in the 5–10 mM range [10]. ATP can be released into the extracellular space in small amounts, as a response to or a consequence of muscle activity [11] or in large amounts following damage or death of muscle cells. Furthermore, nucleotide concentrations in the extracellular compartment are regulated by extracellular hydrolysing enzymes (nucleotidases). For example, ATPases, which catalyse ATP degradation to ADP and further to adenosine.

Activation of all P2X and most of the P2Y receptors results in the increase in intracellular calcium concentrations ($[Ca^{2+}]_i$). However, the relative contribution of specific receptors depends on the animal species, stage of embryonic and postnatal development and stage of muscle cell differentiation.

Moreover, purinergic receptors are not only important under physiological conditions but they have a role in the pathogenesis of muscular dystrophies. This may involve enhancing Ca^{2+} entry into dystrophic muscle cells but also triggering a unique mechanism of autophagic cells death [12] as found in the *mdx* (X chromosome-linked muscular dystrophy) mice as well as in the inflamasome response as shown in dysferlinopathy [13]. However, the relative importance or participation of specific purinergic receptors in these abnormalities has not been evaluated fully [14].

NUCLEOTIDE SIGNALLING AT THE NEURO-MUSCULAR JUNCTION

Nucleotides and nucleotide receptors play a role not only in muscle development and regeneration but also in signalling processes at the neuromuscular synapses. For example, ATP is released from the motor nerve terminals to the neuromuscular junction (NMJ) [15,16]. NMJ is a specialized, peripheral synapse between a lower motor neuron and a SM fibre which allows muscle fibres to be excited by pre-synaptic motor nerves, leading to a rapid muscle contraction [17]. In the early NMJ development, ATP can be co-released with acetylocholine (ACh), which is the major neurotransmitter in neuro-muscular synapses and ATP stimulates both P2 receptors and ACh nicotinic receptors located on the postsynaptic membrane [18,19]. Both ATP and ACh are released by exocytosis from synaptic vesicles in the pre-synaptic part [20] and ionotropic $P2X_7$ receptors found in the mouse NMJ seem to activate this release from synaptic vesicles [21]. In addition, ATP co-released with ACh from the motor nerve terminals may play an important role in the regulation of SM fibre volume [22]. It has also been shown that $P2X_2$ receptors are expressed together with ACh receptors (AChR) during NMJ development [4] and ATP is thought to stabilize the neuromuscular junction and may play a role in the synaptic modification during development [19,23]. Apart from P2X, metabotropic $P2Y_1$ receptors also seem to participate in the regulation of AChR in cultured chick myotubes. Co-localization of AChR and $P2Y_1$ at the neuro-muscular synapses was also described [24].

Interestingly, in cultured muscle cells, which do not form neuro-muscular junctions because of the absence of innervation, both ACh and $P2Y_1$ receptors are distributed evenly all over the sarcolemma. It may suggest that innervation regulates spatial distribution of these receptors and it might

also indicate close functional interactions between these two proteins [14].

P2X RECEPTORS IN SKELETAL MUSCLE DEVELOPMENT, REGENERATION AND PATHOLOGY

P2X receptors mediate ATP signalling through the three main mechanisms: Primarily they function as trimeric ligand-gated cation channels but under specific conditions can contribute to the formation of a large pore and have the ability to form complexes with other proteins and membrane lipids [25].

P2X subtypes vary in their sensitivity to agonist, regulation and kinetics of action. However, all are Ca^{2+}-permeable channel-forming proteins, thus their activation leads to extracellular calcium influx into the cell and elevation of cytosolic concentrations of this ion. Ca^{2+} entry due to activation of P2X receptors can also result in the plasma membrane depolarization, which in turn may reduce Ca^{2+} influx through the store-operated calcium channels partially driven by membrane potential (SOC) [26]. Thus, P2X-mediated elevation of the cytosolic Ca^{2+} concentration is a principal mechanism of ATP signalling and one which is involved in various physiological processes across the body, such as synaptic plasticity, neurotransmitters release, smooth muscle contraction, cell proliferation or inter-cellular communication (reviewed in [25]).

While a short stimulation of P2X receptors leads to the opening of the ion channel, sustained stimulation with the agonist may contribute to the formation of a large-pore, with a permeability for molecules of several hundred daltons, such as ethidium bromide or YO-PRO1 [27-29]. This property is mainly attributed to $P2X_7$, however, other P2X receptors such as $P2X_2$, $P2X_4$, $P2X_{2/3}$ and $P2X_{2/5}$ hetero-oligomers have also been analysed as potentially forming this large pore [25,30]. Moreover, several studies have suggested that other distinct protein(s) activated by $P2X_7$ receptors may also contribute to this large-pore formation. Particularly, the pannexin-1 channel attracted much attention [27] as its inhibition significantly suppressed the pore formation in both HEK293 cells and macrophages [27,31]. However, pannexin-1 channel has been reported to have no significant contribution to the large pore formation resulting from activation of $P2X_2$ or $P2X_4$ receptors [32,33]. More recent data suggest that pannexin-1 may also form membrane-spanning pores without contribution from purinergic receptors in muscle cells [34].

$P2X_7$ large pore formation has been shown to have an important role in several physiological and pathological processes such as lymphocyte death, microglial proliferation or chronic pain (reviewed in [35]) and recently also in autophagic death of dystrophic muscles [12], however its role as more Ca^{2+}-selective calcium channel in healthy cells must not be ignored [21].

Given that ATP has a significant effect in skeletal muscle development it is interesting that specific subtypes of P2X receptors are sequentially expressed during myogenesis [36]. The expression pattern of P2X receptors in SM varies depending on the developmental stage and also animal species studied. Expression of $P2X_1$, $P2X_4$, $P2X_5$ and $P2X_6$ has been demonstrated in developing chick myoblasts [37,38] while an expression of $P2X_2$, $P2X_5$ and $P2X_6$ has been reported in rat muscles [4]. Specifically, no P2X receptor has been reported to be expressed up to the E15 stage of the rat embryonic development. Immunoreactivity of $P2X_5$ receptors becomes detectable first at E15 in the small number of cells at the ends of muscles [4]. At E16, $P2X_6$ expression appears. However, both $P2X_5$ and $P2X_6$ immunoreactivity disappears by E20 [4]. In contrast, $P2X_2$ starts to be expressed at E18, particularly in the lower limb SM and its immunoreactivity can be detected up to one week into the postnatal development [4]. Thus, $P2X_5$ is the first ionotropic receptor, which is expressed during skeletal muscle development, followed by $P2X_6$ and eventually by $P2X_2$ (Fig. 1). Similar role of $P2X_5$ receptors have previously been shown in proliferating and developing striated squamous epithelia [39], which suggested that ATP play a role in these two processes in different tissues. Indeed, this ATP function has been reported during muscle satellite cells differentiation, as $P2X_5$ activation inhibits their proliferation and promotes differentiation by enhancing the phosphorylation of MAPK p38 [40]. It has been demonstrated that activation of these receptors by ATP contributes to the shift in the balance between satellite cells proliferation and differentiation. As shown in rat myoblasts, it reduced rate of proliferation with increased differentiation marker levels [40]. $P2X_4$ receptors have been reported to localize inside T-tubule membranes in rat muscles [15], which could suggest some role in the excitation-contraction coupling. $P2X_2$, $P2X_4$ and $P2X_7$ receptors have been demonstrated to be expressed in both myoblasts and myotubes, however, $P2X_2$ mRNA has only been detected in myotubes [36]. $P2X_7$ and $P2X_4$ receptors were shown to be up-regulated upon cells differentiation, and specific heteromeric channel formation

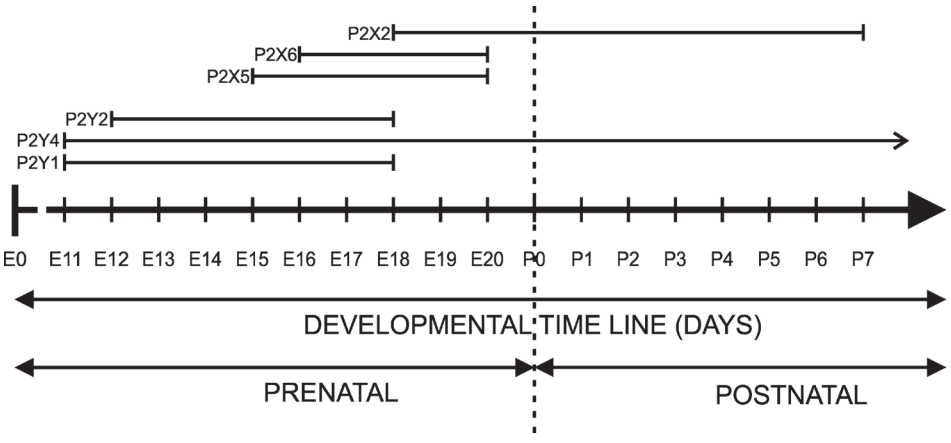

Figure 1. Temporal changes in P2 receptors in rat skeletal muscles [4,5]. $P2Y_4$ receptor expressed postnatally is involved in muscle fibres maturation [5].

between these subunits, which changes receptor pharmacology seems to be possible [41,42]. However, a precise role of $P2X_4$ receptors in myoblasts is not fully understood [43].

Mechanical injury or inflammatory processes in muscles may damage muscle fibres and result in a local increase of extracellular concentrations of many intracellular compounds, including ATP and other nucleotides. Such a scenario is envisaged in various muscular dystrophies [44].

Muscular dystrophies are a class of genetic diseases affecting various groups of human muscles and leading to disability. One of the most severe of these, and also the most common, is Duchenne muscular dystrophy (DMD). This disease, leading to a premature death of young adults is caused by the mutation(s) in the *DMD* gene encoding dystrophin protein [45,46]. Dystrophin is a cytoskeletal protein responsible for linking the actin cytoskeleton with membrane proteins, and indirectly, with extracellular matrix. This arrangement is responsible for stabilizing muscle fibres during contraction and lack of dystrophin results in higher susceptibility of sarcolemma to damage [47,48]. Importantly, in the early stages of Duchenne muscular dystrophy, muscle damage is followed by cycles of regeneration.

Together with ATP released from the motor nerve terminals and from muscle fibres during contraction [49-51] nucleotides released due to a damage lead to an excessive extracellular ATP concentration (above 100 μM), which cannot be efficiently counterbalanced by ecto-ATPases. One of proteins with ecto-ATPase activity is α-sarcoglycan, which is a component of a dystrophin-associated protein (DAP) complex found in skeletal muscles [52]. Improper assembly of DAP in the absence of dystrophin result in a reduced amount of α-sarcoglycan on the cell surface and therefore less effective ATP degradation. Similarly, mutations in sarcoglycan subunits, which cause specific muscle dystrophies e.g Limb-Girdle Muscular Dystrophy may be accompanied by increased concentrations of extracellular ATP.

Considering that skeletal muscles store more ATP than most tissues, it seems plausible that ecto-ATPases may be not able to cope with the effects of ATP overload in dystrophic muscles and various subtypes of P2 purinergic receptors may get over-activated. While low-level ATP plays a significant role in regulating skeletal muscle differentiation under physiological conditions (as mentioned earlier) and also muscle fibre regeneration in disease [44], excessive stimulation of particular P2X receptors could aggravate progression and increase severity of muscle damage.

Regeneration of damaged muscle can occur as long as satellite cells are available and this process generally resembles muscle development. However, local extracellular environment in regenerating muscle may substantially differ from that found under physiological/developmental conditions. It is usually influenced by the local inflammatory response and the presence of immune cells, which are a source of many factors, including ATP, influencing muscle cells. Moreover, these cells also express purinergic receptors. For example, DNA microarray analyses showed an up-regulation of $P2X_4$ transcripts in dystrophic skeletal muscle. However, this increase has eventually been shown to be due to the increased numbers of macrophages infiltrating the muscle [53] and thus the $P2X_4$ overexpression found to be secondary to the damage of DMD fibres. $P2X_7$ was also found both in human and mouse macrophages, however in the case of this receptor its presence in muscle cells has been convincingly confirmed [53,54]. This difference illustrate the complexity of purinergic signalling in dystrophic muscles. Moreover, apart from increased ATP levels, this disease is also characterized by increased expression of P2 receptors [54]. Such over-activation of P2X receptors due to increased agonist levels combined with specific overexpression were observed in muscles of the *mdx* mouse model of DMD. Therefore changes in P2X receptors activity could contribute to the abnormal cytosolic Ca^{2+} homeostasis, which has been found in this pathology [55].

Abnormal expression of P2X receptors is not unique to muscle disorders. Changes in the expression of distinct P2X have also been found in the inflammatory and chronic pain, epilepsy, depression and in some cancers [56] and this led to experimental therapeutic approaches with the use of P2X agonists [25,56]. Interestingly, overexpression of P2X7 receptor was also found in lymphoblasts from DMD patients, indicating non-muscle phenotypic manifestation of dystrophin deficiency [57].

In addition to $P2X_7$, $P2X_2$ and $P2X_5$, normally absent from healthy skeletal muscle cells, have been observed in dystrophic *mdx* muscles [44]. As mentioned earlier, $P2X_5$ receptors appear on satellite cells first, then followed by $P2X_2$ expression on newly formed myotubes. This may indicate accelerated differentiation of satellite cells in dystrophic mouse muscles.

P2Y RECEPTORS IN MUSCLE DEVELOPMENT AND REGENERATION

In contrast to ionotropic nucleotide receptors, which have been extensively investigated in skeletal muscles, the knowledge of P2Ys in this tissue is less comprehensive. Of the 12 members of the P2Y family, eight ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, and $P2Y_{14}$) have been found in humans. Other four types represent either nonmammalian orthologs or orphan receptors with no evidence of being nucleotide receptors ([58], for review see: [59]).

All P2Y receptors influence cell metabolism *via* interaction with G-proteins and specificity for particular G-protein subtype determines mechanism of their action involving either activation of calcium signalling by stimulation of phospholipase C ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$) or inhibition of adenylate cyclase ($P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, $P2Y_{14}$). $P2Y_{11}$ may exert both activities. (To find more information read the article by Barańska in this issue of Postępy Biochemii). In terms of muscle physiology and pathophysiology most of the available data concern the first category while the knowledge of nucleotide receptors acting *via* adenylate cyclase is rather limited. Moreover, the P2Y effects in skeletal muscles seem to be species-specific. For example, it was suggested that activation of $P2Y_{13}$, a receptor highly sensitive to ADP, stimulates Na,K-ATPase functions in rat skeletal muscle. In con-

trast, stimulation of $P2Y_{11}$ (absent from rat muscles), which is relatively less sensitive to ADP, resulted in an inhibition of Na,K-ATPase activity in human muscles. Thus, species-specific expression of particular receptors determines cellular response to the same stimulus [60].

It is well established that P2Y expression in muscle cells (similarly to P2X) varies with the developmental stage. For example, during rat embryonic skeletal muscle development three metabotropic receptors, $P2Y_1$, $P2Y_2$ and $P2Y_4$ were identified. Their expression patterns change along progression of the early muscle formation. The expression of the $P2Y_1$ and $P2Y_4$ receptors begins at E11 and of $P2Y_2$ at E12 and it is correlated with an appearance of myoblasts-specific markers. All three receptors were exclusively detectable in myotome. After next few days of embryonic development (by E18) $P2Y_1$ and $P2Y_2$ receptors expression was down-regulated while expression of $P2Y_4$ ceased postnatally [5]. It has been suggested that such patterns of P2Y expression are important for activation and regulation of sequential steps of muscle formation, including proliferation of muscle progenitors, migration and fusion [61].

Similar studies of muscle formation in mice have also revealed participation of the $P2Y_6$ receptor. Its expression in the dermamyotome appeared at E9 and from E15 and postnatally it gradually declined. The expression of $P2Y_6$ is also temporarily activated during regeneration of injured mouse muscle [62].

Despite intensive studies the role of P2Y receptors in SM both in health and disease in men and animal models is still poorly understood where we have but fragmented pieces of data. For example, Borno *et al*. [7] demonstrated the presence of $P2Y_4$ and $P2Y_{11}$ receptors in human muscle using Western blotting. Furthermore, at the transcriptional level, $P2Y_1$ and $P2Y_2$ receptors were identified in human skeletal muscles [63]. Ryten *et al*. [44] working with mouse primary muscle cells showed expression of the $P2Y_1$ receptor in mononuclear cells and early myotubes, whilst $P2Y_4$ receptors were only expressed in myotubes. Presence of $P2Y_1$ and $P2Y_4$ in mouse myotubes was also described by others [14]. Some differences and apparent discrepancies between available experimental data concerning P2Y expression and activity may be explained at least partially by temporal changes in the expression of P2Y receptors, which are specific for particular cell stages. Moreover, differences between P2Y expression patterns due to analyses being performed in various species must also be considered.

Changes in the P2Y expression profile were also demonstrated *in vitro,* in C2C12 murine cells [36]. Transcripts encoding for $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$ and $P2Y_{12}$, the latter activating adenylate cyclase, were identified in both myoblasts and myotubes. However, the expression of particular mRNAs changes during differentiation. In myoblasts, the mRNA encoding $P2Y_1$, $P2Y_4$ and particularly $P2Y_2$ predominated while expression of $P2Y_6$, and $P2Y_{12}$ was relatively lower. In myotubes, $P2Y_1$, $P2Y_{12}$, $P2Y_4$ and $P2Y_6$ were substantially reduced. These receptors are sensitive to ADP, UTP and UDP, respectively. In contrast, expression and activity of ATP-sensitive $P2Y_2$ receptor was unchanged and still high in myotubes [36].

Considering P2Y in SM functions, Banachewicz *et al*. [36] showed that ATP stimulated a rapid and transient increase of level of phosphorylated p42/ERK2 and p44/ERK1 in myotubes and myoblasts. Activation of ERK1/2 in myotubes was due to $P2Y_2$ activity and this effect was dependent on Ca^{2+}. Authors demonstrated that all nucleotides activated ERK1/2, but stimulation of cells with UDP produced the lowest phosphorylation level of ERKs. In these myoblasts ERK1/2 activation seems to be dependent on $P2X_5$. Furthermore, these effects were dependent on Ca^{2+} ions, because lack of extracellular Ca^{2+} strongly inhibited ERK1/2 activation [36]. However it must be noted that in dystrophic murine myoblasts (*mdx*) stimulation of P2X receptors, which are exclusively sensitive to ATP ,was found to activate ERK1/2 phosphorylation in the Ca^{2+}-independent manner [54]. It was also shown that that the $P2Y_6$ receptor activation significantly reduced the dramatic elevation of NF-κB induced by TNF-α in C2C12 myoblasts while it did not affect NF-κB level in untreated cells [64]. Moreover stimulation of $P2Y_6$ receptor evoked attenuation of TNF-α apoptosis in mouse skeletal muscle, which was accompanied with ERK1/2 activation [64]. However, conformation and complete explanation of antiapoptotic role of P2Y6 in myoblasts *in vivo* needs further investigation.

To summarize, both P2X and P2Y nucleotide receptors are currently a focus of attention due to their widespread expression and the significant role they play in various physiological processes in different cells. Additionally, multiple reports showed that some of these purinergic receptors play a role in the Duchenne muscular dystrophy pathology. Complete understanding of their involvement needs further investigations. It cannot be excluded that they offer a potential therapeutic target for stimulation of skeletal muscle regeneration after injury or in treatment of muscular dystrophy.

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Receptory purynergiczne w prawidłowych i dystroficznych mięśniach szkieletowych

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Słowa kluczowe: dystrofia mięśniowa, mięśnie szkieletowe, receptory nukleotydowe (purynergiczne)

STRESZCZENIE

Nadrodzina receptorów purynergicznych (nukleotydowych) składa się z dwóch rodzin białek. P2X są receptorami jonotropowymi tworzącymi kanały jonowe natomiast P2Y są receptorami metabotropowymi aktywującymi szlaki sygnałowe zależne od trimerycznych białek G. Występowanie przedstawicieli obu rodzin w komórkach mięśni jest niejednakowe i zależy od etapu ich różnicowania. Istnieją dowody wskazujące na to, że sekwencyjne pojawianie się tych białek oraz zmiana ich względnych ilości w sarkolemie są ściśle związane z tworzeniem się mięśni podczas rozwoju embrionalnego oraz ich wzrostu w okresie postnatalnym. Receptory nukleotydowe uczestniczą także w regulacji regeneracji mięśni po uszkodzeniu. Ponadto, zwiększona ekspresja genów kodujących specyficzne receptory nukleotydowe wraz ze zwiększonym stężeniem ATP w przestrzeni pozakomórkowej są istotnymi czynnikami w patofizjologii dystrofii, zwiększającymi ostrość przebiegu tej choroby.