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Clinical Aspects of Skeletal Muscle Modulators in Type 2 Diabetes Mellitus

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1. Introduction

Isotonic and isometric striated muscles contraction, as well as their extensibility and elasticity, are modulated by the central nervous system. Modulation at the level of neuromuscular synapses is also very compound, but precisely regulated, and essential for the induction of signals to muscle cells (Farahat & Herr 2010). The induced signal starts a cascade of multiple processes, necessary for sustaining muscle homeostasis. Without it, and also without muscle fuel utilization, muscle movement and skeletal support are deeply impaired. We therefore begin our description with electrochemical transmission, because its effects are subjected to modulation.

2. Calcium and ATP - mediators/modulators of ion channels in myocyte and its contractile activity

When a threshold potential is reached, an impulse travels along the muscle cell membrane and opens calcium gates in the membrane of the sarcoplasmic reticulum (SR). This is a trigger for the myofibrils and myofilaments located in the sarcoplasm, which turns the muscle "on". A muscle stops contracting, if the impulse is no longer being transferred from the neuron to the sarcolemma. At that moment, calcium gates close and calcium ions move back into the SR. At the terminal cisternae of SR with intracellular Ca^{2+} stores, the ryanodine receptor channel isoform 1 (RyR1) is located. It is an integral component of excitation–contraction coupling and the receptor activation plays a key role in this process. Excitation-contraction coupling may be triggered by a single-pulse of electrical stimulation and results in massive release of Ca^{2+} from the SR *via* the RyR1 to the cytosol after depolarization of the muscle plasma membrane. However, skeletal muscle function *in vivo* is generally regulated during repetitive firing of short trains of action potentials (Diaz-Sylvester et al., 2008).

The free cytosolic Ca^{2+} concentration in a skeletal muscle at rest is about 120 nM and in the millimolar range in its intracellular stores (Eltit et al., 2011). The RyR1 is activated by an increase in cytosolic Ca^{2+} levels (with peak activation at ~100 µM); regardless of the presence or absence of Mg^{2+}/ATP, and it is called calcium induced calcium release mechanism. A millimolar Ca^{2+} concentration also inactivates *per se* the RyR1. The receptor may also be inhibited by Mg^{2+} or activated by caffeine and ATP. The RyR1 channel is furthermore modulated by ryanodine, calmodulin, 12-kDa FK-506-binding protein (FKBP12) and so-called Homer proteins, as well as by various redox processes (Diaz-Sylvester et al., 2008; Eltit et al. 2011; Feng et al., 2008; Ye et al., 2012; Lawler et al., 2010).

Variations in the intracellular levels of endogenous RyR1 modulators are relevant to individuals with genetic disorders of skeletal muscles associated with mutations in the RyR1 of SR. Some of the disorders were investigated in malignant hyperthermia (MH) provoked by halothane. The RyR1 becomes more susceptible to activation by halothane, when Mg^{2+} levels decrease and/or Ca^{2+} levels increase in the cytosol. ATP binding greatly increases the RyR1 activity as well. Moreover, halothane-induced RyR1 activation is enhanced by increases in SR Ca^{2+} loads. Knowledge about cytosolic modulators may help us understand, why decreased Mg^{2+} sensitivity may result in higher sensitivity to halothane and why RyR1 carrying MH mutations are less sensitive to Mg^{2+} inhibition. Taking into account the fact that insulin decreases intracellular Mg^{2+} in muscles, we are able to explain why MH susceptibility has been associated with increased insulin levels (Diaz-Sylvester et al., 2008).

Another calcium channel is the dihydropyridine receptor (DHPR), serving as a voltage sensor in excitation-contraction coupling and a modulator of RyR1 through physical interactions (a conformational change of DHPR allosterically activates RyR1). In continuously depolarized skeletal muscle fibers, DHPR voltage sensors are inactivated and unable to initiate SR Ca^{2+} release. Both DHPR and RyR1 receptors bind with Triadin (a modulator from a family of proteins of the junctional sarcoplasmic reticulum) that is involved in many crucial aspects of muscle functions and E-C coupling in skeletal muscles (Diaz-Sylvester et al. 2008; Perez, 2011). Dihydropyridine-receptor agonists and antagonists can modulate both a single pulse electrical stimulation (which mainly triggers a fast calcium signal sensitive to RyR1) and tetanic stimulation (which induces a long-lasting, inositol triphosphate (IP_3)-generated signal) (Lawler et al., 2010).

Ca^{2+} release plays an essential role in initiating muscle contraction, increases glucose uptake (although its signalling is unresolved), activates numerous genes required for mitochondrial biogenesis, and results in ATP production in mitochondrial and cytoplasmic compartments during exercise (Hawley et al. 2006). A lasting contraction causes energy expenditure and ATP supply diminishes at some point (but usually no more than about 20 % of it even during very intensive exercise). This decline in ATP level causes muscle fatigue. The myosin heads remain bound to actin and can no longer swivel. Even when a nervous impulse is being transmitted to the muscle and calcium ions are still present, contraction/or strong contraction is not possible. Several different energy sources (phosphocreatine, muscle glycogen, blood glucose and fatty acids from adipose tissue) are used by myocytes to

maintain ATP levels in a working muscle. Although glucose is a predominant fuel for the muscles, diminished ATP levels in the myocyte are a signal to switch to the use of fat fuel, leading to an increased flux of free fatty acids and changes in the AMP/ATP ratio, contributing to fiber shifts. Fuel economy depends on the type of muscle fibres involved, the length of the physical effort and its type. There are high speed fibres which require carbohydrate fuels and generally used slowly contracting economical fibers with a fat-based aerobic metabolism (de Lange et al., 2007).

The AMP/ATP ratio is important for the activation of AMP–activated protein kinase (AMPK), which stimulates energy generating processes (glucose uptake and fatty acid oxidation). AMPK plays a key role in controlling muscle economy, inmaintaining muscle homeostasis, and in inducing a cascade of events within cells in response to the ever-changing energy charge of the cell (de Lange et al., 2007; Lira et al. 2010).

3. Modulators of the AMP–activated protein kinase relevant in type 2 diabetes mellitus

AMPK was discovered in skeletal muscles in 1995 (Verhoeven et al., 1995). It is a heterotrimeric enzyme comprised of two catalytic (α1 or α2) subunits and two regulatory (β1 or β2 and gamma1, gamma2, or gamma3) subunits (all are encoded by separate genes). AMPK activity inhibited preparations of acetyl-CoA carboxylase (ACC) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) was first discovered. Later, it was noticed that AMPK activity can also be regulated by physiological stimuli, independent of the energy charge of the cell (like hormones and nutrients) (Lim et al., 2010; Steinberg & Kemp, 2009).

AMPK is activated during contraction. Its modulation (related to the muscle energy state) depends on two distinct mechanisms – on an AMP-dependent pathway mediated by kinase LKB1 and on a Ca^{2+}dependent pathway mediated by the calmodulin-dependent protein kinase (CaMKKb). AMPK in skeletal muscles increases fatty acid oxidation and mitochondrial biogenesis (Lim et al., 2010). These processes require phosphorylation of the peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) and SIRT1. The last protein works as an NAD^+-dependent protein deacetylase or ADP-ribosyltransferase. It also activates PGC-1α involved in fatty acid utilization and mitochondrial respiration (de Lange et al., 2007; Zhang et al., 2009).

Mitochondrial dysfunction observed in type 2 diabetes mellitus leads to a decrease in ATP levels and possibly to changes in NAD^+/NADH levels. It can influence methylenetetrahydrofolate dehydrogenase ($NADP^+$) activity, which depends on the concentration of NAD^+ and on the ATP/ADP ratio (Zhang et al., 2009; Mailloux & Harper, 2010). NADH inhibits and βNAD activates AMPK, but NAD is a much weaker activator than AMP (we also do not know, if AMP is a direct activator). AMPK activity is modulated not only by nucleotides, but also by kinases, fatty acids, insulin, cytokines and reactive oxygen species (ROS) (Rafaeloff-Phail et al., 2004; Steinberg & Kemp, 2009; Zhang et al., 2009).

The major glucose transporter - GLUT4 translocation to sarcolemma, is also a result of AMPK-activated PGC-1α, where SIRT1 activity is required (Steinberg & Kemp, 2009). This pathway of glucose uptake in skeletal muscles is stimulated by palmitate (PA) (regardless of AMP concentrations) (Pu et al., 2011). It takes place only when skeletal muscles are exposed to PA for a short time. Chronic exposure to PA blocks Akt phosphorylation and inhibits insulin induced glucose uptake. Besides PA, linoleic, oleic, and stearic acids can stimulate AMPK and Akt (Pu et al., 2011).

5-Aminoimidazole-4-carboxyamide ribonucleoside (AICAR) is another AMPK activator increasing GLUT4 translocation to sarcolemma and glucose uptake in rats' skeletal muscles. AICAR as well as physical effort, leads to AMPK activation, which enhances a specific protein fatty acid translocase – FAT/CD36 in sarcolemma. Either AICAR or physical effort, stimulate AMPK activity in obese and type 2 diabetes mellitus, which can further enhance muscle lipid breakdown and the capacity for ATP generation (by the activation of mitochondrial fatty acid β-oxidation enzymes) (de Lange et al., 2007; Steinberg & Kemp, 2009).

Physical effort enhances the production of ROS. ROS is produced continuously in mitochondria and its level is reduced by the activation of AMPK. This process has especially been investigated in smooth muscles, because oxidative stress (e.g. induced by free fatty acids) in patients with a metabolic syndrome contributes to the development of cardiovascular diseases (Steinberg & Kemp, 2009).

In response to the contraction of a myocyte, interleukin-6 (IL-6) is produced and released. Although AMPK participates in the regulation of IL-6 release from oxidative muscle, IL-6 significantly increases AMPK activity in myotubes as well as enhances fatty acid oxidation and insulin-stimulated glucose uptake.

The effect of adiponectin on AMPK activation is not well known. AMPK is probably indirectly activated by increases in levels of intracellular ATP, but it is known that leptin directly stimulates the α2 and β2 catalytic subunits expression of AMPK in skeletal muscle. This occurrence correlates with enhanced fatty acid oxidation and the inhibition of lipogenesis. Such leptin action was reported in healthly individuals, but AMPK in obese individuals was not activated by leptin.

Cytokines may also inhibit AMPK activity - tumor necrosis factor α (TNFα), which signals through the TNF receptor (TNFR) 1, upregulates protein phosphatase 2C (PP2C) and suppresses AMPK. This in turn suppresses fatty-acid oxidation and increases intramuscular diacylglycerol accumulation in skeletal muscle.

AMPK is a major cellular energy sensor and a master regulator of metabolic homeostasis - several processes necessary for the mechanical function of muscles are controlled by 1 enzyme. Today, AMPK is already the target of several classes of drugs used for type 2 diabetes mellitus, including metformin and tiazolidinediones (Steinberg & Kemp, 2009; Zhang et al., 2009).

4. Myocyte modulators and insulin resistance

Adipose tissue protects other cell tissues from "lipotoxicity", but obesity causes dysregulation of lipolysis and lipid oversupply into muscles and other tissues. Adipose tissue also informs the brain and other tissues about this dysregulation through adiponectin, leptin, resistin, IL-6 and TNFα (Steinberg & Kemp, 2009). Not only is the adipose tissue recognized as an endocrine organ, it also produces modulators relevant for IR. There is also the hepatic insulin sensitizing substance (HISS), which after being released from the liver, acts on skeletal muscles to stimulate glucose storage in the form of glycogen. The intramyocytal signaling cascade in type 2 diabetes mellitus is impaired due to insulin modulation by HISS and in the future we will probably differentiate these two types of diabetes mellitus in the GP's surgery (Lautt et al., 2010).

It is clear that insulin activates the pathway of kinase Akt and hampers AMPK activity, but despite the developing knowledge about AMPK, we still do not know enough about IR. When skeletal muscles become unable to switch between glucose and fatty acid use, the cause of glucose uptake and utilization is dramatically lessened.

There is evidence that nitric oxide (NO) is a modulator of insulin action and insulin resistance is linked to inducible NO synthase (iNOS) induction in skeletal muscle cells (and in other insulin target cells as well). An increased expression of multiple inflammatory cytokines (TNFα, interferon-c, IL-6, and IL-1β) observed in obesity has to induce iNOS as it was shown on an animal model of acute systemic inflammation that iNOS in muscle (also in liver and adipose) tissue was induced by the administration of the endotoxin lipopolysaccharide (LPS). Cytokines modulate glucose transport in the skeletal muscle by inducing the expression of iNOS. Moreover, a high-dose of aspirin improves glucose metabolism in patients with type 2 diabetes mellitus. There is also genetic evidence that iNOS mediates skeletal muscle IR in obese high-fat fed mice and that the induction of iNOS in skeletal muscle modulates whole-body glucose metabolism (Cha et al., 2011; Soskić et al., 2011).

AMPK phosphorylates and activates NOS, and physiological levels of NO can stimulate glucose uptake and oxidation in human skeletal muscles, but the meaning of NOS for glucose homeostasis is still cloudy (Steinberg & Kemp, 2009). Physical effort increases NOS activity and the expression of neuronal (nNOS) and endothelial (eNOS) NOS. There is some evidence that mitochondrial respiration in myocytes is inhibited by NOS activity. NO donors, such as sodium nitroprusside, raise skeletal muscle cGMP content and increase glucose uptake in rats, but the AICAR effect is not blocked by NOS inhibitors (McConell & Wadley, 2008). Chronic administration of NOS inhibitors (monomethylarginine - L-NAME) in drinking water decreases glucose tolerance in rats (Balon et al., 1999).

Another therapeutic target in insulin resistance may be stearoyl-CoA desaturase (SCD). The major product of SCD - oleic acid, may play an important role in the regulation of intracellular ceramide synthesis, which is recognized as an insulin-desensitizing lipid molecule. The lack of the SCD1 gene increases the rate of fatty acid ß-oxidation - it results in a decrease of free fatty acids and long-chain fatty acyl-CoAs content in the soleus and red gastrocnemius SCD1-/- mice models. The AMPK pathway is also involved in this process. It

increases this enzyme's phosphorylation and contributes to an increase of insulin sensitivity in the muscles. The expressions of a protein-tyrosine phosphatase 1B (PTP-1B) is down regulated in the case of SCD1 deficiency. This expression is responsible for the sustained insulin receptor autophosphorylation (Dobrzyn & Dobrzyn, 2006; Dobrzyn et al., 2010).

PUFA, cholesterol, vitamin A, hormonal signals (e.g. insulin, glucagon), environmental and developmental factors (temperature changes, metals), alcohol, thiazolinediones, peroxisomal proliferators modulate stearoyl-CoA desaturase (SCD) expression in adipose tissue and liver. It is proven that some of these compounds are able to modulate SCD by catalyzing the synthesis of monounsaturated fatty acids (mainly oleate and palmitoleate acids) in muscles. Glucose is probably the most important modulator of SCD expression in the skeletal muscle. Its long-term oversupply increases SCD expression and enzyme activity - it leads to fast and specific changes in fatty acid metabolism. Further investigations of SCD modulators may be relevant, because stress and inflammatory stimuli can also modulate Transcriptional regulation of SPT, which is the first committed step in *de novo* ceramide synthesis (Dobrzyn & Dobrzyn, 2006).

There is also evidence that insulin resistance and type 2 diabetes mellitus are linked to the reduction of insulin receptor substrate (IRS-1) expression, and the impairment of PI3K and kinase Akt activity in skeletal muscle. Impaired insulin-mediated glucose transport is a characteristic defect in type 2 diabetes mellitus. There is normal expression of the human GLUT4 gene in type 2 diabetes mellitus, but a cause of insulin resistance is searched out in traffic of this glucose transporter to sarcolemma. The translocation of GLUT4 to the membrane increases its glucose permeability. GLUT4 intracellular redistribution is directly linked to a signaling protein known as AS160 which may be activated by both the insulin pathway and AMPK. Hampering of the Akt substrate of 160 kDa (AS160), phosphorylation (as a result of Akt phosphorylation in the position of Thr308) diminishes the activity of AS160. Impaired insulin-stimulated phosphorylation of AS160 has been discovered in patients with insulin resistance or/and type 2 diabetes mellitus (Treebak et al., 2007).

When no muscles stimulation exists, then only about 10% of GLUT-4 transporters are located in the sarcolemma, but their amount increases to 50% after 2-3 minutes of stimulation with insulin. Relocation of GLUT4 from an intracellular pool of myocytes to its membrane is phosphorylated and activated not only by insulin (associated with the activation of kinase PI3K), but also may be activated by IGF1, EGF and AICAR. NO induces the upregulation of GLUT4 mRNA (by the AMPK dependent pathway) (Wang et al., 1996; Russell et al., 1999).

The role of NO in a skeletal muscle has still not been investigated enough. The interaction of AMPK, NOS enzymes, and NO levels in skeletal muscles is intriguing (AMPK activates eNOS and nNOS, but AMPK activation inhibits iNOS expression). We think that the significance of the effect of SCD1 deficiency/downregulation on lipid metabolism and insulin sensitivity in the skeletal muscle is underrated, as lipids are transported through sarcolemma (Steinberg & Kemp, 2009).

The last investigation showed that dysregulation in PA uptake and reduced CD36 protein level in murine myocyte are recognized as a reason of metabolic complications analogous to

"the cardio-metabolic syndrome" in patients treated with a protease inhibitor of the human immunodeficiency virus (Richmond et al., 2010).

It is a real challenge to establish a cause of diabetes mellitus type 2, which is probably multifactorial. One of those factors is a sedentary lifestyle, another one is obesity and a high fat calorie diet, they induce inflammatory cytokines and reduce insulin signaling. This subsequent loss of homeostatic signaling yields a low heat shock proteins (HSP) state (Atalay et al., 2009). The HSPs respond to a wide variety of stress factors (e.g. elevated temperature, hypoxia, altered pH) and first studies in patients with diabetes mellitus type 2 revealed that hot-tub therapy is able to improve glycemic control (Gupte et al., 2009, as cited in Hooper, 1999). Later it was described that HSP90 maintains the Akt and plays an important role in the regulation of glucose transport mediated by insulin (Atalay et al. 2009, as cited in Sato S. et al. 2000). Moreover, a lower level of HSP72 was found in skeletal muscles of patients with type 2 diabetes and some HSPs were strongly induced in skeletal muscle with physical exercises especially in fast-twitch muscles (Atalay et al. 2009, as cited in Bruce, 2003 and Kurucz, 2002). A recent study demonstrated that heat treatment protects skeletal muscles in rats from a high-fat diet–induced insulin resistance and provided strong evidence that HSP induction in skeletal muscles could be a potential therapeutic treatment for obesity-induced insulin resistance (Gupte et al., 2009).

The HSP60 expression improves mitochondrial dysfunction observed in skeletal muscles of patients with type 2 diabetes as measured by oxidative capacity, with a high-fat diet in parallel with increased mitochondrial protein expression (Gupte et al., 2009). Also thiazolidinediones increase expression of an array of mitochondrial proteins in diabetic mousses (it also concerns PGC1α, the master regulation of mitochondrial biogenesis) (Cantó et al., 2009) and we think that mitochondria are a primary target of heat therapy from oxidative stress.

Recently, BGP15 (an HSP inducer) was found as a potent insulin sensitizer, which increases muscle glucose utilization (Literáti-Nagy et al. 2009). It protects the mitochondrial membrane against oxidative damage by the activation of PI-3-kinase – Akt pathway. This well-known cytoprotective pathway is suppressed by Poly (ADP-ribose) polymerase (PARP), which can induce rapid cellular NAD$^+$ and ATP pool depletion leading to mitochondrial dysfunction. The small molecule BGP15 is an inhibitor of PARP presented in eukaryotes and may be a novel strategy for therapies of insulin resistance (Halmosi et al. 2001)

We were able to find more evidence that our surroundings also have input in type 2 diabetes mellitus etiology. Bisphenol-A (BPA), a component of polycarbonate plastics and epoxy resins, widely used in multiple consumer products like plastic food/fluids containers is commonly recognized as a disruptor of glucose homeostasis, which provokes hyperinsulinemia and insulin resistance. The measurable levels of this synthetic estrogen were reported in human serum, urine, breast milk, fetal plasma, and placental tissue. It probably modulates the glucose transporter GLUT4 through two estrogen receptors (ERα and ERβ). Studies showed that elevated BPA level was associated with elevated hemoglobin A1c (HbA1c). Also higher urinary BPA level was found to be associated with diabetes type 2 diabetes mellitus independently of traditional diabetes risk factors (Lang et al., 2008; Vandenberg et al., 2007; Li et al., 2012). On the other hand, α-lipoic acid (LA) (found abundantly in green vegetables)

affects the insulin-signaling cascade and protects myocyte from oxidative stress-induced insulin resistance (Maddux et al., 2001). Also green and black teas suppress insulin resistance by retaining the expression of GLUT4 in skeletal muscle. Epidemiological data suggests that drinking green tea is negatively associated with type 2 diabetes (Anderson & Polansky 2002; Nishiumi et al 2010; Yan et al. 2012). Green tea reduces oxidative stress in animal adipocytes (Yan et al. 2012), it also decrease ROS content of cultured mouse myotubes (Buetler et al., 2002), but we have not yet investigated, if green tea protects myocytes from oxidative stress-induced insulin resistance. Several international prospective studies show a protective effect of coffee on the development of type 2 diabetes (Kempf & Martin 2010). We focused on the modulators crucial for peripheral insulin resistance, but impaired pancreatic glucose sensing is involved in etiology of diabetes mellitus type 2 as well. It is a genetically complex chronic disease, but lifestyle changes can delay progression to diabetes, even in high-risk individuals, for at least a decade (Cho et al. 2012; Knowler WC et al. 2009).

5. Muscular contraction – underestimated modulator

Physical exercise is a potent stimulus for increasing glucose uptake in the complete absence of insulin. This mechanism may be modulated by AMPK, Akt/protein kinase B phosphorylation, NO and Ca^{2+}/calmodulin-dependent protein kinase (CaMK) and protein kinase C (PKC) and is initiated by acute exercise. This is a short–lived effect, which disappears in 16-48 h. However, repeated physical exercise results in an increase in insulin action, sustain in skeletal muscle of patients with insulin resistance and type 2 diabetes mellitus. This improvement in insulin sensitivity is related to increasing AS160 phosphorylation, expression and/or activity protein kinase B (Akt) and AMPK (Hawley & Lessard, 2008; Ismail-Beigi, 2012; Cahová et al., 2007; Wasserman et al., 2011).

Exercise training results also in glucose uptake through an increase in the level of GLUT4 trafficking. Training may cause increasing 30% of GLUT4 in sarcolemma of patients with type 2 diabetes mellitus and 20% of GLUT4 in control group (Wasserman et al., 2011). We outlined above, how muscle contraction my improve insulin sensitivity by increased lipid oxidation. There is also clinical evidence that physical activity (150 min/week) and diet-induced weight loss of 5–7% are able to reduce the risk of progression from impaired glucose tolerance to type 2 diabetes mellitus. Therefore, very recently the guidance in type 2 diabetes mellitus has been changed – more attention is given to muscle contraction as a modulator, which has become a key part of type 2 diabetes mellitus self-management (Sigal et al., 2006).

6. Conclusion

Type 2 diabetes mellitus is still a challenge for biochemists, clinicians and epidemiologists. It has been assessed that 23.6 million people lived in the US in 2007 with diagnosed and undiagnosed diabetes (7.8% of the general population). There are forecasts that 366 million people in the world will live with type 2 diabetes mellitus in 2030 (Zhang et al., 2009).

Recently, physical exercise has been recognized by health organizations as an undoubted modulator of glucose uptake in skeletal muscles. We hope that awareness of this fact will be

created by promotion in the GP's surgery and through mass media. Muscle contraction as a modulator of GLUT4 expression, which also improves insulin signal transduction at the level of PI3K and AS160, and activates AMPK, is able not only to diminish a dose of oral medicine in type 2 diabetes mellitus, but also to influencethe future of patients with insulin resistance.

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