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REVIEW

Effect of Caloric Restriction on Aging: Fixing the Problems of Nutrient Sensing in Postmitotic Cells?

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Abstract—The review discusses the role of metabolic disorders (in particular, insulin resistance) in the development of age-related diseases and normal aging with special emphasis on the changes in postmitotic cells of higher organisms. Caloric restriction helps to prevent such metabolic disorders, which could probably explain its ability to prolong the lifespan of laboratory animals. Maintaining metabolic homeostasis is especially important for the highly differentiated long-lived body cells, whose lifespan is comparable to the lifespan of the organism itself. Normal functioning of these cells can be ensured only upon correct functioning of the cytoplasm clean-up system and availability of all required nutrients and energy sources. One of the central problems in gerontology is the age-related disruption of glucose metabolism leading to obesity, diabetes, metabolic syndrome, and other related pathologies. Along with the adipose tissue, skeletal muscles are the main consumers of insulin; hence the physical activity of muscles, which supports their energy metabolism, delays the onset of insulin resistance. Insulin resistance disrupts the metabolism of cardiomyocytes, so that they fail to utilize the nutrients to perform their functions even being surrounded by a nutrient-rich environment, which contributes to the development of age-related cardiovascular diseases. Metabolic pathologies also alter the nutrient sensitivity of neurons, thus disrupting the action of insulin in the central nervous system. In addition, there is evidence that neurons can develop insulin resistance as well. It has been suggested that affecting nutritional sensors (e.g., AMPK) in postmitotic cells might improve the state of the entire multicellular organism, slow down its aging, and increase the lifespan.

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INTRODUCTION

Age-related degradation is associated with metabolic disorders and disruption of the metabolism regulation systems at all levels of organization – from single cells to the entire multicellular organism. In particular, dysregulation of glucose tolerance that progresses with age, results in the development of metabolic syndrome. Caloric restriction helps fighting metabolic disruptions, which is likely why it increases the lifespan of laboratory animals [1-5]. The main components of signaling pathways sensitive to the changes in the nutrient content are insulin, TOR (target of rapamycin), and AMPK (5′-AMP-activated protein kinase). Impairments of these signaling pathways can trigger various metabolic disorders. Thus, disturbed functioning of AMPK results in multiple dysregulations, including development of insulin resistance (IR) [6]. Activation or suppression of metabolic sensors might increase lifespan in various organisms and improve age-related indicators in humans.

One of the consequences of metabolism disruption is dysregulation of the proteolytic system and cell energy metabolism that affect to the most highly differentiated body cells. The lifespan of neurons and myocytes is long and comparable with the lifespan of the organism itself. Normal activity of these cells could be ensured only in the case of adequate functioning of the cytoplasm clean-up system and systems providing nutrients and energy supply. Dysregulation of proteolysis and autophagy, as well as

Abbreviations: AMPK, 5′-AMP-activated protein kinase; AS160, Akt substrate of 160 kDa; CNS, central nervous system; DAG, diacylglycerol; FFA, free fatty acids; GLUT, glucose transporter; IGF-1, insulin-like growth factor 1; IR, insulin resistance; IRec, insulin receptor; IRS, insulin receptor substrate; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; p70S6K, 70 kDa ribosomal protein S6 kinase; PI3K, phosphoinositide 3-kinase; PKB, protein kinase B; PKC, protein kinase C; T2D, type 2 diabetes; TOR, target of rapamycin.

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disruption of the regulatory function of AMPK eventually lead to the degradation and death of postmitotic cells. The cells have their own strategies to fight the development of age-related disorders. For example, type I muscle fibers use 'mild' uncoupling to decrease generation of reactive oxygen species [7]. Although partial uncoupling of respiration and oxidative phosphorylation slows down ATP production, at the same time, it significantly decreases the amount of formed reactive oxygen species. It is likely that the effect of 'mild' uncoupling is very similar to the effect of caloric restriction, because in both cases, the amount of ATP is decreased [8]. In the case of caloric restriction, the reason for the decreased ATP amount is the deficit of calories, while in the case of 'mild' uncoupling, the reduced content of ATP is due to the fact that a fractions of protons passes through the mitochondrial membrane without being used by the ATP synthase for ATP synthesis.

The disbalance of the metabolism regulatory system is likely a side effect of the organism development and occurs naturally. The development of musculoskeletal and nervous systems in humans ends by the age of 21-23. Following a certain period of optimal functioning, the number of muscle fibers and neurons decreases, almost unnoticeably at first; however, later this process gradually accelerates. Reduction of calorie intake or physical exercise, which burns the "extra" calories, could normalize the functioning of the nervous and cardiovascular systems that deteriorate with age.

All mentioned signaling pathways are highly conserved and, hence, can be investigated in very different organisms. The model of chronological aging in yeast is widely used to study the aging of postmitotic cells and the model of 'stationary phase' aging (age-related degradation of cells under conditions of restricted proliferation in the stationary growth phase) of bacterial and mammalian cells is used less often [9-14]. It is known that activation of autophagy and AMPK (SNF1, *s*ucrose-*n*on*f*ermenting, in yeast) or inhibition of TOR also extend the lifespan of cells in culture, which confirms the relevance of such models [15-17].

Despite a large number of studies on caloric restriction, many issues are still widely debated. Could mimetics fully replace caloric restriction in the fight against aging? What are the consequences of excessive activation of signaling pathways extending the lifespan? How to increase the lifespan of actively functioning highly differentiated cells that require high energy supply? So far, there are no conclusive answers to these and many other questions. In this review we attempted to answer at least some of them.

METABOLIC DISRUPTIONS

The cells possess a complex metabolic network that ensures the supply of energy and building materials from the sources in the environment or blood. The main sources are glucose, glutamine, and fatty acids. There is also a wide spectrum of metabolic sensors, including such unobvious ones as sensors of extracellular nucleotides and RNA-based sensors [18].

Glucose metabolism and processes associated with glucose sensitivity disorders (IR, obesity, diabetes, and metabolic syndrome) have been extensively analyzed in numerous gerontological studies. It is difficult to overestimate the role of glucose in the metabolism of cells and entire organism. Glucose is not only an essential energy source, but also an important activator of cell proliferation. In humans, formation of metabolic pathways regulating energy supply and maturation of the corresponding nerve structures occur at the late stages of fetal development [19]. These processes are necessary for the transition from fetus nutrition through the placenta to the endogenous production of glucose. That is why premature babies have energy deficit, which results in the decreased levels of insulin-like growth factor 1 (IGF-1) and disruption of glucose metabolism [20]. Low IGF-1 content is one of the main reasons for the underdevelopment of many organs and systems, in particular, central nervous system (CNS). Moreover, starvation of the mother or disruption of the nutrient transport through the placenta at the prenatal stage could affect further life and even determine the lifespan of the baby [21-26]. Excessive caloric intake by the mother also results in the disruption of glucose metabolism and affects the development of the fetal CNS and some structures [27]. If mother has gestational diabetes and IR, maternal insulin does not cross the placenta, while glucose is transported to the fetus. As a result, the fetus experiences hyperglycemia and responds to the elevated glucose levels by the increased insulin release [28]. Therefore, glucose is one of the important metabolic factors determining the development of an organism.

Insulin is secreted by the pancreatic β-cells in response to the glucose entry to the blood. Insulin stimulates the uptake of glucose, amino acids, and other compounds by the cells, activates the synthesis of glycogen and fatty acids, promotes glycolysis, and suppresses gluconeogenesis, lipolysis, and proteolysis. Hence, all the effects mediated by glucose are associated with the activation of anabolism and inhibition of catabolism. The research models commonly studied in gerontology, such as *Drosophila*, nematodes, and yeast, lack insulin; however, they possess IGF-1. The insulin/IGF-1 signaling pathways, which are responsible for the organism growth and development, are evolutionary conserved. In humans, insulin also affects to some degree the mitogenic processes; however, in this review, we will focus primarily on its metabolic effects and will not discuss in detail IGF-1 and insulin/IGF-1 pathway.

AMPK and TOR play an important role in the metabolism regulation in organisms, including those

lacking insulin. AMPK is activated by the increase in the AMP/ATP ratio (hence, the name AMP-activated) and, therefore, acts as a principal sensor of energy deficit [29]. The main purpose of AMPK is to shut down the anabolic processes and to initiate the catabolic ones. Its regulatory role is manifested in all organs and tissues as the inhibition of lipogenesis and gluconeogenesis, suppression of synthesis of cholesterol, triglycerides, fatty acids, and proteins, or activation of the uptake of glucose and fatty acids followed by their oxidation. AMPK is a serine/threonine protein kinase. It is a heterotrimer formed by three subunits. Each of the subunits has several isoforms: two isoforms of the catalytic alpha-subunit (α1 and α2), two isoforms of the regulatory beta-subunit (β1 and β2), and three isoforms of the regulatory gamma-subunit (γ1, γ2, and γ3). The structure and numerous functions of AMPK have been described in detail in a number of reviews [29-31]. The action of AMPK is mostly opposite to the action of the mTOR (mechanistic target of rapamycin) complex. mTOR is activated upon the energy excess (when glucose is present in large amounts) and initiates anabolic processes. mTOR is a serine/threonine protein kinase that belongs to the family of phosphatidylinositol 3-kinase (PI3K)-related protein kinases and activates a large number of key metabolic targets in the cell. mTOR is found in the composition of two protein complexes – mTORC1 (rapamycin-sensitive complex of mTOR, Raptor, and mLST8) and mTORC2 (complex of mTOR, Rictor, Sin1, and mLst8). Both complexes control cell growth and survival, but only mTORC1 is involved in the regulation of metabolic reactions [32]. mTORC1 is a pivotal component that coordinates cell growth with the availability of nutrients, energy, and growth factors [33]. Signal transduction by mTOR is involved in aging and has been thoroughly studied in the model organisms (*Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Drosophila melanogaster*, rodents). Rapamycin, an inhibitor of mTOR, was found to extend the lifespan of these organisms [15, 34-36]. At the same time, excessive activation of the mTORC pathway occurring with age likely causes aging and aggravates the course of oncological diseases and diabetes [37]. The positive effect of caloric restriction has been commonly associated with the activation of AMPK and inhibition of the mTORC1 pathway.

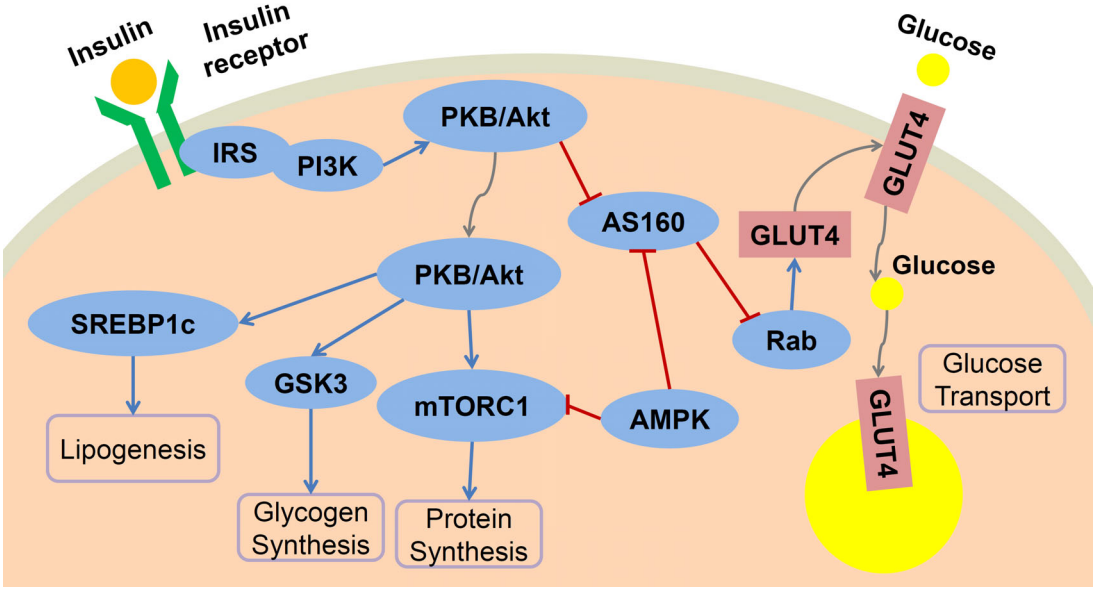
Insulin resistance. IR is a reduced response of tissues to the insulin stimulation. It is characterized by disrupted glucose uptake and oxidation, decreased glycogen synthesis, and, to a lesser degree, suppression of lipid oxidation [38].

Although IR development takes place simultaneously in several organs and tissues, here we focus on its effect in neurons, cardiomyocytes, and skeletal muscle myocytes, i.e., cells with the lifespan close to the lifespan of the organism itself (with exception of particular cases, such as emergence of new nerve cells in the hippocampus and olfactory bulb or death of myocytes in sarcopenia). It should be emphasized that the role of nervous and muscle tissues in glucose metabolism is different.

Insulin is a peptide hormone secreted by β-cells of the pancreas. It interacts with receptors on the plasma membrane of target cells and regulates complex anabolic responses to the available nutrients [39]. Insulin is synthesized mostly in response to the increase in the blood glucose concentration; however, its synthesis and release could be also initiated by changes in the content of amino acids, acetylcholine, cholecystokinin, and other compounds [40]. As an anabolic hormone, insulin facilitates energy accumulation (uptake of glucose, amino acids, and fatty acids) and cell growth and inhibits catabolic processes (glycolysis, lipolysis, proteolysis). Insulin exerts both direct and indirect effects on the target tissues. The indirect effects of insulin are difficult to model, as they are to a large degree interconnected with other effects and depend on numerous factors. They have been investigated much less than the cell-autonomous effects of the hormone, which could be modeled in cell cultures [39].

A simplified scheme of the metabolic effects of insulin is presented in the figure. Insulin receptor (IRec) consists of two extracellular alpha subunits and two intracellular beta subunits. Due to its tyrosine kinase activity, IRec phosphorylates tyrosine residues in the adapter proteins from the family of IRec substrates (IRS, insulin receptor substrate) and activates PI3K. Among the six members of the IRS family identified so far, IRS-1 and IRS-2 are responsible for the majority of insulin effects associated with the activation of two major signaling pathways – PI3K–PKB/Akt (PKB/Akt – protein kinase B) and Ras–MAPK (mitogen-activated protein kinase) [28]. IRS-1 is especially important in skeletal muscles, adipose tissue, and cerebral cortex, while IRS-2 functions mostly in the liver and hypothalamus. Activated IRS stimulates signal transduction through the PI3K–PKB/Akt pathway. PKB/Akt regulates phosphorylation of many intracellular proteins, including mTORC1, GSK3β (glycogen synthase kinase-3 beta), and SREBP1c (sterol regulatory element-binding protein 1c); it also stimulates the transfer of glucose transporters to the plasma membrane via phosphorylation of AS160/TBC1D4 (Akt substrate of 160 kDa/TBC1 domain family member 4) [39-42]. IGF-1 also binds to and activates IRec, while IRec and IGF receptors can initiate similar trophic processes [40].

According to the currently dominating hypothesis, the causes of the typical obesity-associated IR are the defects of insulin signaling rather than the reduced insulin binding to IRec. However, it was demonstrated that both the reduced content of the surface IRec and the disruption of insulin signaling contribute to the typical obesity-associated IR [39]. The control of glucose level in the blood to a large degree depends on the balance between insulin and other hormones with the opposite activity that bind to the appropriate receptors in the muscles, adipose tissue, and liver.



Insulin signaling pathways. The metabolic branch of insulin signaling occurs through the IRS (insulin receptor substrate) activation. Insulin binding to insulin receptor, results in the activation of IRS, which then activates the PI3K–PKB/Akt pathway. Fast effects include activation of glycogen and protein synthesis, while slow effects involve stimulation of lipogenesis. Stimulation of glucose uptake by insulin occurs due to the transfer of the GLUT4-containing storage vesicles to the plasma membrane. Activated AMPK inhibits protein synthesis and activates glucose transport. Blue arrows, activation; red lines, inhibition; gray arrows, transport.

IR causes not only hyperglycemia, but hyperlipidemia as well [40]. Since each of these issues deserves a detailed review, we focused mainly on the disruption of glucose metabolism and IR development (which facilitates the disruption of lipid and protein metabolism) and discussed other metabolic disorders only briefly.

AGE-RELATED METABOLIC DISRUPTIONS IN SKELETAL MUSCLE MYOCYTES

Along with the adipose tissue, skeletal muscles play a vital role in many metabolic processes, including regulation of blood glucose level, the rate of metabolism during rest, the maintenance of inner body temperature, etc. [43]. Muscles comprise 40% of body mass [44] and indirectly consume 60-70% of insulin produced by the body [45]. Hence, it is not surprising that the development of many age-related pathologies is strongly associated with the muscle tissue. The appearance of glucose in the blood initiates insulin-mediated synthesis of glycogen in the muscles. In both muscle and fat cells, glucose is transported by GLUT4 [45]. The functioning of GLUT4 depends on insulin, since the transporter is activated only when the level of glucose is sufficiently high for the production of reserve metabolites.

Insulin resistance in skeletal muscle cells. IR in skeletal muscle is characterized by the reduced stimulation of glucose uptake by insulin due to the impaired insulin signaling and suppression of the GLUT4 translocation. IR in skeletal myocytes facilitates increase in the postprandial glucose levels and reduces glucose tolerance, because skeletal muscles are responsible for the uptake of the larger portion of glucose after a meal [46].

As a hormone that promotes energy storage, insulin first stimulates glycogen synthesis in myocytes and, to a lesser degree, glycolysis [39]. Disruption of the ability of skeletal muscle cell for the insulin-induced uptake of glucose is the main component of typical IR associated with obesity and type 2 diabetes (T2D). Insulin-activated synthesis of muscle glycogen in patients with T2D and in lean and healthy insulin-resistant offspring of patients with T2D is reduced by 50% [39]. IR in the skeletal muscles is associated with the defects in the most proximal levels of insulin signaling involving IRec, IRS-1, PI3K, and PKB/Akt. Distal defects of IR have also been found in muscle cells, but it remains unclear whether these defects emerge independently or are secondary to the proximal defects [39]. It is known that some lipid fragments, such as diacylglycerol (DAG), ceramides, and acylcarnitines, are also involved in the IR pathogenesis in the liver and skeletal muscles [47, 48].

Proximal defects. Both IRS-1 and IRS-2 are expressed in the skeletal muscles. However, the knockdown of only *IRS-1* resulted in the disruption of the insulin-stimulated glucose transport in the primary human myotubes [49] and rat L6 myotubes [50]. Both isoforms of the PI3K catalytic subunit and both forms of Akt are also expressed in skeletal muscles. It was found that suppression of the *Akt2* expression in primary human

myotubes by RNA interference abolished the insulin-stimulated glucose uptake and glycogen synthesis, while the knockdown of *Akt1* had no effect on these processes [49]; hence, it can be suggested that Akt2 is more important for the insulin-stimulated glucose metabolism. The significance of Akt2 for the normal insulin action was corroborated by identification of the partial loss-of-function mutation in *Akt2* (p.Pro50Thr), which is found only in the Finnish population with very rare exceptions (mutation frequency of 1.1% in the Finish cohort versus 0.02% in the European non-Finnish cohort). This mutation disrupts the insulin-stimulated glucose uptake in the muscle and adipose tissue, increases production of endogenous glucose, and, therefore, increases the risk of T2D development [51]. The fact that glucose transport is responsible for the decrease in the insulin-stimulated glycogen synthesis in the muscles of patients with diabetes had been demonstrated many times already in 1990s using magnetic resonance spectroscopy with ^{13}C and ^{31}P isotopes [39]. Therefore, these defects influence on insulin binding to IRec and translocation of GLUT4. It is important to note that IR does not affect signal transduction through MAPK in the skeletal muscle of patients with obesity or T2D [52].

It should be also mentioned that liver and muscles absorb free fatty acids (FFAs) circulating in the plasma, which results in the ectopic lipid accumulation that also promotes IR development in the liver and muscles [53].

Circadian rhythms (both central and peripheral) could play an important role in the IR development, since they coordinate glucose metabolism [46]. In particular, peripheral clock in the muscles, adipose tissue, and liver regulates the sensitivity of these tissues to insulin. Considering that this peripheral clock receives no information on direct illumination, it should be sensitive to other synchronizers, such as metabolic signals associated with meals [54, 55]. Molecular clock in muscles is synchronized by the physical activity [56, 57]. The optimal metabolic health is achieved when various 24-h cycles (including fasting/feeding and sleep/wakefulness behavioral cycles), the rhythms of the vegetative nervous and hormonal systems and the rhythms of the central and peripheral clocks are synchronized. And *vice versa*, an imbalance between components of these systems, e.g., between behavioral and tissue clocks, could disrupt circadian rhythms and lead to the development of IR and T2D [46]. However, it is still unclear whether it is disruption of the central or peripheral clocks (or both) that causes IR at the tissue level.

Cell proliferation in skeletal muscles and age-related myocyte loss. In the skeletal muscles, myocytes fuse into a multinucleated skeletal muscle fiber and cannot divide. Only a small population of the skeletal muscle satellite cells can divide in adult humans. Usually, resting satellite cells are activated by the muscle damage, which is followed by the cell division and differentiation into new myonuclei that fuse with the existing fibers [58]. Autophagy plays an important role in the viability of resting satellite cells and preparation for their transition out of the resting state [59]. Proliferation of muscle cells is possible only under condition of functional autophagy.

Higher muscle mass (relative to the body mass) is associated with a higher sensitivity to insulin and decreased risk of pre-diabetic state or true T2D [60]. Numerous studies have demonstrated that the onset of T2D in people with predisposition to this disease can be delayed by physical exercise [61-65]. Regular physical exercise could help patients with the already developed diabetes to improve a number of indicators, including sensitivity to insulin [66-68]. Muscular strength is inversely proportional to the all-cause mortality [69], which can be reduced by strength training [70]. Both muscle mass and strength are important protective factors against the development of one of the most severe consequences of IR – metabolic syndrome [71-73]. At the same time, muscle atrophy and sarcopenia facilitate IR development. Obesity-independent sarcopenia is associated with the disruption of glucose metabolism (it is important that this association is especially strong in persons below 60 years of age). This suggests that the low muscle mass could be an early predictor of predisposition to diabetes [74]. The peak of the musculoskeletal activity in humans is at the age of 20-30 years; after that, the muscles start to lose fibers [75], although this does not affect the absolute strength until the age of 60 [43]. Age-related sarcopenia characterized by the decrease in both the size and the number of type I and type II muscle fibers, especially due to the atrophy of type II muscle fibers, is typical for older people [76, 77]. Not only the number of muscle fibers, but also their quality decrease with age. The longitudinal study of a cohort of participants 70-79 years old showed that the age-related reduction in the muscle strength in this group could be several times higher than the decrease in muscle mass [78].

The development of IR in the muscles is likely associated with the disruption of AMPK functioning. The basal activity of this kinase in the muscles of old rats is lower than in the muscles of young animals [79]. Despite the fact that the AMP/ATP ratio in the elderly individuals is increased, the AMPK sensitivity decreases with aging [80]. AMPK is activated in myocytes during physical activity. Low-molecular-weight activators of AMPK promote glucose uptake and fatty acid oxidation both *in vitro* and in animal models [6, 81]. It is important to note that direct pharmacological activation of AMPK in the liver does not reduce the plasma glucose levels, while direct activation of this enzyme in the muscles facilitates glucose utilization. This makes AMPK a promising target for new anti-diabetic drugs [6].

Signal transduction by mTORC1 (but not mTORC2 [82, 83]) is very important for the stimulation of muscle growth. Even a short-term activation results in the devel-

opment of muscle hypertrophy [84], while the long-term activation, on the contrary, promotes atrophy due to the autophagy suppression [85]. Hence, alternating periods of high and low activity of mTORC1 (and, likely, AMPK) are required for the optimal functioning of muscles, as it happens in the normal feeding-fasting cycle [37].

Finally, there is a certain contradiction between the experimental results obtained in model objects and the data of epidemiological and clinical studies. While the lifespan of laboratory animals is often extended by suppression of signaling pathways activating mitogenic effects (which decreases the risk of cancer development), the quality of life and the lifespan of humans depend on the activity of muscles and their mass, which is incompatible with the suppression of mitogenic effects and caloric intake restriction. This issue has been discussed in detail in the review by McLeod et al. [76]. Rapamycin inhibits anabolic processes in the muscles of young healthy individuals [86, 87] and, therefore, interferes with the maintenance of healthy muscle mass. Hence, the data obtained in animals exposed to the inhibitors of anabolic processes do not allow us to state the high life *quality* of these animals. Moreover, there are reasons to believe that all existing antimitogenic drugs weaken the treated individuals. At the same time, the risk of cancer development in humans can be reduced through aerobic and strength exercises [88, 89]. The effects of training could be also studied in animals, as it has been done by Danish scientists who established that the voluntary high-resistance wheel running helped to sustain the muscle mass in old mice at the level typical for the middle-aged animals. Furthermore, muscle fibers became more "oxidative" in the process [90]. The selected animal models should be appropriate for studying the effect of skeletal muscle development on the lifespan. A good example is the works by Arshavsky, who used various factors to achieve a pronounced muscle development accompanied by the increase in the longevity and *quality* of life in rabbits and other laboratory animals [91, 92]. Considering the current state of our knowledge on the age-related metabolic disorders, more such studies are needed.

Taking into account that skeletal muscle system is one of the main users of body energy, its activity (which also reduces the number of calories, similarly to the caloric restriction) is a required condition for longer life. Insufficient physical activity results in the accumulation in an organism of excessive nutrients, which are inevitably transformed into fat. To avoid weight gain, one should balance energy consumption and utilization.

Unfortunately, the complexity of casual relationships in the age-related metabolic disorders prevents easy understanding of the mechanisms underlying such disorders, but in our opinion, investigating the anti-aging effects of physical activity is more promising than the search for the mimetics of caloric restriction.

Other metabolic disorders in skeletal muscles. Sarcopenia is characterized by the disruption of proteolysis and, as a result, by aberrant protein metabolism, impairment of mitochondrial functions, inflammation, neuromuscular degeneration, etc. Beside IR, there are other metabolic disorders that can lead to such consequences. In particular, in the skeletal muscles of old mice, prostaglandin E2, which is required for the stimulation of muscle stem cells and repair of damaged muscles, is cleaved by 15-hydroxyprostaglandin dehydrogenase. Overexpression of this enzyme in young mice causes loss of muscle mass, while its short-term inhibition in old mice prevents muscle wasting [93].

In addition to glucose metabolism, metabolism of amino acids is also important for skeletal muscles. Since non-essential amino acids do not stimulate protein synthesis in the muscles [94], the muscle mass is positively affected mostly by the essential amino acids, especially leucine. Leucine is one of the main factors that stimulate mTORC1 signaling involved in the protein translation initiation [94, 95]. Leucine activates the synthesis of muscle proteins via insulin-dependent and insulin-independent pathways [96]. Aging muscles become less sensitive to the anabolic action of amino acids [97]; elderly people develop the so-called anabolic resistance of protein synthesis in muscles [98]. That is why in order to achieve the positive results of training, older people must not only consume protein-enriched food, but supplement meals with leucine [94, 95, 97].

Metabolic disorders in cardiomyocytes. In mammals, the heart has to contract constantly and, hence, requires large amounts of energy [99]. Cardiomyocytes have the highest content of mitochondria (one third of the cell volume) among all other cells [100]. The amount of ATP consumed by the human heart every day is 15 to 20 times higher than its own weight [99].

Although heart utilizes less glucose than some other organs, it is still an insulin-sensitive organ [101]. It has been demonstrated using aerobic perfusion of rat hearts that under normal physical load, the heart produces energy mainly via oxidation of fatty acids (mostly, FFAs) and to a lesser degree, via glycolysis and oxidation of pyruvate and other substrates [102]. FFAs are the main substrates for the ATP production in the adult human heart (50-70% of the required amount), although other substrates, such as glucose and lactate (25-30%), amino acids, and ketone bodies, are also utilized [38]. Interestingly, up to 40% of glucose-mediated ATP production in the heart is provided by glycogen [103]. Because FFAs disrupt the insulin-mediated glucose consumption and inhibit glycolysis and pyruvate oxidation, their high levels inhibit insulin signaling [101]. Although GLUT4 is the main glucose transporter in both cardiomyocytes and skeletal muscle myocytes [104], the former can also transport glucose via GLUT1, although at a lower basal level [38]. By modulating the activities of PI3K and AMPK, insulin

stimulates translocation of GLUT4 to the sarcolemma of cardiomyocytes and simultaneously inhibits FFA release from the adipose tissue [101]. Hence, the level of glucose consumption is closely associated with the FFA concentration in the circulation. An imbalance between lipid oxidation and glucose oxidation results in the development of specific diabetic cardiomyopathy. This explains the fact that diabetic dyslipidemia is often observed several years before T2D, i.e., disruption of lipid metabolism is an early event in the development of cardiovascular diseases in T2D [105]. From this point of view, the most promising approach to the treatment of diabetic cardiomyopathy would be restoring of the balance between the oxidation of lipids and glucose [106].

Insulin sensitivity in the heart decreases significantly in both type 1 diabetes and T2D [107]. In the case of IR, the heart is surrounded by the environment enriched with fatty acids and glucose; the availability of the substrates exceeds the requirements for the ATP synthesis [38, 99]. However, myocytes cannot utilize this glucose, which results in the accumulation of the intermediate products of glycolysis followed by the development of glucotoxicity [38]. Excessive concentration of insulin in the IR facilitates the uptake of FFAs due to the stimulated production of the CD36 protein (cluster differentiating protein 36), which facilitates FFA transport [108]. While the ability of the heart to utilize FFAs is reduced, the delivery of FFAs increases, leading to the accumulation of intramyocardial lipids (ceramides, DAG, acylcarnitines) [109]. Large amounts of lipids accumulated in the heart [110] cause the development of lipotoxic cardiomyopathy, disruption of mitochondrial functions, abnormal cell contractile activity, and heart hypertrophy [111-113].

Cardiovascular disorders associated with diabetes are caused by the elevated activity of protein kinase C (PKC) [107]. More accurately, it is a family of PKC isoenzymes differing in their functions, activation mechanisms, and tissue distribution. These enzymes mediate and inhibit the action of insulin in the liver, muscles, and adipose tissue [107, 114]. Insulin signaling is suppressed by the DAG-sensitive PKC isoforms. It is likely that this biochemical mechanism can explain the association between IR and disruption of lipid metabolism in the muscles [107, 114].

FFAs can inhibit insulin signaling through ceramide at the level of PKB [115]. Interestingly, the defects of the muscle IRec, IRS, PI3K, PKB, or atypical PKC enzymes are unlikely to result in the hereditary form of muscle IR, because defects in these proteins vary rarely lead to the diabetes development. A more likely reason is the impairment of the insulin-stimulated GLUT4 translocation [101].

AMPK increases the sensitivity of insulin secretion to the glucose consumption in the heart and regulates various components of insulin signaling [116-118]. Similarly to insulin, AMPK stimulates glucose uptake and glycolysis in the heart through the regulation of GLUT4 translocation [116], but at the same time, it counteracts the stimulating effect of insulin on protein synthesis by inhibiting mTOR and PKB/Akt-mediated activation of ribosomal p70S6K kinase and phosphorylation of eukaryotic elongation factor 2 [41, 119]. Insulin, in its turn, downregulates the AMPK-dependent signal transduction. Activated PKB/Akt phosphorylates AMPK, thus suppressing AMPK activation induced by ischemia [120].

Following activation by insulin, mTOR–p70S6K phosphorylates IRS-1 at serine residues, which results in the IRS-1 inhibition and impairment of insulin signaling. AMPK modulates the action of insulin by inhibiting this negative feedback loop [121]. However, in this case, it is important to distinguish between the mitogenic and metabolic effects. Thus, inhibition of the mTOR–p70S6K-mediated negative feedback loop in cardiomyocytes is insufficient to increase the sensitivity to insulin. It is likely that other yet unknown mechanisms exist in the heart that increase its sensitivity to insulin and stimulate glucose uptake upon the action of AMPK [122]. Furthermore, AMPK can stimulate glucose uptake directly through phosphorylation and inactivation of AS160 [123] at the intersection of the insulin- and AMPK-mediated signaling pathways (figure).

IR is a risk factor for the development of cardiovascular diseases; however, IR can be also provoked by the heart failure (due the loss of skeletal muscles, sedentary lifestyle, hyperactivity of sympathetic nervous system, and deterioration of endothelial function). This initiates a vicious circle, in which heart failure and IR aggravate each other [38]. It should be also noted that in addition to aforementioned, heart dysfunction in obesity and diabetes is associated with the elevated oxygen consumption by the myocardium, decrease in the heart functional efficiency, and promotion of oxidative stress [99].

Heart has a very flexible metabolic system that easily adapts to the utilization of substrates abundant in the blood. Lactate production by skeletal muscles increases during physical exercise, and in this case, the heart switches to lactate utilization for the energy production [124]. Long-term fasting or ketogenic diet increases the level of ketone bodies, which promotes their utilization as an energy source by the heart [99]. Ketone bodies are also used by the heart as a source of aerobic ATP production in cardiovascular diseases [125]. It is acknowledged that ketone bodies cannot provide the heart with sufficient energy; however, cyclic ketogenic diet helped mice to maintain ‘young’ heart phenotype [126]. Ketogenic diet (with low carbohydrate content and high fat and protein content) increases the lifespan of mice [127]. Short- and medium-term low-calorie diet helps to achieve weight loss and decreases the risk of cardiovascular and neurodegenerative diseases in humans. However, the long-term consequences of such diet are

still unknown, and only few data on this topic are available [128]. The effects of ketogenic diet could be mediated through the suppression of insulin signaling and inhibition of the mTOR pathway [129].

METABOLIC DISRUPTIONS IN NEURONS

Age-related IR-associated pathologies in neurons. Insulin causes multiple metabolic, synaptic, neuronal, and behavioral effects in the brain. These effects influence eating behavior (IR in the brain likely facilitates weight gain [130]), peripheral metabolism, and even cognitive abilities [28, 131]. Aging, obesity, T2D, and dementia disrupt the action of insulin in the CNS. T2D significantly increases the risk of the late-onset neurodegenerative diseases, especially Alzheimer's disease [40]. Moreover, there are reasons to believe that neurons (similar to myocytes and adipocytes) can develop the hyperinsulinemia-induced IR [42, 132]. Hence, IR in the CNS could be a pathological indicator and, to a certain degree, a cause of metabolic and cognitive disfunctions.

The modulating effect of food ingestion on the activity of different brain regions caused by the nutrient signaling generally decreases with age [133]. Brain networks responsible for appetite, hedonism, mood, and memory affect eating behavior and correlate external cues with the internal physiological needs. Introduction of insulin in the brain ventricular system suppresses food consumption and promotes body weight loss. It is likely that multiple behavioral and metabolic effects of insulin in the brain are associated with its action on the reward system, homeostasis, and cognitive control [28].

Neurons are sensitive to insulin, although the level of the IRec expression in the brain (as in the pancreas) is much lower than in the typical insulin-sensitive tissues; moreover, the effects of insulin in these organs are usually non-metabolic [131]. In particular, insulin exhibits the neurotrophic effects in peripheral neurons [134]. IRecs are expressed in all types of brain cells, but not uniformly. The highest density of IRecs is in the olfactory bulb, hypothalamus, hippocampus, brain cortex (the upper layers of the cortex are especially sensitive to insulin), striatum, cerebellum, and intermediate lobe of the pituitary gland [135-137]. In neurons, IRecs and IRSs are expressed both in the cell body and in axons [42]. Both the presynaptic and postsynaptic membranes are characterized by the IRec content [40] (with the highest concentration in the postsynaptic membrane [138]). The number of IRecs in the brain decreases with age [139].

The main glucose transporter in neurons is the insulin-independent GLUT3, while the dominating transporter in the glia and vessels of the blood-brain barrier is GLUT1. Both proteins exhibit high affinity to glucose, which allows them to supply brain with glucose even when its blood level is low [45]. In hypoglycemia, glial cells absorb glucose via GLUT1, convert it to lactate, and transport lactate to neurons as an alternative energy source (lactate shuttle) [140, 141]. It is believed that this mechanism is initiated when the brain requires large amounts of energy; however, contribution of this pathway to supplying the brain with the nutrients is not yet fully evaluated [40]. Insulin-dependent GLUT4 is also expressed in the brain. It is assumed that GLUT4 is synthesized in the brain regions responsible for cognitive abilities (forebrain, hippocampus, amygdala, cerebral cortex, and cerebellum [142]), because these regions require high glucose uptake due to the high metabolic activity during learning [40].

Insulin circulating in the blood binds to the receptors on the endothelial cells of the blood-brain barrier and then is transported to the brain interstitial fluid [143]. The intensity of insulin transport through the blood-brain barrier decreases in the IR; it is also affected by diabetes, obesity, inflammation, glycemia, and the level of triglycerides circulating in the blood [40]. Insulin binds to numerous receptors in different brain regions, including olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala, and others [28]. Insulin binding to the receptor induces the tyrosine kinase activity of the latter (as in the peripheral tissues), resulting in the receptor autophosphorylation and phosphorylation of tyrosine residues in IRS. IRS-1 and IRS-2 activate both metabolic and mitogenic signaling pathways. Both proteins are expressed in neurons and astrocytes [40]. The neurons can develop IR as a result of hyperinsulinemia and disruption of the PKB/Akt-pathway [132]. Reduction of the PKB/Akt signaling is a common sign of neuronal dysfunction. It was suggested that IR accelerates neuronal dysfunction by suppressing the response of neurons to the neurotrophic action of insulin and by increasing the sensitivity of neurons to various damaging stimuli [42].

The role of IR in neurons is studied insufficiently, and many questions still remain unanswered. It is very difficult to distinguish between IR in the neurons and the glia [42]. Moreover, glia can significantly affect the IR in neurons.

Other age-related metabolic disorders in neurons. While muscle development depends mostly on mTORC1, brain development requires both mTORC1 and mTORC2 [37]. mTOR participates in various processes in the brain (e.g., neuronal control of eating); dysfunction of the mTOR pathway can result in the development of neurodegenerative diseases, autism, and epilepsy [144].

AMPK is one of the most important metabolic sensors in the CNS. It is activated in the brain in the case of energy deficit caused by hypoxia, starvation, and ischemic stroke. AMPK not only participates in the regulation of energy balance in individual cells (autonomic regulation), but also affect eating behavior via hypothalamus (systemic regulation), since AMPK can be activated by both physiological stimuli and hormonal signals.

Systemic regulation also exists in invertebrates. For example, tissue-specific neuronal activation of AMPK in *Drosophila* not only induces autophagy in the brain, but also improves homeostasis in the intestinal tissue [5]. AMPK protects brain cells in the case of energy deficit; however, its excessive activation could have negative consequences [31, 145]. Dysregulation of AMPK is associated with such brain disorders as Alzheimer's disease, Parkinson's disease, Huntington's disease, lateral amyotrophic sclerosis, and stroke [146]. One of the metabolic effects of AMPK in the brain could be facilitation of the GLUT4 and GLUT1 expression [117, 147], which increases the rate of glucose utilization and upregulates ATP production.

The metabolism of amino acids is also important for nerve cells. For example, essential amino acid tryptophan is the only serotonin precursor. Metabolism of this amino acid could be of importance in elderly people, despite the fact that less than 1% of dietary tryptophan is used for the protein synthesis [148]. Utilization of this amino acid is an example of close association between the muscular and nervous systems. Moderate physical exercise stimulates tryptophan metabolism, because muscles actively use branched-chain amino acids, making tryptophan more available for the brain [75]. Regular endurance exercises could be recommended even to the patients with depressive disorders, as they upregulate expression of kynurenine aminotransferase in the skeletal muscles, thus shifting kynurenine metabolism to the production of kynurenic acid unable to pass through the blood-brain barrier, which prevents disruption of the neural plasticity. Energy deficit results in low tryptophan levels, which, in turn, leads to the disruption of serotonin metabolism [149]. The content of tryptophan cannot be increased through consumption of the high-protein diet only, because the availability of this amino acid to the brain cells is paradoxically low due to the competition with other large uncharged amino acids for the transport across the blood-brain barrier [148]. Thus, high protein consumption in the absence of exercise limits the availability of tryptophan, which could affect serotonin synthesis even more and disrupt cognitive abilities, memory, mood, and sleep, eventually increasing the risk of dementia [148].

Neuronal loss with aging. Similarly to muscle fibers, nerve cells decrease in number with age. Moreover, the loss of muscle fibers is associated with the loss of motor neurons innervating them [43]. Despite the ongoing death of neurons, their disappearance becomes noticeable only at the later stages of life, when such functional disruptions become obvious [150]. Both the number of myelinated nerve fibers and their diameter in the ventral roots of human spinal cord decrease with age [151, 152]. Thus, the number of myelinated nerve fibers is reduced by 5% every decade [151]. The number of motor neurons in the lumbosacral segments of the spinal cord in healthy individuals over 60 years of age could comprise 50% of their number in young and middle-age individuals [153]. The age-related loss of neurons also occurs in some ganglia (e.g., vestibular ganglion [154, 155]) and brain regions (hippocampus [156], brainstem and cerebellum [155], cerebral cortex [157, 158], amygdala [159], and thalamus [160]). In was established that in rats, progressive loss of neurons in all brain structures begins at the age of 3 months (the end of the juvenile period), rather than at the old age [150].

The extent of cell loss is different – from negligent to very significant – in different brain regions. Many researchers believe that the neuronal loss in humans and animals not experiencing neurodegenerative diseases is exaggerated, and the decrease in the volume of particular brain regions occurs due to the decrease in the number of dendrites and cell-cell contacts [161-164]. Some studies have even reported that glial cells are dying in larger numbers than neurons [165]. However, other studies have shown that the number of glial cells could increase with age [166]. Methodological challenges of cell quantification, the complexity of brain structure, the necessity to compare only data of cross-sectional studies, and in the case of humans, rather small datasets make it impossible to evaluate with accuracy the changes in the number of neurons and glial cells in the brain. Nevertheless, even if the number of neurons is reduced only in some brain regions, this still disrupts brain functions and facilitates development of cognitive disorders.

CELLULAR MODELS FOR THE INVESTIGATION OF AGING OF POSTMITOTIC CELLS

We would also like to discuss the issue of gerontological studies of metabolic processes in cultured cells. There are several cellular models of aging, each one with its pros and cons. In our opinion, modeling cell aging in experiments with "senescent" cells (Hayflick model [167] and the model of stress-induced premature aging [168]) is extremely useful for investigating the aging of cells capable of proliferation and renewal during the entire organism's lifetime. According to Campisi [169], such cells transit to the senescent state in order to avoid transformation into cancer cells. Highly differentiated neurons and myocytes of an adult organism do not divide and do not transform into cancer cells; hence, modeling their aging requires another approach. It is commonly accepted that aging of these tissues could be investigated in the chronological aging model (mostly in yeasts) or the model of 'stationary phase' aging using animal or human cells [9, 14, 170-173], which is an approach that has been used in our laboratory. Chronological aging model involves induction of the cell cycle arrest followed by the evaluation of the cell survival during the long-term stationary phase. Although this model has many drawbacks, no bet-

ter approach has been suggested so far. Moreover, these cell models provide data [15-17] that are in good agreement with the data obtained with experimental animals. We believe that the most adequate models should use animal and human cells after induced terminal differentiation, although this approach could be very expensive. Obviously, senescent cells might affect the survival of highly differentiated cells; however, highly differentiated cells age differently, although aging of these two types of cells most probably has some common features. Autophagy plays an important role in highly differentiated cells, since it is the only mechanisms providing renewal of components in such cells [77, 174]. At the same time, due to the replacement of "old" cells with accumulated defects with non-damaged "young" ones (e.g., in the intestinal epithelium), a population of dividing cells could avoid accumulation of defects that appear in the postmitotic differentiated cells with time. For example, this might explain accumulation of lipofuscin in the postmitotic highly differentiated (nerve and muscle) cells [175], but not in proliferating cells (with the exception of skin cells). However, as mentioned above, proliferation of satellite muscle cells required functional autophagy, which indicates a certain resemblance of the cell degradation processes in the models of replicative and chronological aging.

CONCLUSIONS

All the above-mentioned data, nevertheless, tell us nothing about what comes first – disruptions in metabolism of postmitotic cells themselves or changes in the cell environment and in vessels that supply the blood to these cells. Neurons and myocytes cold be affected by senescent cells of surrounding renewed tissues. Problems emerging in the organs consisting of postmitotic cells could be caused by some other factors, e.g., brain blood supply could be disrupted due to atherosclerosis, while perfusion of skeletal muscles could be disturbed due to calcification [176]. It is known that disruption of blood supply to the brain is a risk factor in the Alzheimer's disease development [177]. The blood supply to the muscles (in particular, the ability of blood vessels to dilate) worsens with age. This can occur due to various reasons, such as disruption of the endothelium-dependent vasodilation, increased vessel stiffness, excessive effect of sympathetic nervous system, changes in the metabolic or mitogenic control, decrease in the efficiency of skeletal muscle pump, etc. [178]. It is very difficult to understand what is primary and what is secondary and to establish the causative relationships. It appears that all such disorders are interconnected and could develop in parallel. We believe that the gerontological aspects of IR development and its consequences discussed in this review represent a good illustration of an extremely complex character of relationships between different age-related metabolic disorders.

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