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Review

Energy metabolism decline in the aging brain; pathogenesis of neurodegenerative disorders

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Abstract

A growing body of evidence indicates that aging of the brain is strictly related to the decline of energy metabolism. In particular, in older adults, the neuronal metabolism of glucose declines steadily resulting in a growing deficit of ATP production. The decline is evoked by deficient NAD recovery in the salvage pathway and subsequent impairment of the Krebs cycle. NAD deficit impairs also the activity of NAD-dependent enzymes. All these open vicious circles of neurodegeneration and neuronal death. Some brain structures are particularly prone to aging and neurodegeneration. These are pathological foci of neurodegenerative diseases such as Alzheimer's and Parkinson's disease. This review article summarizes the impacts and mutual relationships between metabolic processes both on neuronal and brain levels. It also provides directions on how to reduce the risk of neurodegeneration and protect the elderly against neurodegenerative diseases.

Keywords: brain aging, energy metabolism, neurodegeneration; neurodegenerative disorders

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1. *Energy metabolism*

Energy metabolism is the foundation of life [1]. Its role is to meet all organismal energy needs. The human brain is critically dependent on the supply of energy to meet its high metabolic demands. The brain consumes approximately 20% of organismal energy although its mass comprises roughly 2% of the body's mass [2,3]. The energy is used mainly to reverse ion fluxes that underlie the generation of action potentials, their axonal transmission, and release of neurotransmitters at synaptic junctions [4-9]. Brain energy production is reliant on the uptake and metabolism of glucose and oxygen [3,10-13].

Brain activity, especially axonal and synaptic transmission are highly energy demanding [5,14-17]. The high-energy demand generates the need for a large amount of oxygen delivered via the bloodstream. The brain consumes, on average, six molecules of oxygen per molecule glucose [11,12] whereas the number of oxygen molecules in the arterial blood exceeds the number of glucose molecules by only a factor of 1.5 [11]. During energy production, the oxygen is almost fully reduced to water, while only 1-2% of the O_2 is reduced incompletely to give the superoxide anions [18]. Increasing with age excessive production of free radicals further worsens the mitochondrial function by causing oxidative damage to macromolecules [18,19,20-22] leading to neuronal death [16,20,23-26].

Cellular respiration is a set of metabolic reactions and processes that take place in mitochondria of neurons and glial cells. Mitochondrial activity converts chemical energy from oxygen molecules and glucose into the water and various type the energies, such as chemical of ATP, thermal, electric, and biomechanical necessary for waste product removal. Additional energy is allocated to fix numerous and inevitable errors of metabolic processes that, even on the cellular level, can only be realized with limited efficiency. Thus, we can evaluate physiological and pathological brain status based on the overall energy balance [22].

Neurons are unique cells having only a single life. In the neuronal networks of the basal ganglia, only a marginal number of interneurons are continuously replaced by the progenitor cells in the process of neurogenesis [27-31]. Neuronal metabolism is the set of continuous life-sustaining chemical reactions that requires the delivery of nutrients and energy from outside. Inadequate amounts of essential nutrients, or diseases that interfere with their absorption, resulting in a deficiency state that compromises cellular growth, function, and survival. The energy metabolism pathway depends on several factors such as the supply of substrates and the efficiency of their transport to the cytoplasm [11,32]. Kinetics of all intracellular reactions depends on the temperature and pH of the cytoplasm [33]. All these

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results in a limited efficiency of the metabolic reactions and some energy reserve must be allocated for fixing metabolic errors and removal of waste products [34].

Both oxygen and glucose are essential for the energy metabolism of the brain [11,12,35,36]. The transport of glucose to the brain depends on the concentration gradient between blood and brain tissue. Therefore, even a large increase in the cerebral blood flow (CBF) does not substantially change the glucose levels in the brain [32,37]. In contrast, the cerebral blood flow may control the oxygen availability for the brain [11]. The energy at the cellular level is necessary for setting resting gradients of ions concentration. In particular, the neuronal and mitochondrial resting potentials are determined by specific gradients of sodium, potassium, and chloride ions. The gradients strictly depend on the ATP-controlled the ion pumps and transporters. Generation and transmission of neuronal action potentials is the most energy-demanding process.

The energy production and storage in the electric field are specific for mitochondria [20]. These semi-autonomous organelles, bounded in double-membrane are found particularly abundantly in axons nearby the Ranvier nodes and synaptic junctions. Distribution of axonal mitochondria can vary substantially in number, size, and membrane potential depending on differences in recirculated ATP levels and thus energetic processes [5,6]. Mitochondrial dysfunctions result in a decline in ATP production, oxidative damage, and the induction of apoptosis, all of which are involved in the pathogenesis of numerous disorders [18,25]. The accumulation of mitochondrial DNA mutations accelerates normal aging, leads to oxidative damage to nuclear DNA, and impairs gene transcription [19,20]. In consequence, it requires intensification of the NAD-dependent repair enzymes which additionally impoverishes the intraneuronal NAD pool [15,17,38-41].

Glucose supplies energy to neurons through the glycolytic pathway that converts glucose into pyruvate, and hydrogen ions:

$$\text{Glucose} + 2\,(P_i + \text{ADP}) + 2\,\text{NAD} \rightarrow 2\text{Pyruvate} + 2\,\text{NADH} + 2\,H^+ + 2\,\text{ATP} + 2\,H_2O$$

Glycolysis is one of the two main metabolic pathways in neuronal energy metabolism. As glucose enters neurons, it is phosphorylated by ATP to glucose 6-phosphate (G6P). It is a necessary and irreversible first step of neuronal energy metabolism. The pathway of glycolysis is controlled by ATP positive feedback. The availability of the ATP-derived phosphoryl groups is the main regulator of glucose flux to glycolysis. In the process of glycolysis, each molecule of glucose 6-phosphate is broken down into two molecules of pyruvate, which are then used as a source of energy.

Pyruvate supplies energy to neurons through the Krebs cycle only when oxygen is present. It is converted into acetyl-coenzyme A, which is the main input for the Krebs cycle in mitochondria. The

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main synthesis of ATP is initiated by the oxidation of NADH and the reduction of O_2 in the electron transport chain (ETC) [13]. Humans depend primarily on vitamin B3 as a precursor for nicotinamide adenine dinucleotide (NAD) synthesis [42]. NAD is the main coenzymes in redox reactions in mitochondria [43-45]. During the reduction of NAD, the molecule acquires two electrons and one proton, while the second proton is released into the cytoplasm. In physiological conditions, neurons can recover in the *salvage pathway* most of the used NAD, and only limited amounts of NAD supplemented by *de novo* pathway [46]. In a normal healthy brain, the level of NAD exceeds its neuronal needs [47]. The level, however, declines with age and particularly is reduced in various chronic diseases [40,45,47].

The ETC is a series of complexes that control in mitochondria transfer of electrons from donors to acceptors via redox reactions. The electrons are taken from NADH, through a chain of electron carriers, to the final acceptor, oxygen. During this process, two gradients are built upon the inner mitochondrial membrane. Primary is the oxygen-fixed electrons that result in negative polarization of the mitochondrial matrix relative to the neuronal cytoplasm. The negative polarization attracts positively charged protons (H^+) towards the outer surface of the inner mitochondrial membrane. The concentration of electron and proton gradients produces a strong electric field that presses protons into the inner mitochondrial membrane. The magnitude of the resultant electric field may eventually force the protons (Coulomb force) to break the inner mitochondrial membrane thus making electropores ie., the channels of proton current. The process electroporation allows protons entering the mitochondrial matrix and reacts with the oxygen. The end product of this process is water and heat. In the case of unbalanced electron and proton currents, some oxygen molecules remain unused and are precursors of reactive oxygen species (ROS) [22]. While passing the inner mitochondrial membrane, the proton current is driving a "molecular pump", utilizing the enzyme ATP synthase, to produce an ATP. It converts the energy of the protons to the chemical energy of ATP. Theoretically, at least three protons must pass the inner mitochondrial membrane to recover one ATP molecule.

The ATP recovered in mitochondria is used then as the rate-limiting factor of glycolysis. The ATP controls the level of glucose phosphorylation, which, in turn, limits the intracellular glucose concentration and its use by neurons to produce energy and ATP. The initial process of glucose phosphorylation determines the fate of glucose in cellular metabolism. Glucose itself may easily diffuse bidirectionally across the cellular membrane [32]. G6P cannot leave the cytoplasm and must enter the metabolic pathway of glycolysis. Due to this initial phosphorylation, even in case of an increased level of blood glucose e.g., after a meal, only limited by the ATP amount of glucose can be used by neurons in energy metabolism. A greater level of G6P in addition to the free inflow of oxygen allows adjusting

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ATP production proportionally to neuronal activity increasing the metabolism of glucose [48]. This also sets a level of neuronal oxygen needs. Both glucose and oxygen metabolic pathways closely interact forming, what can be named the ATP-glucose-oxygen metabolic synergy. Other substrates such as lactate support cellular energy metabolism [49,50]. Lactate dehydrogenase catalyzes the pyruvate and lactate interconversion with simultaneous NADH and NAD interconversion. In increased concentrations of lactate, the enzyme exhibits feedback inhibition and lowers the rate of the pyruvate to lactate conversion.

The existence of the ATP-glucose-oxygen synergy in the brain is well documented experimentally [11,12,35,36,48,50,51]. The activity of metabolites (enzymes and proteins) associated with glucose supply and glycolysis is mutually tuned by the availability of oxygen [36]. The lower level of oxygen activates hypoxia-inducible factor 1 (HIF-1) that in turn upregulates both the GLUT 1 and GLUT3 glucose transporters which are responsible for basal glucose uptake and activity of glucose 6-phosphate isomerase [36,37,50,52]. Both transporters intensify anaerobic glycolysis and help to overcome the hypoxia crisis. Similarly, hypoglycemia augments cellular glucose transport and metabolism, with a specific increase in the activity of both glucose transporters GLUT-1 and GLUT-3 [50]. GLUT-1 transporters are located in the endothelial cells lining the brain microvasculature, glial cells, and choroid plexus, while GLUT-3 is expressed in neurons [50,52]. Both isoforms meet the energy demands of the brain by transporting glucose into the central nervous system in an insulin-independent manner [50]. Especially GLUT-3 activity is critical in protecting against hypoglycemia [32,52]. A transient increase in activity of GLUT-3, after either hypoxic ischemia or hypoxia, attempts to preserve the cellular glucose supply, thereby protecting against depletion of cellular ATP stores [50]. Therefore an increase in GLUT-3 is the brain-protective mechanism that may inhibit neuronal death [16,23].

2. *The aging brain*

Aging of the nervous system is a complex process that seems to be triggered by the dysfunction of energy metabolism [1,19,20,24,53-55]. The effects of aging are prominent in the nervous structures that are the most sensitive to energy deficits. The anatomy, and physiology of such structures as the cerebral cortex, hippocampus, and the basal ganglia make them prone to neurodegeneration. They are the primary target of deficient energy metabolism [28,29,56-59].

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Understanding mechanisms to control body metabolism at the hypothalamus level can open new perspectives in the prevention and treatment of neurodegenerative diseases [53] 2018]. The hypothalamus produces and secretes neurohormones and thus functional connects through the pituitary gland the central nervous system with the endocrine system. The hypothalamus controls hunger, thirst, circadian rhythm, sleep, and body temperature. The hypothalamus regulates numerous metabolic processes and many functions of the autonomic and the central nervous system [60]. The lateral hypothalamus, also known as the lateral hypothalamic area (LHA), is the orexinergic nucleus that has extensive projections throughout the nervous system. This system mediates several cognitive and motor processes such as agitation, feeding behavior, digestive functions, pain sensation, control of body temperature, blood pressure, and many others. Clinically relevant disorders involving dysfunction of the orexinergic projection system include narcolepsy, motility disorders, or functional gastrointestinal disorders including visceral hypersensitivity and eating disorders. Sleep disorders, one of the prodromal symptoms of Parkinson's disease [61,62], are associated with a marked reduction in the population of LHA orexinergic projection neurons and lowered level of orexin peptides in the cerebrospinal fluid [3,9,10,62-64].

Hypothalamic neurons regulate systemic energy homeostasis and neuroendocrine functions. The hypothalamic-pituitary-adrenal axis regulates stress levels and the hypothalamic-pituitary-thyroid axis is responsible for metabolism control and regulating visceral functions. Histaminergic, dopaminergic, serotoninergic, noradrenergic, and cholinergic nuclei, to which the *lateral hypothalamus* orexin neurons project. This projection forms the activating network of the reticular formation located throughout the brainstem, which determines the subjective quality of life. Also, the projection of the lateral hypothalamus to the *ventral tegmental area* (VTA) controls the oxytocin reward system establishing positive social relationships such as feelings of friendship, love, and sympathy. Glutamate, endocannabinoids, and neuropeptides (orexin-A and orexin-B), are here the primary neuronal signaling substances. Pathway-specific neurotransmitters include GABA, melanin concentration hormone, nociceptin, glucose, dynorphin peptides, and appetite-regulating peptide hormones (including leptin and ghrelin). It is noteworthy that the cannabinoid receptor 1 (CB1) is co-localized in many output structures of the projection of LHA orexinergic neurons, which can explain the universal "miraculous" therapeutic properties of marijuana, its psychoactive effect, and high efficiency in suppressing convulsive seizures caused by hypoglycemia or insulin resistance.

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There are only 10,000–20,000 orexinergic neurons in the human brain. Their population is reduced by nearly 50% in the process of aging and degenerative disease which may explain why patients with Alzheimer's disease have reduced levels of orexin in the cerebrospinal fluid. In parallel, there is observed neurodegeneration of the suprachiasmatic nucleus - another small (containing only 20,000 neurons) - hypothalamic center regulating the wakefulness/sleep rhythm. Therefore, patients with neurodegenerative diseases suffer from sleep disorders and circadian rhythm disorders [61,62]. In total, the depletion of the hypothalamus function in the course of brain aging and neurodegenerative diseases is associated with mental changes, which are reflected in a decrease in the subjective value of life and the development of depression.

3. Axonal neurodegeneration

Synaptic transmission is one of the most complex processes in the nervous system. This process is highly energy-consuming and it is believed that 80% of the energy necessary for the functioning of the nervous system is used for synaptic transmission and related processes [5,6]. The key to understanding this phenomenon is the close connection of their physiological function with metabolic and trophic processes in all active cells (neurons, muscle, and glial cells). Simply put, active cells are better nourished and kept in better shape than hypoactive cells. On the other hand, excessive cellular activity is also harmful. It is accompanied by the phenomenon of excitotoxicity, i.e. programmed death of overactive cells [65]. This phenomenon has been found, among others, in glutaminergic neurons. Exposure of neurons to excessive glutamate levels is accompanied by abrupt opening of calcium channels. The increased influx of calcium ions into the interior of the neuron activates several enzymes (phospholipases, endonucleases, and proteases) that damage the membranes, cytoskeleton, and cell DNA. Excitotoxicity is thought to accompany many pathological conditions, such as strokes, hearing damage through excessive exposure to noise, and any neurodegenerative disease. Other conditions that can lead to excessive levels of glutamate in neurons are hypoglycemia and dehydration. Dehydration of the body causes both changes in the pH of the cerebrospinal fluid and impairs osmotic control in the brain. Neurotoxicity and loss of neuronal processes induced by amino acids (glutamate and aspartate) is a hallmark of several neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, and Huntington's disease. Besides, the excessive toxic

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concentration of glutamate around neurons may occur in hypoglycaemic states. The excitotoxic effect of glutamate leads to an increase in intracellular calcium ion levels, which triggers a cascade of pathological reactions that culminate in the death of nerve cells. Studies show that intracellular calcium signaling is crucial for synaptic plasticity - the cellular mechanism of learning and memory. Therefore, calcium channel modulators and calcium signaling control are currently of interest to researchers in their potential use as neuroprotective mechanisms. Latrepirdine has been found to act as an inhibitor of NMDA receptors and voltage-gated calcium channels. Latrepirdine inhibition of glutamate-induced calcium signals may be used to protect neurons from excitotoxicity-induced apoptosis. Latrepirdine modifies the permeability of mitochondrial membranes and thereby regulates calcium ion activity in mitochondria. The very high concentration of calcium ions around neurons compared to their low maintained at the nanomolar level, the concentration in the cytoplasm, causes not only a very high osmotic potential but also the electrical potential of divalent calcium ions. Also, the diameter of the hydrated calcium ions is the same as sodium ions. The accumulation of these three factors causes that the electric field rapidly changing during the conduction of functional impulses on the cell membrane of neurons causes focal and rapid changes in the electrical conductivity of the membrane called electroporation. The results of in vitro tests confirmed that the process of pore formation and their subsequent clogging may take up to tens of seconds. We cannot explain how the phenomenon of electroporation works and why it has such a large time constant. We do not know why pore closing is controlled by ATP levels. The activity of calcium ions is particularly observed during the pore reclosing stage. Research suggests that electroporation may be associated with secondary calcium signaling necessary to provide increased somatic and segmental energy metabolism in neurons. This phenomenon is typical for unprotected myelin cell membranes, especially the initial segment of the axon, where functional impulses are generated and for Ranvier nodes.

4. Aging of the brain circulatory systems

The extremely limited capability of brain tissue for the storage of oxygen and glucose requires the continuous delivery of both energetic substrates by cerebral blood flow (CBF) [12]. The almost exclusive ATP production via oxidative phosphorylation may suggest that the CBF response serves both glucose and oxygen delivery increase. Glucose contains a moderate amount of chemical energy per bond as confirmed by the relatively small energy

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output in glycolysis and the Krebs cycle converting glucose to CO_2 and NADH [51]. Only the oxidative phosphorylation allows for a large release of free energy from oxygen bonds. This shows that O_2, rather than glucose, NAD(H), or ATP, is the molecule that provides the most energy to the brain and is crucial for sustaining its life.

The circulation of blood and cerebrospinal fluid supply the brain with oxygen, glucose, and nutrients necessary for the life and functioning of neurons. The circulation of cerebrospinal fluid removes unnecessary and toxic waste. There exists a physiological mechanism that combines in the brain local activity of neuronal networks with energy supply. The functioning of the brain's vascular system depends on the proper activity of neurons which in turn depends on adequate blood flow. Ischemia or abnormal blood vessel function is one of the basic causes of metabolic dysfunctions in the aging brain. The neuronal dysfunctions closely correlate with the development of blood vessel abnormalities, such as capillary basement thickening and endothelial hyperplasia, which contribute to a decrease in oxygen supply (hypoxia).

In the aging brain, the efficiency, and selectivity of the brain's vascular bed and of the blood-brain barrier decline. Microdamages to blood vessels and changes in the permeability of brain-protective barriers cause depletion or even blockage of the supply of substances necessary for the proper functioning of neurons. The inefficient or damaged blood-brain barrier causes undesirable substances and pathogens can invade the brain tissue provoking local inflammations that intensify degenerative and necrotic processes. Pathological effects of unsealed the blood-brain barrier and vascular microdamage are usually augmented by increased blood pressure and type 2 diabetes. Aging strikes also fundamental for the brain functioning process of waste product removal, resulting in pathological accumulation of protein deposits. Accumulated intracellular and extracellular deposits worsen both functioning of individual neurons and neuronal networks. Kinetics of all vital neurochemical processes drop rapidly which additionally intensifies neurodegeneration. The brain's and neuronal capability to repair molecular lesions also collapses rapidly. Neurons that have accumulated a large amount of damaged DNA and misfolded proteins, or those that no longer effectively repair DNA lesions, enter the process of senescence and apoptosis. Depending on which region of the brain is the most affected by aging and neurodegeneration, a characteristic set of clinical symptoms emerges.

NAD-dependent enzymes in the aging brain

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NAD plays a fundamental role as a cofactor in cellular energy metabolism [66]. It serves as an electron transporter to power oxidative phosphorylation and ATP production. Besides that NAD is also used by NAD-consuming enzymes such as ADP-ribose transferases and poly(ADP ribose) polymerases (PARPs), cADPribose synthases, sirtuins, and NAD hydrolase SARM1 [15,17,38,39,67]. They mediate several intracellular reactions includes DNA repair, chromatin silencing, transcriptional regulation, metabolic switching, and calcium mobilization. Sirtuins are NAD-dependent histone deacetylases regulating metabolic function, longevity, and aging [66,68]. PARP over-activation has been associated with dopaminergic neuron toxicity and atrophy [69,70], as well as disruption of the mitochondrial ultrastructure [71].

Studies on sirtuins, whose enzymatic activity is closely related to NAD biosynthesis, provided extremely interesting data. Sirtuins regulate the metabolic responses of cells and tissues by adapting them to the level of available nutrients [72]. They also participate in response to cellular stress and in repairing cellular structure damage caused by their metabolism disorders. Since the activity of sirtuins is dependent on NAD, maintaining the physiological level of NAD in cells plays a critical role in their function [43,45,47,73]. The decline caused by aging and in the course of many diseases impairs the function of sirtuins. A decline in the energy metabolism of neurons is accompanied by a decrease in their resistance to stress, an increase in damage to the cytoskeleton along with progressive impairment in neuronal processes: bioelectric activity and synaptogenesis. The process of neurogenesis being crucial for forming neuronal networks is also impoverished.

Sirtuins are the main effectors of the cellular response to metabolism changes and cellular stress. The key function of nuclear sirtuins is to regulate genome homeostasis under stress. The loss of sirtuin function is associated with genomic instability and deterioration of cell viability as well as the escalation of neurodegenerative processes. In particular, patients with Alzheimer's disease have reduced expression of sirtuin 1 (SIRT1). The physiological activity of SIRT1 can reduce the amount of oligomerized beta-amyloid by increased alpha-secretase synthesis. Thus, SIRT1 promotes brain networks function and survival [15]. The decrease in SIRT1 synthesis in aging neurons of the cerebral cortex and hippocampus impairs learning and memory, and thus undermines cognitive functions of the brain. Sirtuin 1 also has an important impact on glucose-induced insulin secretion in pancreatic β-cells, which up to a point maintains normal brain metabolism. Besides, SIRT1 counteracts insulin resistance of cells in peripheral tissues, including adipose tissue, liver, and skeletal muscle.

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Sirtuin 1 has also been shown to improve vascular function by affecting many of the pathways important for endothelial function. SIRT1 inhibits the expression of inflammatory factors, including interleukin-6 (IL-6), monocyte chemotactic protein 1 (MCP-1), intercellular adhesive molecule 1 (ICAM-1), matrix metalloproteinase 14 (MMP14), and vascular cell adhesion molecule 1 (VCAM-1). Also, sirtuin 1 improves blood levels of free fatty acids, triglycerides, cholesterol, and glucose. These protective effects of SIRT1 indicate that it acts as an anti-atherosclerotic agent that slows down the aging process of the brain and the whole body. Thus nicotinamide mononucleotide therapy may improve the function of blood vessels in older people, partly by activating sirtuin 1 [72].

The sirtuins may play a role in alleviating the symptoms of depression induced by energy metabolism dysfunctions. Under chronic stress, in the dentate gyrus of the hippocampus, the level of sirtuin 1 and 2 expressions decline rapidly which is accompanied by symptoms of depression. Supplementation of SIRT1 may exert anti-depressant effects since it is a potent inhibitor of monoamine oxidase A (MAO-A). Also, increased SIRT2 expression has antidepressant effects. Finally, the mitochondrial activity of SIRT3 is very sensitive to the decrease of NAD [45].

5. *Energy metabolism and neurodegenerative disorders*

The etiology of neurodegenerative diseases remains enigmatic; however, evidence for defects in energy metabolism, excitotoxicity, and for oxidative damage is increasingly compelling [19,16,20, 24,38,53]. Mitochondria are particularly susceptible to oxidative stress, and there is evidence of age-dependent damage and deterioration of respiratory enzyme activities with normal aging [19,20].

Neurodegenerative diseases are disorders characterized by irreversible and progressive destruction of the structure and function of the brain [28,55, 58,73,74] Luca et al. 2018. This process usually begins in specific areas of the brain, and depending on it, cognitive deficits (Alzheimer's disease, frontotemporal dementia) or motor symptoms (Parkinson's disease and Huntington's disease) dominate in the clinical phase [56, 64]. Usually, the occurrence of neurological symptoms is preceded by increasing metabolic dysfunctions, such as weight gain or loss, which is accompanied by changes in eating habits and preferences.

Several preclinical and clinical data indicate that the modified energy homeostasis intensifies the progress of neurodegenerative processes [55,62]. The decline of the hypothalamus function primarily leads to energy homeostasis disorders [55,57]. In brain imaging studies, hypothalamic atrophy (over 10% by volume) was observed in patients with Alzheimer's disease [75]. The hypothalamic atrophy appears in the early clinical stages, which

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may suggest that hypothalamic lesions are a significant cause of neurodegenerative changes [60].

5.1 Proteinopathies and Alzheimer's disease

From a neuropathological perspective, Alzheimer's disease is identified by the presence of neurofibrillary tangles in the brain, composed of intraneuronal fibrous aggregates of hyper- and incorrectly phosphorylated tau proteins, and extracellular accumulation of beta-amyloid [57,73-75]. Under physiological conditions, beta-amyloid is continually produced in neurons by the sequential action of two proteases: beta and gamma secretases, which cleave the amyloid precursor protein (APP). This protein is synthesized in the endoplasmic reticulum and then transported to the plasma membrane. There, enzymes called secretases cut APP into bioactive fragments. Some of the cleaved APP fragments are transferred then to the vicinity of synaptic areas, where, during bioelectrical activity, follicular fusion occurs necessary for the release of neurotransmitters. Thus, APP appears to modulate interactions with intracellular signaling systems responsible for the growth of axons and dendrites and support for various functions involved in the maintenance of synapses. In adult brains, APP and its fragments function as sensing molecules. In response to the neuronal activity, they control cholesterol homeostasis, the supply of neurotransmitter carriers, and synaptogenesis. These processes are particularly important in large neurons, in which APP can act as a long-range sensor that transmits feedback information on synapse functioning and their activity back to the cell body.

In adult brain neurogenesis, APP plays a role in neuroblast migration. APP activity is intensified during the maturation of the brain and synaptogenesis in the processes of learning and memory. These observations suggest that APP plays a fundamental role in the formation of synaptic connections as well as in the shaping and maintaining neuromuscular junctions. Since protein synthesis precursor amyloid is regulated synaptic activity, APP and fragments thereof can regulate neuronal lipid metabolism, necessary for the regeneration of the cell membrane and mitochondrial membranes, which structure is permanently exposed to micro damages (micropores) in the course of bioelectric activity of neurons.

The amount of beta-amyloid remaining in brain tissue depends on both the level of neuronal activity and the efficiency of the brain's cleaning process(es). The decline in the efficiency of beta-amyloid removal leads to the accumulation of toxic oligomers and the formation of deposits damaging the structure and functions of the brain. The process of creating beta-amyloid deposits and neurofibrillary tangles is commonly existing in every aging brain. The glymphatic system is the brain's

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metabolite clearance system connected to the peripheral lymphatic system. Under physiological conditions, cerebrospinal fluid is pumped into the brain tissue in the rhythm of heart contractions and next it returns to the ventricular system while simultaneously flushing out waste, including pathogenic beta-amyloid and tau proteins. The glymphatic system is particularly active during sleep and its functioning improves with physical activity.

The accumulation of toxic proteins exerts the most destructive effects on areas of the brain with the highest activity [74]. As a result of proteinopathy, hypoactive neuronal centers emerge that are destroyed then due to impaired metabolism and reduced energy supply. In the aging brain, structures with high physiological activity such as the cerebral cortex, hypothalamus, and striatum, are prone to proteinopathy resulting from the decline of neuronal activity due to age-related insulin resistance. This process strikes the functioning of the hypothalamus most [76]. Pathologies include in particular the lateral periventricular nucleus of the hypothalamus, suprachiasmatic nuclei, tuber-mamillary bodies, and supraoptic nuclei, that all are responsible for the systemic control of energy metabolism. This closes the vicious circle of brain aging.

5.2 Neurodegenerative processes in Parkinson's disease

The basal ganglia and the nigrostriatal system is the second area of the brain with high susceptibility for degenerative changes [29]. Many factors contribute to this increased vulnerability. Firstly, relatively high energy supply is required to maintain an extremely extensive nigrostriatal movement memory network [29,77-79]. Motor learning and adaptive plasticity of the nigrostriatal network rely on the continuous exchange of a fraction of the striatal GABA interneurons [27,28]. Additionally, the high resting activity of the entire nigrostriatal system poses a great metabolic challenge. Relatively high energy cost is necessary to maintain such a network making it prone to neurodegeneration [5,63].

In neurons, most energy is spent on axonal transmission. Such morphological factors as axonal fiber length, its myelinization, and axonal arborization are the main determinants of neuronal energetic demands. A single dopaminergic neuron of substantia nigra can form up to thousands of synapses with GABAergic neurons of the striatum. Also, the structure of nigrostriatal connections is very dynamic and changes depending on individual motor activity and motor learning. Hipokinesia reduces energy supply for the nigrostriatal system that initiates the adaptive process of pruning of unused and unnecessary synapses [17]. The process of synaptic pruning can be followed by axonal degeneration, and eventually dopaminergic cell death [28,80]. The main symptom of the nigrostriatal network reduction is increased muscle stiffness and, consequently, further reduction of motor activity in older

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adults. Depleted motor activity reduces the expression of glia-derived neurotrophic factor (GDNF) in the striatum, which is important for the synaptogenesis thus functioning of the entire nigrostriatal network. This causes a further reduction of dopaminergic synapses and the death of dopaminergic neurons of the substantia nigra. Increasing nigrostriatal interaction inhibits neurogenesis of GABA interneurons in the subventricular zone that escalates dysfunction of the striatum and the death rate of dopaminergic neurons of the substantia nigra. Only fractional, compensatory nigrostriatal synaptogenesis delays the appearance of the first clinical motor symptoms of Parkinson's disease until the majority (60-70%) of dopaminergic neurons are destroyed [29]. The results gathered up to date on the pathogenesis of idiopathic Parkinson's disease suggest that the age-related decrease in nigrostriatal interaction is the main cause of the motor pathology in the course of the disease. Therefore, the search for new therapies in Parkinson's disease should now focus on slowing degenerative processes in the GABAergic striatum and restoring fully functional GDNF synthesis - the main chemoattractant for dopaminergic synaptogenesis and neurogenesis and migration of GABA interneurons.

6. *Neurogenesis in the aging brain*

Understanding the process of neurogenesis in the striatum and identify the factors that contribute to the continuous renewal of the interneuronal network of the striatum should facilitate the development of new therapeutic strategies [27-30,81]. The statement that interneurons are exchanged continuously in the adult brain raises the question of whether this process can be used therapeutically in the treatment of Parkinson's disease [28,79]. In the neurogenesis and differentiation of progenitor cells play key role chemoattractants, such as the neurotransmitter GABA and neurotrophic factors. Especially glial-derived neurotrophic factor (GDNF) has an impact on neurogenesis in the subventricular zone (SVZ) and nigrostriatal synaptogenesis as well. This suggests a high potential of GDNF in the treatment of motor symptoms of Parkinson’s disease.

GDNF is involved in the development of dopaminergic synapses in the nigrostriatal complex. Thus, it prevents damage to this system and inhibits the death of dopaminergic neurons of the substantia nigra pars compacta (SNPC). The dopaminergic neurons projecting to the striatum express two GDNF receptors: the RET receptor tyrosine kinase and the GDNF family alpha1 receptor (GFRα1). GFRα1 is the main receptor of the dopaminergic SNPC neurons. In animal models of Parkinson's disease, the injection of GDNF into the striatum

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allows the recovery of nigrostriatal function by creating new synaptic connections. Importantly, GDNF acts as a chemoattractant for both the axonal endings of SNPC neurons and for the activation and migration SVZ progenitor cells [27,82]. It also promotes functional and morphological differentiation of neuroblasts reaching the striatum. Thus, GDNF signaling through the RET receptor and GFRα1 is of fundamental importance for the maintenance of the functional structure of the striatum and reconstruction dopaminergic nigrostriatal projection. GDNF through GFRα1 signaling participates in the growth of axons and promotes the formation of synapses on striatal GABAergic medium spiny neurons. In particular, GDNF activity contributes also to the rapid differentiation and incorporation into the striatal network of GABAergic interneurons. Unfortunately, progress in the development of new pharmacological based on the GDNF is slow, since this factor does not cross the blood-brain barrier. However, there is an emerging another possibility. There is growing evidence that vitamin D increases tyrosine hydroxylase expression levels, suggesting that it can modulate dopaminergic processes. Vitamin D is a powerful inducer of endogenous GDNF which may support the survival of dopaminergic neurons. Thus, adjunctive vitamin D therapy may prove useful in the treatment of Parkinson's disease. Supplementation of vitamin D also helps in mitigating the effects of insulin resistance in neurons.

The most straightforward GDNF therapeutic effect can be achieved by increasing the level of a patient's physical activity. Studies in rodents have shown an activity-induced increase of GDNF expression in several brain structures including the striatum. This result suggests that the therapeutic effect of the neuroprotective and neurodegenerative GDNF can be simply controlled by physical activity. Physical activity causes in the nigrostriatal system synaptogenesis to increase while limits the apoptosis in SNPC neurons. GDNF signaling by the RET receptor tyrosine kinase has an impact on the integrity and function of the blood-brain barrier and thus plays a potential role in the survival of neurons of the central nervous system. Finally, GDNF plays an important role in the activity of the microglia, which suggests that it can offer protection against neurodegeneration by blocking the inflammatory processes in the brain.

7. The problem of excitotoxicity

Some NAD can be made via the *de novo* pathway, starting from the essential amino acid tryptophan [45]. The kynurenine pathway accounts for the catabolism of ingested tryptophan and is

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the starting point for the biosynthesis of serotonin and melatonin [83,85]. The kynurenine pathway consists of eight enzymatic steps and one non-enzymatic reaction. At the step catalyzed by the nicotinamide mononucleotide adenylyltransferases, the NAD *de novo* biosynthesis and NAD *salvage* pathways converge. In the brain, tryptophan is mainly metabolized via the kynurenine pathway [18,83-84]. A central compound of the pathway is kynurenine, which can be metabolized in two separate ways: one furnishing kynurenic acid, and the other 3-hydroxykynurenine and quinolinic acid, the precursors of NAD [18].

Kynurenic acid is one of the endogenous excitatory amino acid receptor blockers with a high affinity positive modulatory binding site at the AMPA receptor. Kynurenic acid has proven to be neuroprotective. Depending on the tissue type, kynurenine either continues down its pathway towards the tricarboxylic acid cycle or is transformed to kynurenic acid in microglial cells or astrocytes, respectively [85].

Contrary, quinolinic acid, which is a biosynthetic precursor to NAD acts as an agonist of NMDA receptors and neurotoxin [86]. A defect in energy metabolism may lead to neuronal depolarization, excessive activation of NMDA receptors accompanied by an increase in intracellular calcium, and apoptosis [19,20]. There are several neurodegenerative disorders whose pathogenesis has been demonstrated to involve multiple imbalances of the kynurenine pathway metabolism [18]. The kynurenine pathway is an additional source of cellular energy as it can degrade about 90% of dietary tryptophan into NAD. Changes in brain tryptophan concentration directly alter the rate of serotonin and quinolinic acid synthesis. Quinolinic acid acts as an agonist of the NMDA receptor setting basic cellular metabolism of neurons. In low concentrations it is fully catabolized to NAD, thus plays a neuroprotective role. In higher doses, however, it may act as a neurotoxin, gliotoxin, proinflammatory mediator, and pro-oxidant molecule [85,86]. Especially high levels of quinolinic acid appear in the brain in response to inflammation. Pathological levels of quinolinic acid can impair neuronal function and even trigger the apoptosis [16,23,24,26, 85,86]. Increased levels of quinolinic acid destabilize also the cytoskeleton of astrocytes and blood vessels endothelial cells, which leads to degradation of the blood-brain barrier. This in turn escalates neuroinflammation and further increases the synthesis of quinolinic acid. Such a pathological sequence escalates neurotoxic effects that accompanied neurodegenerative diseases. Chronic mild stress can lead to an increase in the metabolism of quinolinic acid in the amygdala and striatum and its reduction in the cingulate cortex. The pathological changes can lead to axonal neurodegeneration in the involved brain areas [85].

Inhibition of the KYN pathway results in an additional decline of NAD level, which correlates with a decrease in cell viability, NAD-dependent SIRT1 activity, and CNS function unless

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alternative precursors for NAD synthesis are made available [26,84]. Excessive activation of the kynurenine pathway, however, increases the neurotoxic activity of quinolinic acids [86]. Quinolinic acid at nanomolar concentrations can promote NAD synthesis in astrocytes and neurons [84]. High quinolinic acid concentrations in cerebrospinal fluids have been observed in several neurodegenerative diseases: Alzheimer's and Parkinson's disease, multiple sclerosis, depression, epilepsy, and Huntington's disease (for review [83]). These findings point to the production of quinolinic acid by the kynurenine pathway as a contributing factor to neurodegenerative diseases.

8. Perspectives for the treatment of neurodegenerative disorders

Nowadays, the recovery of efficient systemic energy metabolism is the most rational target for maintaining organismal homeostasis, physiology, and life. This hypothesis initiated an intensive search for strategies targeting brain and neurons energy metabolism in attempts to find antineurodegeneration therapy. It has been discovered recently that NAD supplementation can effectively restore energy metabolism on both the cellular and organismal level [12,47,87-89]. It seems, that supplementing the brain with NAD precursors should ameliorate the age-related functional brain deficits by counteracting neuronal aging and neurodegeneration. The newest studies have confirmed the therapeutic potential of supplementing NAD intermediates, such as nicotinamide riboside, providing a proof of concept for the development of the new effective intervention [47,53,89]. NAD has a critical role as the substrate of NAD-dependent enzymes including sirtuins and poly-ADP-ribose polymerases (PARPs) [90]. Whereas PARPs facilitate repair and maintenance of genomic integrity, the activity of sirtuins regulates protein quality control pathways, in particular catabolism of the unfolded proteins. Unfortunately, both PARPs and the sirtuins must compete with ATP for the same, limited, and decreasing with age, the intracellular pool of NAD. Since ATP controls energy metabolism, its deficiency impairs all metabolic processes their impairment is only a matter of time. Consequently, the age-related deficit in energy metabolism well explains progressing insulin resistance, neurodegeneration, as well as the formation of alfa-synuclein inclusions, amyloid plaques, and neurofibrillary tangles [47,53,91]. Thus the intracellular accumulation of misfolded protein aggregates is caused by the age-related energy metabolism crisis which is multiplied by the misfolded protein accumulation. Supplementation of key NAD intermediates can ameliorate a variety of age-associated disorders related to energy metabolism decline. Supplementation of these intermediates appears to restore NAD levels in both the nuclear and mitochondrial compartments of neurons [47,89]. The therapy might be only effective in the early stage of neurodegenerative processes.

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