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Mitochondrial Functions in Mood Disorders

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1. Introduction

Depression is a serious mental disorder manifested by depressed mood, pessimistic thoughts, feelings of worthlessness, feelings of guilt, tearfulness, reduced or increased sleep, appetite loss or appetite disturbance, weight loss or weight gain, social restlessness, loss of interest, difficulty concentrating. Mania is characterized by abnormally elevated or irritable mood, arousal, and/or energy levels. Bipolar disorder features intermittent episodes of mania or hypomania and depressive episodes; rapid cycling, mixed states, and psychotic symptoms occurring in some cases. Depression and mania are thought to be heterogeneous illnesses that can result from dysfunction of several neurotransmitters or metabolic systems.

The predisposition to the disease is determined by genetic, psychosocial and biological factors; individual sensitivity to depressogenic effects during stressful life events is also a contributing factor. Pathophysiology of mood disorders is not sufficiently elucidated and about 1/3 of patients do not respond to pharmacotherapy sufficiently. The exact molecular site and the primary cause of signal transduction disturbance associated with the symptoms of depression or mania are still unknown.

Recently, attention in the research of biological basis of mood disorders has been devoted to an overlapping set of molecular and cellular mechanisms of mood disorders, antidepressant response, neuroplasticity, and chronic stress [1], e.g. to changes in neuroprogression, inflammatory and cell-mediated immune response, antioxidant capacity, oxidative and nitrosative stress, and mitochondrial functions [2]. Therefore, changes in the activities of compounds of these intracellular signalling pathways are studied with the aim of discovering new biological markers of mood disorders or predictors of response to antidepressant treatment [3-4]. Mitochondrial dysfunctions are assuming an increasingly important role in hypotheses of mood disorders, bipolar disorder mainly. Recently discussed biological hypotheses of mood disorders include the neurotrophic and neuroplasticity hypothesis of depression [1,5-8] and the mitochondrial hypothesis [9-11].

It is well-known that mitochondria strongly affect many intracellular processes coupled to signal transduction, neuron survival and plasticity. Impaired mitochondrial functions manifest themselves in various ways, they may be related to many psychiatric and neurodegenerative diseases, including bipolar disorder, major depressive disorder, schizophrenia, psychosis and anxiety [12-16]. Impaired functions of mitochondria can be assessed both in isolated mitochondria and in intact or permeabilized cells. Better insight into molecular mechanisms of cellular respiration, control of oxidative phosphorylation (OXPHOS) and effects of antidepressants and mood stabilizers on these processes is likely to lead to a better understanding of pathophysiology of neuropsychiatric disorders.

2. Mitochondria

Mitochondria are small cellular structures consisting of an outer and inner membrane, an intermembrane space and an intracellular matrix. The outer membrane covers the organelle, the inner membrane folds and forms cristae. This settlement extends the surface and enables plenty of chemical reactions. In the mitochondrial matrix, the enzymes of the tricarboxylic acid cycle (TCA, also called citric acid cycle or Krebs cycle) are localized. It is the central pathway of metabolism; its main function is oxidation of acetyl-CoA derived from carbohydrates, amino acids and fatty acids (FAs). The TCA is organized into a supramolecular complex that enables interaction with mitochondrial membranes and the electron transport chain (ETC) in OXPHOS [17]. Most of the TCA enzymes provide other additional “moonlighting” functions, e.g. they stabilize the mitochondrial DNA (mtDNA) or are associated with mitochondrial RNA (mtRNA) translation, oxidative stress, iron metabolism and tumour suppression [18].

In addition to their crucial role in generation of adenosine-5'-triphosphate (ATP), mitochondria are involved in other important processes, such as regulation of free radicals, neurotransmitters, calcium, and apoptosis. They are also involved in neuronal development - synaptogenesis, synaptic development and plasticity. Impaired function of mitochondria leads to impaired bioenergetics, decrease of ATP production, impaired calcium homeostasis, increased production of free radicals and oxidative stress [19-20]. Furthermore, monoamine oxidase (MAO), the enzyme responsible for the metabolism of monoamine neurotransmitters, is localized in the outer mitochondrial membrane.

Mitochondrial proteins are encoded by both nuclear and mitochondrial DNA. All 13 polypeptides encoded by mtDNA form subunits of respiratory chain complexes I, III, IV and V [21-22]. Furthermore, the mitochondrial genome encodes transfer RNA (tRNA) and ribosomal RNA (rRNA) used for RNA translation [23]. Complex II is encoded only by nuclear DNA (nDNA). OXPHOS is under the control of the nuclear genome as well as the mitochondrial genome, which is only maternally inherited. Nevertheless, the dominant role in the regulation of mitochondrial activity has a nucleus; nuclear-encoded transcript factors control the activity of the mitochondrial genome and coordinate the expression of nuclear and mitochondrial genes to mitochondrial proteins [23-24].

Genetic defects or stress can cause mitochondrial dysfunctions, which leads to increased oxidative stress and/or altered calcium homeostasis [25]. An excess of glutamate in the synapse [26] leads to an excess of cytosolic calcium, which produces overactivity of calcium-dependent enzymes and an overload of mitochondria by calcium; it leads to cytoskeletal degradation, protein malformation, decrease of ATP production, and increase of oxygen radical generation. These processes can lead to atrophy or death of neurons [27-28]. Different stimuli, such as hypoxia-ischemia, seizure and hypoglycemia, all activate this pathway. Thus, enhancing mitochondrial function may represent a critical component for the optimal treatment of stress-related diseases [11].

Eukaryotes synthesize ATP mainly by glycolysis in the cytosol and by OXPHOS in the mitochondria; i.e. the majority of cellular ATP is generated by glycolytic degradation of glucose to pyruvate in cytosol followed by aerobic cellular respiration. When pyruvate is converted to acetyl coenzyme A (acetyl-CoA), acetyl-CoA enters the TCA cycle and the result of this process is ATP production by OXPHOS in mitochondria [29]. OXPHOS yields about 17 times more ATP than glycolysis. Therefore, it is considered as the main energy source and a key element of bioenergetics [30-31]. Integration of main metabolic pathways coupled to OXPHOS is illustrated in Figure 1.

The highest number of mitochondria is present in organs demanding the most energy - brain, liver and muscles. Neurons usually utilize glucose as a source of energy. Since the brain stores only a very small amount of glycogen, it needs a steady supply of glucose. Neurons are known to have a lower glycolytic rate than astrocytes and when stressed they are unable to upregulate glycolysis. Following inhibition of mitochondrial respiration, neurons die rapidly, whereas astrocytes utilize glycolytically generated ATP. Glucose metabolism in neurons is directed mainly to the pentose phosphate pathway, leading to regeneration of reduced glutathione, which probably supports antioxidant controlled neuron survival [32]. The regulative processes of OXPHOS are tightly related to reactive oxygen species (ROS) production, integrity of mitochondrial membranes, apoptosis, and intramitochondrial Ca^{2+} levels. Although this is known, the control mechanisms have not yet been sufficiently investigated.

2.1. Physiology of oxidative phosphorylation

The respiratory chain is localized in cristae, structures formed by the inner mitochondrial membrane and extending to the surface [34]. ETC consists of complexes with supramolecular organization, where mitochondrial proton pumps (complexes I, III and IV) transport protons and generate a proton gradient [31,35]. Continuously, electrons are transported to complex III and finally complex IV enables the conversion of O_2 to H_2O . Most of the ATP synthesis comes from the electrochemical gradient across the inner membranes of mitochondria by ATP synthase (complex V). The CoQ cofactor is responsible for transferring electrons from complexes I and II to complex III; the second important cofactor is cytochrome *c* (cyt *c*), which transfers electrons from complex III to complex IV [36]. Both cofactors modulate energy and free radical production [37-38]. Processes in the inner mitochondrial membrane are depicted in Figure 2.

Energy saved in ATP is used in synaptic ion homeostasis and phosphorylation reactions. ATP is essential for the excitability and survival of neurons, OXPHOS is involved in synaptic signalling and is related to changes of neuronal structure and function. Therefore, mitochondria are included in neurotransmitter exocytosis, in recovery, and in ion homeostasis, and in presynaptic nerve terminals.

Oxidative phosphorylation enzymes and MAO are key mitochondrial enzymes studied in molecular psychiatry.

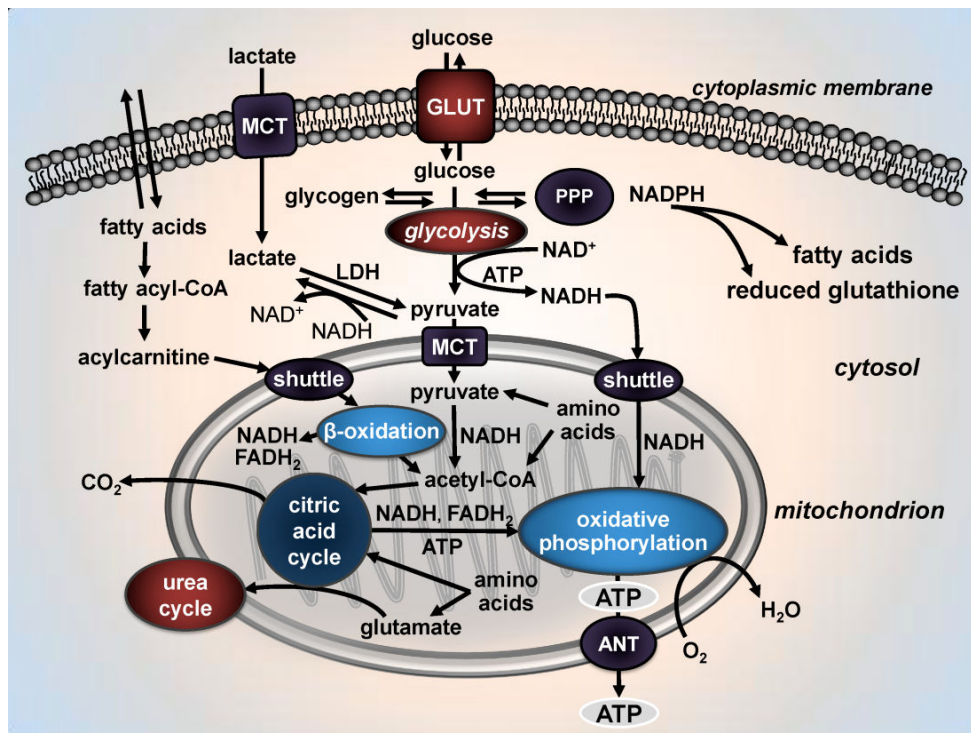


Figure 1. Integration of metabolic pathways. Glucose is transported over a plasma membrane by a glucose transporter (GLUT) and is metabolized to pyruvate by glycolysis. Pyruvate is converted to acetyl-coenzyme A (acetyl-CoA) in the mitochondria, where it is oxidized to CO_2 through the citric acid cycle; redox energy is conserved as reduced nicotinamide adenine dinucleotide (NADH). The mitochondrial respiratory chain couples NADH oxidation to the formation of the electrochemical proton gradient across the inner mitochondrial membrane, which is used to form ATP. ATP produced from OXPHOS is transported from the mitochondrial matrix to the cytoplasm by the adenine nucleotide translocator (ANT). Glucose may be stored as glycogen. Fatty acids and amino acids can also be bioenergetics precursors; however, glucose is considered to be the only metabolic substrate in the brain. Glucose can also be metabolized via the pentose phosphate pathway (PPP), a process that generates pentoses and that is the most important cytosolic source of reduced nicotinamide adenine dinucleotide phosphate (NADPH), a cofactor for biosynthetic reactions and the oxidation-reduction involved in protecting against the oxidative stress, e.g. for fatty acids biosynthesis or regeneration of reduced glutathione. During activation the brain may transiently turn to anaerobic glycolysis occurring in astrocytes, followed by the oxidation of lactate by neurons [32-33]. Monocarboxylate transporters (MCTs) carry lactate or pyruvate across biological membranes; lactate dehydrogenase (LDH) catalyzes the interconversion of pyruvate and lactate with concomitant interconversion of NADH and NAD^+ .

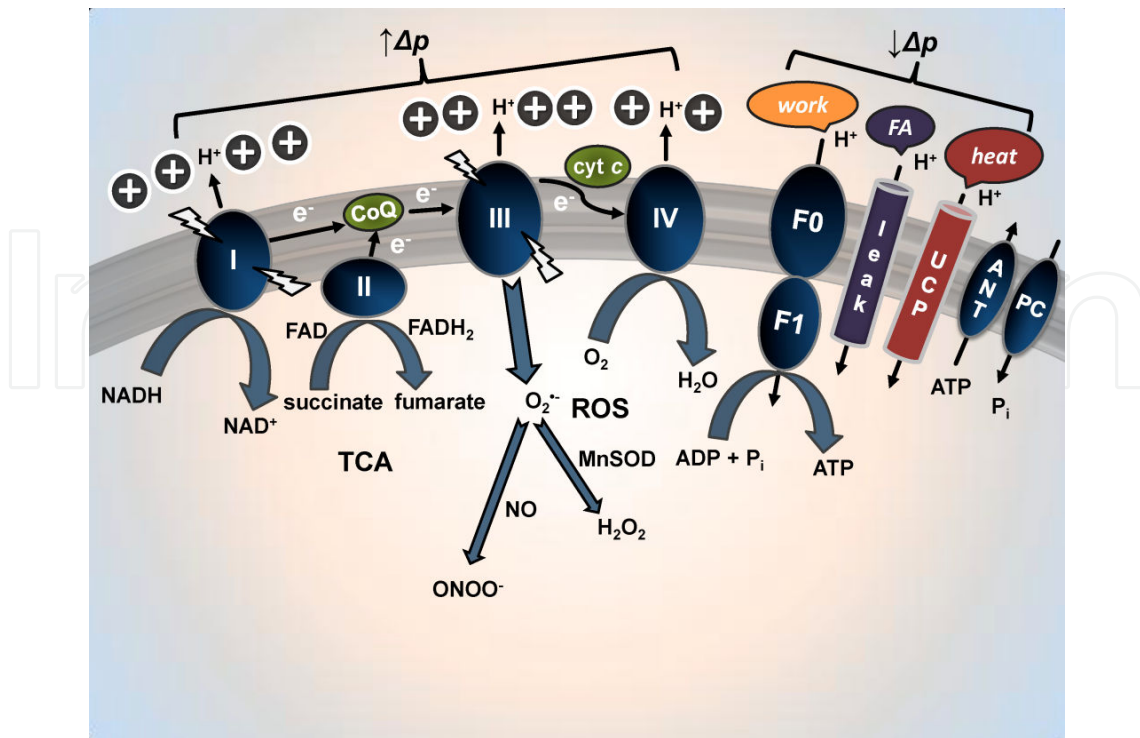


Figure 2. Representation of processes in the inner mitochondrial membrane. ETC consists of I - IV complexes that transfer electrons, pump protons outwardly, and create proton motive force (Δp). Complex I catalyses oxidation of nicotinamide adenine dinucleotide (NADH), complex II oxidizes succinate to fumarate. CoQ as a cofactor accepts electrons from complexes I and II, and carries them to complex III; the second mobile carrier cyt c move electrons from complex III to complex IV, where O_2 is finally reduced to water. The proton gradient is primarily consumed by F_0F_1 ATP synthase for ATP synthesis from ADP and inorganic phosphate P_i . Secondary consumers causing decreased Δp are uncoupling proteins (UCPs), they response to heat production, proton leak is mediated e.g. by FAs. Transport of ADP and ATP across the membrane is enabled by adenine nucleotide translocator (ANT); mitochondrial phosphate carrier protein (PC) catalyses movement of P_i into the mitochondrial matrix. Simultaneously, electron transport is accompanied by generation of reactive oxygen species (ROS), the highest amount of superoxide ($O_2^{\cdot-}$) is formed by complexes I and III. $O_2^{\cdot-}$ can be further transformed by manganese superoxide dismutase (MnSOD) to H_2O_2 , or can react with nitric oxide (NO) to form peroxynitrite ($ONOO^-$). $O_2^{\cdot-}$ production leads to increased mitochondrial conductance through UCPs.

2.1.1. Oxidative phosphorylation enzymes

Complex I (EC 1.6.5.3, NADH: ubiquinone oxidoreductase, NADH dehydrogenase, NADH-ubiquinone oxidoreductase) is a crucial point of respiration. It catalyzes oxidation of reduced nicotinamide adenine dinucleotide (NADH), thus, regenerates NAD^+ for the TCA cycle and fatty acids (FAs) oxidation, and reduces coenzyme Q_{10} (ubiquinone, CoQ) to ubiquinol [39]. Four protons are pumped from the matrix into the intermembrane space during electron passing through the complex I. Complex I is also a rate-limiting enzyme for oxygen consumption in the synapses [40].

Complex II (EC 1.3.5.1, succinate:ubiquinone oxidoreductase, succinate dehydrogenase (ubiquinone)) is the side entry into Electron transport chain, directly involved in the TCA cycle. It is a 4 subunit membrane-bound lipoprotein, which couples the oxidation of succinate to the reduction of CoQ [41]. Complex II does not contribute to the proton gradient. Hence, com-

plex II subunits are encoded only by nDNA, complex II is suspected to normalize the activity of ETC, when mtDNA defects are suspected [42].

Complex III (EC 1.10.2.2, ubiquinol:ferricytochrome-*c* oxidoreductase, CoQ-cytochrome *c* reductase) consists of two centers, Q_i center - facing to matrix; and Q_o center - oriented to intermembrane space [43]. Complex III catalyses the oxidation of one molecule of ubiquinol and the reduction of two molecules of cytochrome *c*. Reaction mechanism of complex III occurs in two steps called the Q cycle [44]. In the process of Q cycle four protons are released into the inter membrane space.

Complex IV (EC 1.9.3.1, ferrocycytochrome-*c*:oxygen oxidoreductase, cytochrome *c* oxidase, COX) enables the terminal reduction of O₂ to H₂O, retains all partially reduced intermediates until full reduction is achieved [45]. The complex IV mediates pumping of 4 protons across the membrane. Previously, it was suggested as an endogenous metabolic marker for neuronal activity [46].

Complex V (EC 3.6.3.14, ATP synthase, F₀F₁-ATPase) consists of two regions: 1. F₁ portion is soluble domain with three nucleotide binding sites, it is localized above the inner side of the membrane and stably connected with F_o domain; 2. F_o portion is proton pore embedded in the membrane, it consists of three subunits and spans the membrane from the inner to the outer side [47-48]. This formation enables the conversion of electrochemical potential energy to chemical energy - a portion of the F_o rotates as the protons pass through the membrane and forces F₁ as motor to synthesize ATP [47,49].

2.1.2. Monoamine oxidase

Monoamine oxidase (MAO, EC 1.4.3.4) is located in the outer mitochondrial membrane and catalyses the oxidative deamination of amine neurotransmitters as well as xenobiotic amines. It regulates the metabolic degradation of catecholamines and serotonin (5-hydroxytryptamin, 5-HT) in neural and other target tissues. A major physiological role of intraneuronal MAO is to keep cytosolic monoamine concentrations very low. This membrane-bound enzyme is a flavoprotein, which use FAD as cofactor. The cofactor was identified as the site, where irreversible inhibitors of MAO are covalently linked [50-51]. It exists in two isoforms MAO-A and MAO-B, they differ in substrate preference, inhibitory specificity, tissue and cell distribution, and in immunological properties [52]. MAO-A metabolizes 5-HT and is sensitive to inhibition by low concentrations of clorgyline, whereas MAO-B prefers benzylamine or 2-phenylethylamine (PEA) as substrate and is sensitive to inhibition by low concentrations of *l*-deprenyl. Tyramine, tryptamine, dopamine, norepinephrine (NE) and epinephrine are equally well oxidized by both isoforms of MAO [50]. The high levels of both forms are found in the brain; MAO-B is found in dopamine-secreting neurons in the brain.

Monoamine metabolism by MAO involves oxidative deamination to corresponding aldehyde and free amine. Catalysis in MAO depends on the transfer of electrons to FAD, and mechanism-based inhibitors, such as the irreversible antidepressants, modify flavin [53]. The aldehyde is rapidly metabolized by aldehyde dehydrogenase to acidic metabolites. Metabolism of monoamines by MAO is a major source of hydrogen peroxide (H₂O₂) in the

brain. Normally the H_2O_2 is then inactivated by glutathione peroxidase but it can be converted, chemically, by Fe^{2+} ions (Fenton reaction) into the highly reactive hydroxyl radical. This radical has widespread deleterious effects which can cause neuronal damage and death and may account for associated health-related problems [51,54].

MAOs have important role in brain development and function, and MAO inhibitors (MAOIs) have a range of potential therapeutic uses [53]. Generally, selective inhibitors of MAO-A and nonselective MAOIs seem to be effective in the treatment of patients with depression, panic disorder, and other anxiety disorders [55]. It is supposed that MAO-B inhibition may slow the course of various neurodegenerative disorders; so, selective inhibitors of MAO-B may be efficacious in treating of Parkinson's disease [56] and possibly Alzheimer's disease [57]. MAO-B is the sole type in human platelets and the amino acid sequences of MAO-B in both platelets and brain are identical [58]; thus, platelet MAO can be adopted as a useful surrogate model for the study of aspects of central neuronal function related to monoaminergic neurotransmission [3].

2.2. Regulation of OXPHOS

There are five levels of OXPHOS regulation: 1. direct modulation of ETC kinetic parameters, 2. regulation of intrinsic efficiency of OXPHOS (by changes in proton conductance, in the P/O ratio or in the channelling of ECT intermediate substrates), 3. mitochondrial network dynamics (fusion, fission, motility, membrane lipid composition, swelling), 4. mitochondrial biogenesis and degradation, 5. cellular and mitochondrial microenvironment [59].

OXPHOS efficiency is dependent on delivery of reducing equivalents into ETC and on activities of participating enzymes or enzyme complexes. The optimal efficiency and flow ratios are determined by control of complex I (reflects integrated cellular pathway) and complex II (TCA cycle precedes) [60]. Depletion of TCA cycle intermediates plays an important role in the OXPHOS flux control. In respirometry assays, supplies of complex I as well as complex II are required. Convergent electron input and reconstitution of the TCA cycle are needed to achieve maximal respiration [30]. It is controlled also by the availability of adenosine 5'-diphosphate (ADP) for the adenine nucleotide transporter in the inner mitochondrial membrane [61].

Complex I is suggested to be responsible for adaptive changes and physiological set up of OXPHOS efficiency [62]. The stoichiometric efficiency of OXPHOS is defined by the P/O ratio, or the amount of inorganic phosphate (P_i) incorporated into ATP per amount of consumed oxygen. P/O ratio was analysed in rat brain, liver and heart mitochondria. There were found tissue-specific differences and dependency of the P/O ratio on the respiratory rates with complex I, but not with complex II substrates [62]. Metabolic control analysis, which compared ETC activities and oxygen consumption rates, determined the role of complex I in rat brain synaptosomes. Results of the study suggest complex I as rate-limiting for oxygen consumption and responsible for high level of control over mitochondrial bioenergetics [40].

As mentioned above, mitochondria exhibit transmembrane potential across the inner membrane that is necessary for OXPHOS. Protons are transported outwardly and create proton motive force (Δp), which consists of electrical part $\Delta\psi_m$ (negative inside) and chemical part ΔpH [63-64]. In mitochondria, the Δp is made up of the $\Delta\psi_m$ mainly. The $\Delta\psi_m$ controls the ability of the mitochondria to generate ATP, generate ROS and sequester Ca^{2+} entering the cell. The $\Delta\psi_m$ and ATP synthesis express a degree of coupling; optimal ATP synthesis requires $\Delta\psi_m$ values between the range -100 mV and -150 mV. These values are reached primarily by $\Delta\psi_m$, which maintain at higher values (about -200 mV) and by secondary control mechanisms, which decrease the $\Delta\psi_m$ to lower levels [49]. Changes of $\Delta\psi_m$ influence permeability of biological membranes and ROS production, more negative $\Delta\psi_m$ (< -150 mV) leads to exponentially increased permeability as well as $O_2^{\cdot-}$ and H_2O_2 production [31]. Similarly, mitochondrial membranes increase exponentially their permeability for protons [49]. On the other hand, lower mitochondrial Δp and $\Delta\psi_m$ (e.g. caused by inhibition of respiratory chain) can result in hydrolysis of cytoplasmic ATP and slightly lower potential than that generated by the respiratory chain [65]. Therefore, $\Delta\psi_m$ is precisely controlled and can be regulated by various parameters.

ATP production is controlled by different mechanisms, depending on energy demands, thermogenesis, etc. [49]. First mechanism of OXPHOS control has been called as "respiratory control", and is based on feedback mechanisms controlling the rate of ATP synthesis, first of all by Δp and $\Delta\psi_m$. Higher levels of ADP in mitochondria lead to stimulation of ATP synthase together with decrease of Δp . Originally, pilot studies of OXPHOS dynamics used the terminology of respiratory steady states, described by Chance and Williams. Respiration was characterized by respiratory states (Table 1), by active state 3 (ADP stimulated) and followed by controlled state 4 (decrease after conversion of ADP to ATP) [66-67]. Decreased P/O ratio (caused mostly by increased Δp) leads to energy waste - proton leak (slip in COX), the decrease in the coupling, and increased thermogenesis [68]. However, conception of states had limited applicability in intact cells and in isolated mitochondria, did not include for instance COX, adenine nucleotide transporter, and extramitochondrial ATP/ADP ratio.

Recently, primary control has been implemented by secondary control mechanisms that are Δp independent [49,70]. Mitochondrial Ca^{2+} levels have been included [31]. Ca^{2+} transport was presumed to be important only in buffering of cytosolic Ca^{2+} by acting as sink under conditions of Ca^{2+} overload. When the cytoplasmic Ca^{2+} level was overloaded, Ca^{2+} accumulated in mitochondrial matrix and utilized $\Delta\psi_m$ [65,72-73]. Nowadays it is considered that Ca^{2+} regulates of activities of dehydrogenases via phosphorylation; ATP synthesis is switched on by cAMP-dependent phosphorylation and switched-off by calcium induced dephosphorylation [29,74].

In the TCA cycle, glycerophosphate dehydrogenase, pyruvate dehydrogenase, isocitrate dehydrogenase, and α -ketoglutarate dehydrogenase are influenced by Ca^{2+} levels and their phosphorylation lead to increased ATP production, production of glycogen, and glucose oxidation [73]. Reversible phosphorylation of pyruvate dehydrogenase complex mediated by calcium partly regulates the supply of reducing equivalents (NADH/NAD⁺ ratio). Activation of the TCA cycle enhances the NADH production that triggers movement of electrons down complexes I through to complex IV by initially donating of complex I [75].

	ADP level	Substrate level	Respiration rate	Rate-limiting component	Relevance
State 1	Low	Low-endogenous	Slow	Phosphate acceptor	Initial activity of the sample
State 2	High	Approaching zero	Slow	Substrate	1. Exhaustion of endogenous substrate utilized in OXPHOS of ADP 2. Residual oxygen consumption (ROX)
State 3	High	High	Fast	Respiratory chain	1. OXPHOS capacity at saturating ADP (State P) 2. Electron transfer system capacity at optimum uncoupler concentration (State 3u)
State 4	Low	High	Slow	Phosphate acceptor	1. Exhaustion of added ADP 2. LEAK respiration (resting state when oxygen flux is maintained mainly to compensate for the proton leak after inhibition of ATP synthesis) (State 4o, L)
State 5	High	High	Zero	Oxygen	1. Anoxia 2. Antimycin A treatment

Table 1. Characterization of respiratory states [30,69]

Regulation of complex I and COX subunits via specific protein kinases and protein phosphatases was observed. cAMP-dependent protein kinase catalyses phosphorylation of complex I subunit and stimulates ETC [76]. At low Ca^{2+} levels, protein phosphatase dephosphorylates and inactivates complex I. It is presumed that COX is regulated by allosteric inhibition of ATP at high ATP/ADP ratios [31]. Extramitochondrial ATP/ADP ratios regulate COX activity by binding to the cytosolic subunit of COX, whereas high mitochondrial ATP/ADP ratios cause exchange of ATP by ADP at COX and induce allosteric inhibition [77]. Similarly, increased intracellular Ca^{2+} levels are suggested to activate mitochondrial phosphatase, which dephosphorylates COX and turns off the allosteric inhibition [78]. This respiratory control by phosphorylated enzyme is assumed to keep the Δp low as prevention of increased Δp , which leads to the slip of protons in COX and decreased H^+/e^- stoichiometry [79-80]. However, in isolated mitochondria high $\Delta\psi_m$ was measured even with high ATP/ADP ratios. The decrease was measured after addition of phosphoenolpyruvate and pyruvate kinase and could be explained as reversal of gluconeogenic enzymes [61]. Under the physiological conditions, allosteric inhibition is modulated by increased Ca^{2+} levels, high substrate concentrations, and thyroid hormones. Ca^{2+} dependent dephosphorylation induced by hormones results in loss of respiratory control by the ATP/ADP ratio and associated with the increased Δp and respiration [79].

Thyroid hormone, mainly triiodothyronine (T3) and diiodothyronine (T2), has important effects on mitochondrial energetics and mitochondrial genome [81]. Mechanism of allosteric inhibition of COX has been closely linked to regulation by thyroid hormones. 3,5-diiodo-

thyronine (T₂) mediates short term effects of thyroid hormones and increases immediately basal metabolic rate. T₂ is formed by intracellular deiodination of T₃ and binds to specific T₂ binding sites, which were identified in the inner mitochondrial membrane [82]. This binding to subunit Va of COX abolishes the allosteric inhibition of respiration by ATP [83] that could result in partial uncoupling of OXPHOS via increased $\Delta\psi_{m'}$ and continue to intrinsic uncoupling of COX by higher membrane potentials [49]. Therefore, thyroid hormones enhance the proton permeability; hyperthyroidism stimulated mitochondrial proton leak and ATP turnover in rat hepatocytes, where non-mitochondrial oxygen consumption remained unchanged [84-85]. Oppositely, in rat hypothyroid cells significant decrease of non-mitochondrial oxygen consumption and proton leak were observed, ATP turnover was unaffected [86].

2.3. Proton permeability of membranes

OXPHOS in cells is not fully efficient. Decrease of the proton gradient across the inner mitochondrial membrane by “proton leak” causes uncoupling of fuel oxidation from ATP generation, and some energy is lost as heat. The mechanism of the basal proton conductance of mitochondria (insensitive to known activators and inhibitors) is not understood. There is correlation between mitochondrial proton conductance and composition of inner membrane: phospholipid fatty acyl polyunsaturation correlates positively and monounsaturation correlates negatively with proton conductance [87].

Uncoupling proteins (UCPs) and adenine nucleotide translocator (ANT) are two types of mitochondrial carrier, which cause inhibitor-sensitive inducible proton conductance. UCPs themselves do not contribute to the basal proton conductance of mitochondria; however, they are important metabolic regulators in permitting fat oxidation and in attenuating free radical production [88]. The amount of ANT present in the mitochondrial inner membrane strongly affects the basal proton conductance of the membrane and suggests that ANT is a major catalyst of the basal FA-independent proton leak in mitochondria [89].

2.3.1. Fatty acids

Long-chain fatty acids (FAs) are weak acids that can cross the membrane in both protonated and deprotonated forms. Effects of FAs are interrelated to 1. increase uncoupling, 2. increase ROS production, 3. opening mitochondrial permeability transition pores (MPTP) [90]. Further, they can modulate effects of thyroid hormones as well as sex steroid hormones [84]. FAs can act as like classic OXPHOS uncouplers with protonophoric action on the inner mitochondrial membrane and/or interactions of FAs with ADP carrier, COX and ATP synthase are presumed [91]. Recent study suggests that FAs are not only inducers of uncoupling, but they also regulate this process. It supposes that transport of FA anions participates in both ADP/ATP antiport and aspartate/glutamate antiport, at the same time [92]. On the other hand, studies using lipid membranes suppose that FAs are capable of spontaneous flip-flop [93]. Since FAs move across the membrane spontaneously and rapidly, no protein transporters are necessary. Further, coupling/uncoupling effects depend on their concentrations pH gradient across the membranes [94-95].

2.3.2. Uncoupling proteins

Uncoupling diverts a significant proportion of energy to thermogenesis. UCPs are mitochondrial carriers catalysing a regulated proton leak across the inner membrane [96-97]. There are five types of UCP in mammals. UCP1 is presented exclusively in the inner mitochondrial membrane of brown adipose tissue, and its main function is to catalyse adaptive thermogenesis [98]. It can be stimulated by FA and has synergic action of norepinephrine and thyroid hormones [49,99]. Concentrations of UCP2 and UCP3 in tissues are much lower than of UCP1, and their functions are not exactly known. They probably minimally contribute to basal metabolic rate, control of adaptive thermogenesis, preventive action against oxidative stress and ROS control, control of cellular energy balance, regulation of Ca^{2+} homeostasis, regulation of FA oxidation and ATP synthesis [100-103]. UCP2, UCP4 and UCP5 are present in the central nervous system (CNS); they have been suggested to have effects protecting neurons from the Ca^{2+} overload and/or oxidative stress [104-105].

UCP activities can be positively or negatively regulated by different factors. UCP are stimulated by FA and by ROS, generated by as a side reaction between CoQ and oxygen [106]. UCP mediate the FA dependent proton influx that leads to uncoupled ATP synthesis and heat production [107]. It is supposed that UCP and FA decrease $\Delta\psi_m$ if it is sufficiently high.

2.4. Reactive oxygen species production

Reduction of O_2 to water by aerobic respiration is accompanied by reactive intermediate formation. Generally, complex I and complex III are considered as the major $\text{O}_2^{\bullet-}$ sources [108].

Complex I releases $\text{O}_2^{\bullet-}$ to matrix, complex III can release $\text{O}_2^{\bullet-}$ to both sides of the inner mitochondrial membrane [109]. Additionally, other ROS sources, e.g. MAO, present in the outer mitochondrial membrane, and α -ketoglutarate dehydrogenase (α -KGDH), the TCA cycle enzyme complex, are able to generate H_2O_2 . MAO catalyses the oxidative deamination of biogenic and xenobiotic monoamines and increases the amount of ROS in mitochondria. H_2O_2 production by α -KGDH is dependent on NADH/NAD⁺ ratio. Higher NADH leads to higher H_2O_2 production, therefore, α -KGDH could significantly contribute to oxidative stress in mitochondria [110].

Physiologically generated H_2O_2 and $\text{O}_2^{\bullet-}$ from ETC are dependent on the magnitude of Δp and the respiratory state of mitochondria [111]. State 4 is characterized with high rate of ROS production, contrary to state 3 with high rate of oxygen uptake and slow ROS production. State 5, described as anoxic, with limited oxygen supply and lack of respiration produce minimum ROS [98,112]. In isolated rat liver mitochondria ROS production and $\Delta\psi_m$ were studied in state 3 and state 4. These states attenuate $\Delta\psi_m$ and ROS, correlation of ROS with $\Delta\psi_m$ was observed [113]. However, this correlation with respiratory states was not observed in the study using isolated mitochondria, ROS production correlated directly with $\Delta\psi_m$ [114].

Complex I is considered to be the primary source of ROS in brain under physiological conditions, as well as in pathological processes (e.g. neurodegenerative disorders). ROS seem to be the key factors in brain aging processes and mitochondrial respiration with ROS produc-

tion significantly contributes to functional changes in brain during aging. Study in isolated rat mitochondria found significantly increased H_2O_2 production and 30 % reduction of complex I activity in aged rats [115]. Defective mitochondria release large amounts of ROS, similarly, decline of antioxidative enzyme activities (e.g. in elderly) enhances ROS production [116]. Negative results of ROS can affect respiratory chain: complexes I, III and IV seem to be the most affected, whereas function of complex II appears to be unchanged [117].

2.5. Apoptosis

Mitochondrial dysfunctions may accompany the clinical picture of neuropsychiatric disorders and contribute to neural apoptosis [118]; mitochondria play a pivotal role in intrinsic pathway of apoptosis [38]. Several interrelated mitochondrial pathways facilitate cell death: mitochondrial permeability transition (MPT) and the release of apoptotic cell death promoting factors, cytochrome *c* release by proapoptotic members of the Bcl-2 (B-cell lymphoma 2) family of proteins, disruption of ATP production, and alteration of the cell's redox status and overproduction of ROS [114]. If they are activated, change their conformations and induce formation of oligomers to form mitochondrial outer membrane pores, resulting to MPT. In apoptotic cells rapid loss of mitochondrial $\Delta\psi_m$ is accompanied by ROS production. Consequently, other proapoptotic proteins cytochrome *c* and Smac are released and trigger the caspase cascade leading to apoptosis [119]. Released cytochrome *c* in cytosol binds to apoptotic protease-activating factor-1 (Apaf-1) and induces formation of apoptosome [120]. MPT means alteration of permeability properties of membranes, originally was defined as increase of the inner mitochondrial membrane permeability to solutes of molecular mass less than 1500 Da [121]. Decreased MPT and activities of respiratory chain complexes, and increased ROS production were observed in cultured fibroblasts obtained from patients with CoQ deficiency [37]. MPT results from formation and opening of a channel known as MPTP. MPTP is dynamic multiprotein complex that span both the outer and inner mitochondrial membrane and contain the adenine nucleotide translocator (ANT) in the inner membrane, and the voltage-dependent anion channels (VDAC) in the outer membrane and cyclophilin D in the matrix [122]. Once open, MPTP allows the release of pro-apoptotic factors, such as cyt *c* and apoptosis inducing factor (AIF), into the cytoplasm.

2.6. Specific inhibitors of complexes of ETC

Rotenone is a specific complex I inhibitor, thenoyltrifluoroacetone (TTFA) specifically inhibits complex II. Both substances induce $O_2^{\cdot-}$ production that may result to major ROS production [45,123-124]. Pyrrolnitrin inhibits both complex I as well as complex II. It affects electron transport among NADH, CoQ and succinate, whereas COX remains unaffected [125].

Complex III inhibitors antimycin, myxothiazol and stigmatellin differ in their mechanism of action. Antimycin A inhibits the transfer of electrons from cytochrome *b* to CoQ, blocks the Q_i side of complex III. Oppositely, myxothiazol or stigmatellin block electron transfer from reduced CoQ at Q_o side [75]. Stigmatellin inhibits transfer of electrons and recycling of CoQ; myxothiazol inhibits electron transfer from reduced CoQ to cytochrome *c* [126].

Complex IV inhibitors KCN and sodium azide decrease COX activity [127]. Azide specifically blocks crossover between cytochrome *a* and cytochrome *a₃*. Further, it inhibits succinate oxidase activity specific for active respiration (state 3), but without any significant inhibition of state 4 [128]. Inhibition of COX by KCN is reversible, cyanide inhibits both electron and proton transport of COX [129]. Complex V is inhibited by oligomycin, which blocks its proton channel (*F_o* subunit). This inhibitor increases $\Delta\psi_m$ and is used to prevent state 3 of respiration. Oligomycin induces artificially state 4, i.e. state of respiration independent of ADP phosphorylation or resting state (LEAK) [130].

During the oxidation of complex I substrates (pyruvate, malate, glutamate), rotenone inhibition did not increase H_2O_2 ; contrary, oxidation of complex I and II substrates in the presence of antimycin A increased H_2O_2 . Both myxothiazol and stigmatellin inhibited $O_2^{\bullet-}$ production and/or should inhibit the effect of antimycin [126,131]. The maximum of $O_2^{\bullet-}$ production has been observed in human skin fibroblasts with the prolonged treatment of rotenone, but not with antimycin A [132]. Interestingly, rotenone prevented antimycin A to induce ROS production in complex I, but not in complex II [43]. *Q_o* side of complex III was found as the source of increased $O_2^{\bullet-}$ after transient exposure to hydrogen peroxide [75]. KCN and sodium azide increase ROS formation [126]. Oligomycin induces hyperpolarization of inner mitochondrial membrane and can increase $O_2^{\bullet-}$ levels [133].

2.7. Mitochondria and neuroplasticity

Mitochondrial distribution and activity are key factors in neuronal morphogenesis - synaptogenesis, developmental and synaptic plasticity and axogenesis. During the development, neuronal stem cells proliferate and differentiate into neurons; subsequently axons and dendrites form synapses [134-135]. The role of mitochondria in neuroplasticity is illustrated in Figure 3 [20]. Due to ATP production and importance of mitochondria in synaptic ion homeostasis and phosphorylation reactions, mitochondria would be accumulated at sites where ATP consumption and Ca^{2+} concentration are higher. It was reported that mitochondria are more abundant in the regions of growing axons than in the non-growing axons. Mitochondrial net movement is anterograde in growing axons and is retrograde in non-growing axons. Shortly before axogenesis mitochondria congregate at the base of the neurite that is destined to become the axon. Nerve growth factor (NGF) was found as one of the signals inducing accumulation of mitochondria in the active growing cone [136]. Interestingly, when the ATP production is impaired and cells provide alternative source of energy, axogenesis is abolished although growth of dendrites remains relatively unaffected [134].

There are changes in mitochondrial energy metabolism occurring in brain cells during CNS development. During embryonic and early postnatal development fats are primarily used, later on, glucose becomes as fuel. This fact supports the role of mitochondria in biochemical requirements of highly proliferative neuronal stem cells and post-mitotic neurons. During neuronal differentiation the number of mitochondria per cell increases, but the velocity at which individual mitochondria move decreases as neurite outgrowth slows and synaptogenesis occurs [20,137].

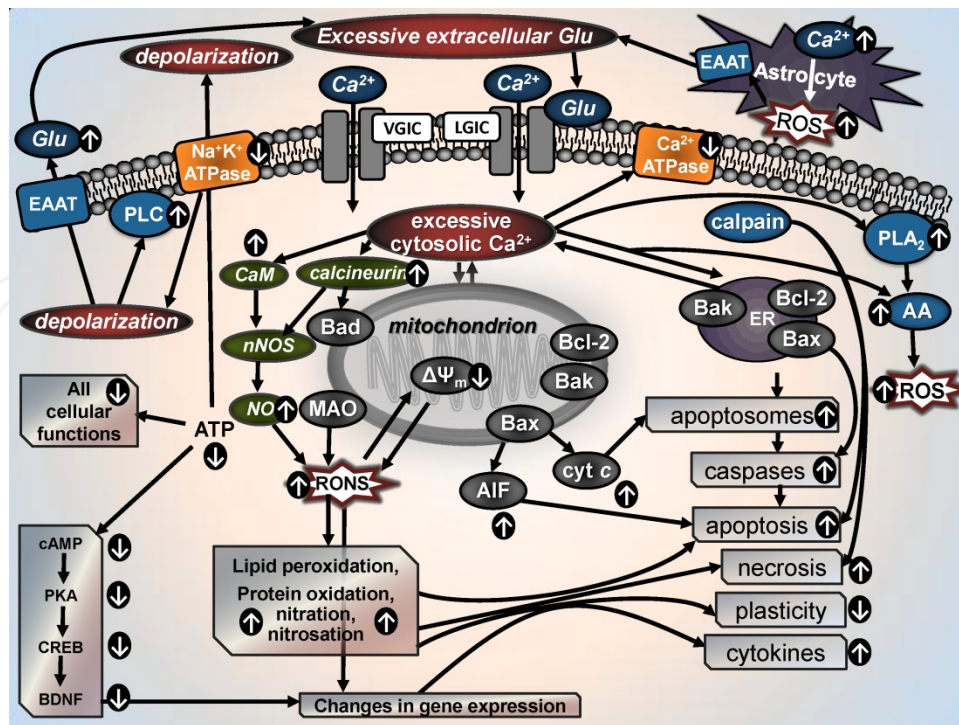


Figure 3. The role of mitochondria in neuroplasticity [20]. Principal mechanisms leading to neuronal impairment and cell death are composed of decreased ATP production, increased production of reactive oxygen and nitrogen species (RONS), initiation of apoptotic processes and impaired calcium homeostasis. Exhaustion of energy supplies and decreased ATP production lead to impairment of ATP dependent processes and therefore to changed cellular functions. Insufficient function of Na^+/K^+ ATPases leads to disturbances of ion transmembrane gradients, efflux of K^+ , and influx of Na^+ , Cl^- and Ca^{2+} . Increased extracellular concentrations of K^+ mediate depolarisation of membranes and change the functions of amino acids transporters. Voltage gated ion channels (VGIC) and ligand dependent calcium channels (LGIC) are activated and mediate increased cytosolic calcium concentrations. Intracellular calcium causes functional changes of amino acid transporters and enhances the increased extracellular concentrations of excitatory amino acids, glutamate especially, and extends neurotoxicity. Increased levels of synaptic glutamate can be mediated by release of glutamate from astrocytes. Following bound of glutamate to NMDA and AMPA receptors causes higher Ca^{2+} influx into cell, calcium activates phospholipases, proteases, and endonucleases, which degrade membranes, proteins and nucleic acid. E.g. activation of phospholipase A_2 (PLA_2) by calcium releases membrane arachidonic acid (AA), which induces production of superoxide. High intracellular calcium levels cause overload of mitochondrial calcium, increase ROS production, and inhibit ATP production. Activation of calcium dependent protein phosphatases (e.g. calcineurin) causes translocation of proapoptotic factor Bad into the mitochondria and triggers apoptosis by sequestration of anti-apoptotic factors Bcl-2 and Bcl-xL. Release of cytochrome c and other proapoptotic factors from the intermembrane space of mitochondria induce the formation of apoptosome, and consequently trigger activation of caspases and apoptosis. Apoptosis inducing factor (AIF) is another factor released by mitochondria. Disengaged AIF is transported into nucleus and trigger caspases-independent apoptosis. Mitochondria in brain are also a target of nitric oxide (NO) action; AA - arachidonic acid; AIF - apoptosis inducing factor; Bax, Bad, Bcl-2 - proapoptotic factors of Bcl-2 family; Bcl-2 - antiapoptotic factor of Bcl-2 family; BDNF - brain-derived neurotrophic factor; CaM - calmoduline; cAMP - cyclic adenosine monophosphate; CREB - cAMP response element-binding protein; cyt c - cytochrome c; $\Delta\psi_m$ - potential on the inner mitochondrial membrane; EAAT - excitatory amino acid transporter; ER - endoplasmic reticulum; Glu - glutamate; MAO - monoamine oxidase; nNOS - neuronal nitric oxide synthase; NO - nitric oxide; PKA - protein kinase A; PLA_2 - phospholipase A_2 ; PLC - phospholipase C; LGIC - ligand-gated ion channel; RONS, reactive oxygen and nitrogen species; ROS - reactive oxygen species; RNS - reactive nitrogen species; VGIC - voltage-gated ion channel

It was demonstrated that neuronal activity is influenced by the mitochondrial functions, defective trafficking and dysfunction of mitochondria from axon terminals is implicated in the

pathogenesis of axonal degeneration [138-140]. In addition, dendritic mitochondria are essential in the morphogenesis and plasticity of spines and synapses [141]. Recent findings suggest roles for mitochondria as mediators of at least some effects of glutamate and BDNF on synaptic plasticity [136]. BDNF promotes synaptic plasticity, in part, by enhancing mitochondrial energy production. It increases glucose utilization and increases mitochondrial respiratory coupling at complex [62,142].

Mitochondria are dynamic organelles; their function is modulated by fission, fusion and moving within the axons and dendrites [38]. Their structure, functions and properties differ in axons and dendrites [141,143]. Transport and positioning of mitochondria are essential for neuronal homeostasis and the mitochondrial movement is a part of regulation by intracellular signals.

3. Advances in biological hypotheses of mood disorders

Findings about intracellular processes associated with mood disorders and long-term effects of antidepressants demonstrate an important role of signalling pathways primarily regulated by monoamine neurotransmitters; this was settled as the basis of many biochemical hypotheses [144-145]. While dysfunctions within monoaminergic neurotransmitter systems are likely to play an important role in pathophysiology of mood disorders, it probably represents the downstream effects of more primary abnormalities in signal transduction. Thus, new theories about the pathophysiology of depression and the action of antidepressant treatment proposes that mood disorders are caused by structural or functional changes in particular molecules and signalling pathways in the brain, and that antidepressants function by counteracting these molecular changes. It is supposed that structural and functional brain abnormalities in patients with depressive disorder may be associated with low levels of brain-derived neurotrophic factor (BDNF), abnormal function of hypothalamic-pituitary-adrenal (HPA) axis, glutamatergic toxicity, activation of inflammatory and cell-mediated immune response, decreased antioxidant capacity and increased oxidative and nitrosative stress, disturbed chronobiological rhythms, and mitochondrial dysfunctions [2,146-148].

Research on the biological basis of mood disorders emphasises the changes of neural networks and synaptic plasticity. Evidence exists for impairment of neuroplasticity in major depression. Chronic stress is known to contribute both to development of major depression in vulnerable persons and to reduction of synaptic plasticity, induction of structural changes in dendrites, and impairment of neurogenesis [1]. Mitochondria may be primary regulators of these processes, as they regulate not only neuronal survival and death, but also plasticity. There is mounting evidence for the role of mitochondrial dysfunction in the pathophysiology and treatment of bipolar disorder [11].

3.1. Monoamine hypothesis

Discovery of the first effective antidepressants, MAOIs and tricyclic antidepressants, implied hypothesis about significant role for the biogenic amine, particularly NE and 5-HT in

the etiopathogenesis of affective disorders. Classic monoamine hypothesis is an early milestone in the field of depression. It proposed that depression might be produced by a 5-HT or NE deficiency at functionally important receptor sites in the brain, i.e. that brain monoamine systems have a primary direct role in depression [149-150]. Soon it became evident that the monoamine hypothesis in its original form could not explain all of the effects of antidepressants [151-152]. In order to test this hypothesis, a series of studies was conducted to evaluate effects of monoamine depletion on depressive symptoms in depressed patients and in healthy controls. Relapse to 5-HT depletion or to catecholamine depletion was found to be specific to the type of antidepressant treatment and type of depletion. 5-HT or NE/dopamine depletion did not decrease mood in healthy controls and slightly lowered mood in healthy controls with a family history of major depressive disorder. In drug-free patients with major depressive disorder in remission, a moderate mood decrease was found for acute tryptophan depletion only. However, acute tryptophan depletion induced relapse in patients in remission who used serotonergic antidepressants [153]. Depletion studies failed to demonstrate a causal relation between 5-HT and NE with depressive disorder [154-155]. The effects of acute tryptophan depletion on cognition in non-vulnerable participants are independent of mood changes [155]. Even simultaneous disruption of 5-HT and catecholamine systems didn't significantly alter mood in unmedicated depressed subjects [156]. These findings forced a major revision of the classic monoamine hypothesis of depression. According to this revised monoamine theory of depression [148,157] monoamine systems are only modulating other brain neurobiological systems that have more primary role in depression.

3.2. Neurotrophic hypothesis

The neurotrophic hypothesis of depression [5-6,8] supposed that vulnerability to depression can arise as a result of neuronal damage, e.g. after chronic stress, long-term increased levels of glucocorticoids, hypoglycemia, ischemia, effects of neurotoxins or certain viral infections, etc. The therapeutic effects of antidepressants consist in the increased function of the noradrenergic or serotonergic system, leading to increased activity of transcription factor CREB (cAMP response element binding protein), higher expression of neurotrophin BDNF and its receptor *trkB*, and consequently to increased neuronal plasticity and resumption of cellular functions.

According to neurogenic hypothesis [158-159], depression may develop due to the decreased neurogenesis in hippocampus, and antidepressants takes effect through the stimulation of neurogenesis. Hypothesis of cellular plasticity [160] relate the neurotrophic and the neurogenic hypothesis to the statement that depression can be generally caused by damaged cellular plasticity leading to inadequate relations between structure and function. Molecular mechanisms leading to a disturbance of neuroplasticity are not known. The bioenergetic and neurochemical model of bipolar disorder attempts to identify these mechanisms and focuses attention on mitochondrial dysfunctions [9,161].

3.3. Inflammatory and neurodegenerative hypothesis

The central nervous system, endocrine and immune systems use neurotransmitters, cytokines and hormones to communicate among them [162]. Now there is evidence that the activation of the immune system is associated with the symptoms of depression [163-164]. The inflammatory and neurodegenerative hypothesis of depression [165] supposes that depression is associated with both inflammatory processes, as well as with neurodegeneration and reduced neurogenesis. According to this hypothesis, enhanced neurodegeneration and impaired neurogenesis in depression are caused by inflammatory processes, related to the production of oxidative and nitrosative stress, tryptophan catabolites along the indoleamine-2,3-dioxygenase pathway, proinflammatory cytokines and lowered ω -3 polyunsaturated fatty acid status. Anti-inflammatory compounds should be able to counteract at least partly the enhanced neurodegeneration and decreased neurogenesis.

3.4. Mitochondrial hypothesis

Mitochondrial dysfunctions (leading to decreased ATP production, oxidative stress, and induction of apoptosis) occur in the early stages of different neurodegenerative diseases, associated often with mood disorders.

The role of mitochondrial dysfunction during bipolar disorder is supported both by observation of the changes of brain metabolism and by effects of mood stabilizers (lithium and valproate) on mitochondrial functions. Metabolic changes in brain were observed in bipolar disorder by magnetic resonance spectroscopy (MRS). It suggests the presumptions that mitochondrial dysfunctions include impaired OXPHOS, final shift to glycolytic production of energy, general decrease of energy (decreased ATP production), changed concentrations of phosphomonoesters and changed lipid metabolism [9].

mtDNA mutations in the brain, associations of mtDNA polymorphisms and bipolar disorder and changes in gene expression related to mitochondria in the brain were observed [10,166]. Mitochondrial dysfunction hypothesis of bipolar disorder is based on these observations. According to this hypothesis, mtDNA polymorphisms/mutations or mtRNA deletions caused by nuclear gene mutations can cause mitochondrial dysregulation of calcium leading to symptoms of bipolar disorder [10,161,167]. Mitochondrial hypothesis corresponds to, above mentioned, neurotrophic hypothesis because of an important role of calcium signalling pathway in synaptic plasticity regulation.

3.5. Biological markers of mood disorders

Biological markers are defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In medicine, a biomarker is an indicator of a particular disease state or a particular state of an organism.

Identification of biologic markers of mood disorders and factors capable of predicting the response to treatment with antidepressants has not been sufficiently successful [3,168-169].

In accordance to actual neurochemical hypotheses of mood disorders, biological markers have been primarily found at the level of neurotransmitter concentrations, their metabolites or precursors. Subsequently, attention was shifted to the receptor systems, and since the 1990's, intracellular processes have become main interest. The chance to find sensitive and specific biological predictors of antidepressant treatment has been increased, because of introduction of new methods of molecular biology. These methods enable us better observation of cellular processes connected with the transduction of nervous signals in the brain. The choice of parameters, which should be studied as perspective biological markers of mood disorders, have been derived first of all from new findings of signalling pathways involved in neurotransmission and from above mentioned neurochemical hypotheses of mood disorders. From the view of intracellular processes, energetic metabolism, activities of PKC, CREB, BDNF, Bcl-2, glycogen synthase kinase-3, caspases or calcium could play a principal role in findings of biological markers of mood disorders. According to the complexity and connectivity of signalling pathways involved in etiopathogenesis of mood disorders, number of chosen parameters is not final.

4. Antidepressants, mood stabilizers and mitochondrial functions

Antidepressants are used mainly to alleviate mood disorders, such as major depression and dysthymia and anxiety disorders. Mood stabilizers are psychiatric medication used in treatment of mood disorders, which are characterized by intense and sustained mood shifts (e.g. bipolar disorder).

The antidepressant activity of the first generation of antidepressants, tricyclic antidepressants and MAOIs, was explained by their effects on availability of monoamine neurotransmitters. The next generations of antidepressants included selective serotonin reuptake inhibitors (SSRIs), norepinephrine reuptake inhibitors (NRIs), serotonin-norepinephrine reuptake inhibitors (SNRI), noradrenergic and specific serotonergic antidepressants (NaSSAs), norepinephrine-dopamine reuptake inhibitors (NDRI), serotonin antagonist and reuptake inhibitors (SARIs), selective serotonin reuptake enhancer (SSRE), melatonergic agonists (MAGAs), sigma receptor agonists etc. The therapeutic response to antidepressants occurs after long-term treatment; therefore, effects of antidepressants are linked to cellular adaptations including density and/or sensitivity of neurotransmitter receptors and transporters, regulation of signal transduction cascades, and changes in gene expression [170].

Most of mood stabilizers are anticonvulsants (valproate, carbamazepine, and lamotrigine), with an important exception of lithium, which is the oldest and the best known mood stabilizing drug. Some atypical antipsychotics (olanzapine, quetiapine, aripiprazole, risperidone, ziprasidone) have mood stabilizing effects, as well.

Although a wide range of pharmacologically different antidepressants and mood stabilizers is available, molecular mechanisms of their therapeutic effects haven't yet been sufficiently clarified. Relatively little information is known about the association among therapeutic and/or adverse effects of drugs and mitochondrial enzyme activities. Incom-

plete data exist on the effect of pharmacologically selective antidepressants and mood stabilizers on MAO activity. Measurement of both mitochondrial respiration and membrane potential during action of appropriate endogenous and exogenous substances enables the identification of the primary sites of effectors and the distribution of control, allowing deeper quantitative analyses [171].

4.1. Inhibition of MAO

MAO inhibition is the best known direct action of some antidepressants on mitochondrial enzymes. The antidepressant effect of MAOIs has been established more than 50 years ago. Iproniazid became the first MAO inhibitor to be used successfully in the treatment of depression; it is an irreversible and nonselective MAO inhibitor [172]. It is known to act as a pro-drug and can be converted into isopropyl hydrazine which binds covalently to MAO [173]. Clorgyline is an irreversible inhibitor preferential for MAO-A, structurally related to pargyline (MAO-B inhibitor). It has antidepressant activity, and may potentially be useful in the treatment of Parkinson's disease. Selegiline (l-deprenyl) is an irreversible inhibitor preferential for MAO-B; it is used for the treatment of Parkinson's disease, depression and senile dementia. Inhibitors of MAO lose its selectivity at high doses. Moreover, there are feedbacks and interconnections of intracellular signalling pathways which lead to mutual interactions of monoaminergic and other systems [4]. So, inhibiting of MAO-B should influence processes mediated primarily by substrates for MAO-A, and vice versa. The major disadvantage was the incidence of the cheese reaction with those early inhibitors [51].

The selective reversible MAO-A inhibitors such as moclobemide increase the content of 5-HT, NE and dopamine in the brain [174] but did not provoke the cheese reaction. Moclobemide has been extensively evaluated in the treatment of a wide spectrum of depressive disorders and social phobia. Overall, moclobemide appears to be safe and devoid of major side effects, although it is considered as a mild antidepressant, better tolerated by older patients [175-181]. Moclobemide undergoes extensive metabolism with less than 1 % of the dose being excreted unchanged. Metabolic pathways of moclobemide include mainly oxidative attack on the morpholine moiety [182]. However, major metabolites in plasma were found to be less effective MAO-A inhibitors than moclobemide or pharmacologically inactive [183-184].

MAO inhibitors were developed as antidepressants but many drugs, including the oxazolidinone antibacterial agents, share similar molecular properties and have MAO inhibitory activity. These compounds were of interest as potential antidepressants because they could be selective inhibitors of either the A or B isoforms and were usually reversible [53].

Antidepressants which act primarily as 5-HT and/or NE reuptake inhibitors show inhibitory activity towards MAO also. It has been suggested that tricyclic antidepressants exert some of their therapeutic effect by inhibiting MAO [185]. They are able to inhibit MAO-B both *in vitro* [186-187] and *in vivo* [188-189]. However, *in vivo* inhibition of the human platelet MAO-B in the patients taking tricyclic antidepressants was not confirmed by others [190-191]. Five tricyclic antidepressants, amitriptyline, clomipramine, desipramine, imipramine and iprindole, have comparable potencies as inhibitors of MAO in rodent brain and liver [192]. These

antidepressants have been shown to partially protect mouse brain MAO *in vivo* from the irreversible enzyme inhibition produced by subsequent injection of phenelzine [193]. Concentrations of tricyclic antidepressants, which showed a pronounced inhibitory effect on the MAOs activity, were significantly higher than plasma levels of the drug found under therapeutic conditions [194-195]. MAO activity was inhibited after long-term administration of viloxazine, nomifensine, zimelidine, maprotiline, imipramine, amitriptyline, and nortriptyline in systematic studies of Egashira [196-197]. Competitive inhibition of MAO-A and non-competitive inhibition of MAO-B was found for these drugs. Similar results were obtained when different tricyclic antidepressants and SSRIs were examined with isolated rat brain mitochondria [198]. Fluoxetine and norfluoxetine showed affinities both for MAO-A [199] and MAO-B [200]. Fluoxetine and norfluoxetine also significantly inhibited the binding of the specific radioligands to MAO *in vivo*. These results support a potential role of MAO inhibition in the therapeutic effects of fluoxetine.

4.2. Effects of antidepressants on mitochondrial functions

There is relatively little data about effects of antidepressants on mitochondrial functions as summarized in the Table 2. *In vitro* study examined influence of pharmacologically different antidepressants and mood stabilizers on activity both mitochondrial MAO [201] and respiratory chain complexes; imipramine, desipramine, amitriptyline, citalopram, and mirtazapine were found as complex I inhibitors in isolated pig brain mitochondria [202]. In isolated rat liver mitochondria effects of imipramine and clomipramine were compared to classic uncouplers, drugs enhanced ATP synthase activity, hindered ATP synthesis and released respiratory control [203]. In isolated rat liver mitochondria, nefazodone was found as inhibitor of mitochondrial complexes I and IV; buspirone inhibited complex I but had no effect on complex IV. Trazodone did not affect on both complex I and complex IV [204], but decreased oxygen consumption and reduced Na⁺, K⁺-ATPase activity. Trazodone acts also as uncoupler of OXPHOS [205].

Effects of antidepressants on apoptotic markers, e.g. cytochrome *c* release and DNA fragmentation, seem to be different. Various antidepressants exhibited potential anticancer properties and caused cytotoxic effects. Paroxetine, fluoxetine and clomipramine increased levels of apoptotic markers leading to apoptosis in glioma and neuroblastoma cells, whereas imipramine and mianserin do not [206]. Desipramine induced apoptosis in rat glioma cells by activation of caspases, without any change of mitochondrial membrane potential $\Delta\psi_m$ [207]. Fluoxetine and amitriptyline protected PC12 cells from cell death induced by hydrogen peroxide [208]. Amitriptyline and tranylcypromine prevented the loss of mitochondrial $\Delta\psi_m$, over expression of Bax, reduction in Bcl-2 level, cytochrome *c* release, caspase-3 activation, and formation of ROS. In contrast, fluoxetine seemed to have additive toxic effect to 1-methyl-4-phenylpyridinium (MPP⁺) against neuronal cell damage by increasing mitochondrial damage and oxidative stress [209]. Nortriptyline was identified as strong inhibitor of MPT and was observed as potential inhibitor of neuronal cell death; it protected isolated mitochondria against programmed cell death, inhibited release of apoptotic mitochondrial factors and caspases, increased Ca²⁺ retention in mitochondria and delayed the Ca²⁺ induced loss of $\Delta\psi_m$, further leading to neuronal cell death [210-211].

4.3. Effects of mood stabilizers on mitochondrial functions

Mood stabilizers affect multiple sites in intracellular signalling pathways [4]. Main targets of mood stabilizers are neurotrophin BDNF, ERK pathway, and pathways modulated by GSK-3 or Bcl-2 [8,226-227]. Molecular and cellular targets of mood stabilizers include enzymes inhibited by lithium (inositol monophosphatase, inositol polyphosphate 1-phosphatase, GSK-3, fructose 1,6-bisphosphatase, bisphosphate nucleotidase, phosphoglucomutase), enzymes inhibited by valproate (succinate semialdehyde dehydrogenase, succinate semialdehyde reductase, histone deacetylase), targets of carbamazepine (sodium channels, adenosine receptors, adenylate cyclase), and components of signalling pathways regulated by multiple drugs (PKC, cAMP, arachidonic acid) [228]. Furthermore, lithium and valproate reduce transport of myo-inositol into the cells, which leads to reduced PKC activity. Lithium and valproate increase Bcl-2 concentrations [229] and inhibit GSK-3 activity (lithium directly, valproate indirectly). Valproate activates MAPK signalling pathway and regulates stress proteins of ER [230]. Through the effects on Bcl-2 and p53 (proapoptotic protein), lithium affects mitochondria by stabilization of membrane integrity and prevention of MPTPs opening; i.e. by regulating the key process in cell death leading to at least temporary loss of $\Delta\psi_m$, input of water into matrix and equilibration of ions concentrations. Both lithium and valproate have neuroprotective effects based on protection from glutamatergic neurotoxicity by inactivation of NMDA receptors, on activation of cell survival factors such as phosphoinositide 3-kinase/protein kinase B pathway, and on induction of neurotrophic and neuroprotective proteins. Lithium protects against DNA damage, caspases activation, and apoptosis of neurons [231]. Increased concentrations of N-acetyl aspartate (NAA, marker of neuronal viability and functionality) in grey matter after the chronic lithium administration support its strong neuroprotective and neurotrophic effects in humans.

Effects of mood stabilizers on monoaminergic activity have been studied; majority of data is about the effects of lithium. Lithium enhances the antidepressant effect both of MAOIs and inhibitors of the reuptake of 5-HT and/or NE [232-234]. The mode of action for the lithium augmentation of antidepressants is partly mediated by an increase of 5-HT neurotransmission [235-237]. However, lithium could not either inhibit MAO-A or MAO-B in the brain mitochondrial [195,201]. Unipolar and bipolar depressive patients showed significantly higher platelet MAO activity than controls, but there was no significant change in activity after the institution of lithium treatment [191].

Antidepressant	Biological model	Affected mitochondrial function	Reference
Imipramine	Isolated rat liver mitochondria Beef heart submitochondrial particles	Uncoupling effects on OXPHOS (release of respiratory control, hindered ATP synthesis, enhanced ATP synthase activity) Inhibition NADH oxidation, inhibition of ATP synthase	[203]
Imipramine	Rat brain mitochondria	Increased state 3 and state 4 respiratory rates	[212]
Imipramine	Rat liver mitochondria	Increased state 3 and state 4 respiratory rates	[213]

Antidepressant	Biological model	Affected mitochondrial function	Reference
Imipramine, clomipramine, citalopram	Human peripheral lymphocytes and lymphoblasts	Dose-dependent induction of apoptosis	[214,215]
Imipramine, clomipramine, citalopram	Human acute myeloid leukaemia HL-60 cells	Loss in cell viability, increased ROS production, loss of $\Delta\psi_m$	[216]
Clomipramine, desipramine, norfluoxetine, Tianeptine	Rat heart isolated mitochondria and CHO cells	Reductions of $\Delta\psi_m$, decrease in state 3 respiration, inhibition of activities of complexes I, II/III and IV Insignificant change of $\Delta\psi_m$, decrease in state 3 respiration, inhibition of complex I activity	[217]
Tianeptine	Rat liver mitochondria	Inhibited beta-oxidation and TCA cycle	[218]
Fluoxetine	Rat liver mitochondria	Inhibition of state 3 respiration, stimulation of state 4 respiration, decrease of RCR and uncoupling effects on OXPHOS	[219]
Fluoxetine	Rat brain mitochondria	Inhibition of OXPHOS, decreased activity of ATP synthase	[220]
Amitriptyline, fluoxetine	Differentiated rat pheocytochroma PC12 cells	Prevention of the loss of $\Delta\psi_m$, cyt c release, formation of ROS induced by MPP ⁺	[209]
Amitriptyline, fluoxetine	Rat pheocytochroma cells	Attenuation of H ₂ O ₂ neurotoxic effects, upregulation of superoxide dismutase	[208]
Nortriptyline	*ALS mouse	Strong inhibitor of MPT	[210]
Nortriptyline	Mouse model of ischemia	Inhibition of $\Delta\psi_m$, inhibited release of mitochondrial factors and caspase 3 activation	[211]
Nortriptyline	Rat brain mitochondria	Inhibitor of MPT, inhibition of ETC, mild uncoupling	[221]
Fluoxetine and/or Olanzapine	Rat brain homogenates	Increased citrate synthase activity after acute, but not chronic treatment	[222]
Nefazodone Trazodone	Isolated rat liver mitochondria	Severe inhibition of oxygen consumption, inhibition complexes I and IV Modest inhibition of oxygen consumption, inhibition of complex I	[204]
Nefazodone Trazodone	Isolated rat liver mitochondria	Complex I and complex IV inhibitor No effects	[205]
Fluoxetine	Hippocampal synaptic plasma membranes	Increased ATP synthase activity	[223]

Antidepressant	Biological model	Affected mitochondrial function	Reference
Sertraline	Isolated rat liver mitochondria	Uncoupling effects on OXPHOS, inhibition of complex I and complex V activities, induction of Ca ²⁺ mediated MPT	[224]
Venlafaxine, paroxetine, nortriptyline	Rat brain homogenates (after 15 days of drug administration)	Differences in brain areas: increased or unchanged citrate synthase and SDH activities	[225]
Paroxetine, fluoxetine, klomipramine	Rat glioma and human neuroblastoma cell lines	Increased cyt c release, caspase-3-like activity, induction of apoptosis	[206]
Desipramine	Rat glioma cells	Activation of caspases 3 and 9, no changes of $\Delta\psi_m$	[207]

ALS mouse – model of neurodegeneration

Table 2. Effects of antidepressants on mitochondrial functions

Studies have shown effects of mood stabilizing drugs on mitochondria. In isolated brain mitochondria lithium caused desensitisation to calcium, antagonized permeability transition, and diminished cytochrome *c* release [238]. In isolated rat liver mitochondria valproate inhibited OXPHOS [239]. In isolated pig brain mitochondria both lithium and valproate inhibited respiratory chain complexes I and IV [202]. According to study performed in rats [240], valproate reversed the decreased activity of citrate synthase caused by amphetamine and lithium prevented the inhibition. The cytoprotective effect of lithium and valproate was observed after 7 days, of pre-treatment of human neuroblastoma (SH-SY5Y) cells against cytotoxicity resulting from oxidative stress evoked by rotenone and H₂O₂. This effect was not observed after one day of pre-treatment [241]. Chronic treatment of SH-SY5Y cells prevents reduction of methamphetamine-induced reduction of cytochrome *c*, mitochondrial anti-apoptotic Bcl-2/Bax ratio and mitochondrial COX activity [242]. Interestingly, long-term lithium and valproate did not protect SH-SY5Y cells against endoplasmic reticulum stress-induced cytotoxicity [241]. Lithium and carbamazepine could facilitate activation of CREB, valproate and lamotrigine did not affect BDNF-mediated signalling [243]. Thus, these mood stabilizers likely decrease the vulnerability of mitochondrial functions caused by oxidative stress and have neuroprotective effects [241].

Chronic treatment with lithium, valproate and carbamazepine protects against NMDA-mediated toxicity [244]. Interestingly, recent study performed with epileptic children examined the influence of carbamazepine and lamotrigine on mitochondrial functions - both drugs influenced respiratory chain complexes and significantly affected ATP production, carbamazepine decreased the production, oppositely to stimulatory effect of lamotrigine [245]. Carbamazepine interferes in adenylate cyclase pathway: inhibits adenylate cyclase and the synthesis of cAMP [246]. Lamotrigine prevented the toxicity caused by rotenone and MPP⁺ in rat PC12 cells by suppressing the MPT formation, which leads to cytochrome *c* re-

lease and subsequent apoptosis. Though, lamotrigine seems to have neuroprotective effect due to the mitochondrial respiratory complex I inhibition [247].

Effects of mood stabilizers on mitochondrial functions are summarized in the Table 3.

Mood stabilizer	Biological model	Affected mitochondrial function	Reference
Valproate	Rat liver mitochondrial fractions	Inhibition of oxygen consumption rate, sequestration of intramitochondrial CoA	[248]
Valproate	Isolated rat liver mitochondria	State 3 rates of oxygen consumption inhibited	[239]
Valproate	Isolated beef brain α -KGDH	Inactivation of α -KGDH complex	[249]
Valproic acid	Isolated rat hepatocytes	CoA, acetyl-CoA and long chain acyl-CoA fractions decreased (accumulation of valproyl-CoA; without any evidence of this metabolite in brain tissue)	[250]
Valproate and its metabolites	Submitochondrial particles from rat liver	Inhibition of pyruvate uptake	[251]
Valproate	Rat liver mitochondria. Digitonin permeabilized rat hepatocytes	Inhibition of pyruvate-driven OXPHOS. Inhibition of the rate of ATP synthesis (pyruvate as substrate used, no inhibitory effects caused by succinate and glutamate as substrates)	[252]
Valproate and lithium	Rat brain tissue obtained from animals pretreated by d-amphetamine	No modification of complex I, II, III and IV activities after the treatment with valproate and lithium in controls	[253]
Valproate and lithium	Rat brain tissue obtained from animals pretreated by d-amphetamine	Treated animals with lithium and valproate prevented inhibition caused by d-amphetamine	[240]
Valproate and lithium	Rat brain tissue obtained from animals pretreated by d-amphetamine	Reversed ATP synthase activity (increased after d-amphetamine) after lithium and valproate treatment	[254]
Valproate and lithium	Human neuroblastoma and glioma cells	Protective effects against H ₂ O ₂ or rotenone induced cytotoxicity in neuroblastoma cells	[241]
Valproate and lithium	Human neuroblastoma cells	Reduction of methamphetamine-induced reduction of cyt c, antiapoptotic Bcl-2/Bax ratio and COX activity	[242]
Lithium	Plasma synaptic membrane from rat brain	Impaired function of ATP synthase was modulated (reversed by lithium, and prevented by lithium pretreatment)	[255]
Lithium	Isolated brain mitochondria	Desensitisation to calcium, antagonized MPT, diminished cytochrome c release	[238]

Mood stabilizer	Biological model	Affected mitochondrial function	Reference
Lithium	Postmortem human brain cortex	Dose-depedent increased activities of complexes I+III, II+III and succinate dehydrogenase	[256]
Lithium	Human neuroblastoma SH-SY5Y cells	Attenuation of rotenone-induced caspase-3 activation	[257]
Carbamazepine	Rat liver mitochondria	Decreased state 3 respiration, RCR, ATP synthesis, $\Delta\psi_m$	[258]
Carbamazepine	Rat brain mitochondria	Protection against rotenone induced complex I inhibition	[259]
Carbamazepine, lamotrigine	Human white blood cells	Carbamazepine decreased ATP production, stimulatory effect on production by lamotrigine	[245]
Lamotrigine	Human neuroblastoma SH-SY5Y cells	Suppression of MPT formation, attenuation of rotenone-toxicity, inhibition of ROS production	[247]

Table 3. Effects of mood stabilizers on mitochondrial functions

5. Conclusions

Biological markers of depression, predictors of the response to the drug administration and molecular targets of new antidepressants are searched on the basis of recently known hypotheses of affective disorders. We come out mostly from stimuli of neurotrophic hypothesis and mitochondrial hypothesis. According to these hypotheses, the leading role in the pathophysiology of mood disorders and therapeutic effects of antidepressants has mitochondria, which are destined for changes in energetic metabolism of cells. Mitochondrial dysfunctions and thereby impaired neuronal metabolism can lead to disturbances in neuronal function, plasticity and brain circuitry. Impaired functions of mitochondria contribute to a wide range of diseases; the role of mitochondria in the pathophysiology of schizophrenia, bipolar disorder, and major depressive disorder is supported by studies investigating genomic differences, changes of energy metabolism and mitochondrial changes included.

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