REVIEW

Important Role of Mitochondria and the Effect of Mood Stabilizers on Mitochondrial Function

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Summary

Mitochondria primarily serve as source of cellular energy through the Krebs cycle and β-oxidation to generate substrates for oxidative phosphorylation. Redox reactions are used to transfer electrons through a gradient to their final acceptor, oxygen, and to pump hydrogen protons into the intermembrane space. Then, ATP synthase uses the electrochemical gradient to generate adenosine triphosphate (ATP). During these processes, reactive oxygen species (ROS) are generated. ROS are highly reactive molecules with important physiological functions in cellular signaling. Mitochondria play a crucial role in intracellular calcium homeostasis and serve as transient calcium stores. High levels of both, ROS and free cytosolic calcium, can damage mitochondrial and cellular structures and trigger apoptosis. Impaired mitochondrial function has been described in many psychiatric diseases, including mood disorders, in terms of lowered mitochondrial membrane potential, suppressed ATP formation, imbalanced Ca^{2+} levels and increased ROS levels. *In vitro* models have indicated that mood stabilizers affect mitochondrial respiratory chain complexes, ROS production, ATP formation, Ca^{2+} buffering and the antioxidant system. Most studies support the hypothesis that mitochondrial dysfunction is a primary feature of mood disorders. The precise mechanism of action of mood stabilizers remains unknown, but new mitochondrial targets have been proposed for use as mood stabilizers and mitochondrial biomarkers in the evaluation of therapy effectiveness.

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Introduction

Mitochondria as cellular organelles

The mitochondrion is one of the largest organelles in human cells, occupying approximately 25 % of the cytoplasmic volume. Evolutionarily, they are presumed to be descendants of bacteria on the basis of the endosymbiotic hypothesis of mitochondria origin. This hypothesis may explain the origin of the two organelle membranes border the two mitochondrial compartments: the intermembrane space and the matrix. The outer mitochondrial membrane is smooth and permeable to solutes smaller than 5 kDa. The inner mitochondrial membrane (IMM) is mostly impermeable and contains many transport channels. Its surface is enlarged by cristae, with a higher concentration of integral proteins, which enable adenosine triphosphate (ATP) formation (Lodish *et al.* 2013, Srivastava *et al.* 2018). In addition to ATP production, mitochondria have a role in Ca^{2+} homeostasis, production and disposal of reactive oxygen species (ROS), apoptosis regulation and thermoregulation (de Sousa *et al.* 2014).

Mitochondria are highly dynamic organelles that undergo frequent fusion (merging) and fission (dividing). Fission and fusion were likely developed to prevent the

accumulation of mutated mitochondrial DNA. They are optimal tools for the isolating of damaged segments. Disrupted mitochondrial dynamics are often linked to genetic disorders, indicating that mitochondrial dynamics play important roles in mitochondrial physiology (Lodish *et al.* 2013).

Mitochondria as energy factories

The primary function of mitochondria is to use products of glycolysis, proteolysis, or lipolysis and oxygen through a series of a biochemical reactions leading to ATP formation (Andreazza and Nierenberg 2018). ATP is created *via* oxidative phosphorylation (OXPHOS) using the electron transport chain (ETC) as the machinery (Clay *et al.* 2011).

The pyruvate dehydrogenase complex, which converts pyruvate into acetyl-coenzyme A (acetyl-CoA), is able to control carbon entry from two main sources: carbohydrates and glucogenic amino acids. Fatty acids are metabolized in another way; first, they are converted into acyl-coenzyme A, attached to carnitine, and shuttled into the mitochondria. Second, acyl-CoA undergoes β-oxidation and results in the production of acetyl-CoA. Acetyl group from acetyl-CoA is oxidized into CO_2 concurrently with the production of substrates for OXPHOS: the reduced forms of high-energy carriers nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$). The presence of oxygen is necessary to regenerate the oxidized forms of the electron carriers nicotinamide adenine dinucleotide (NAD^+) and flavin adenine dinucleotide (FAD^+) (Lodish *et al.* 2013, de Sousa *et al.* 2014).

Mitochondria function through a highly effective transport gradient in which electrons move from acceptors with less electronegativity to those with greater electronegativity at the same time that the redox reactions involving both, electron donors and acceptors are in progress. Simultaneously, through electron transport, H^+ ions are pumped into the intermembrane space (IMS), increasing the pH in the matrix, which increases its electronegativity, thereby creating proton motive force (PMF) (Divakaruni and Brand 2011, Lodish *et al.* 2013).

The ETC consists of 4 complexes with supramolecular organization, all of which have several prosthetic groups as heme or iron-sulfur clusters. Heme-based prosthetic groups are bound to cytochromes and are able to delocalize accepted electrons due to their porphyrin structure. Every cytochrome *c* (cyt *c*) molecule has a different reduction potential, and the electrons flow

downhill. Iron-sulfur clusters disperse accepted electrons among iron atoms, and their true charge is approximately 2^+-3^+. Complexes I, III and IV are responsible for pumping H^+ into the IMS (Lodish *et al.* 2013, Ohnishi *et al.* 2018).

Complex I, NADH-CoQ oxidoreductase, is a large, multi-subunit enzyme with a noncovalently bound flavin mononucleotide (Ohnishi *et al.* 2018). Complex I serves as an entry point into the ETC and a key component for the respiration. The high-energy carrier NADH transfers two electrons to complex I, which catalyzes the regeneration of the reduced NADH and electrons are transferred to flavin mononucleotides and, then, further through the iron-sulfur cluster to oxidized coenzyme Q10 (CoQ10), also known as ubiquinone, which is reduced to ubiquinol (Hirst 2009). These redox reactions are exergonic, and every transported electron loses some potential in the process. The released energy is used for actively pumping four H^+ across the IMM (Fig. 1) (Lodish *et al.* 2013, Ohnishi *et al.* 2018). This reaction is completely reversible, and through PMF, the electrons can be transferred backward, while a massive amount of superoxide anion is produced in a process known as reverse electron transfer (Dubouchaud *et al.* 2018). Complex I is easily inhibited by psychopharmaca; therefore, it is an interesting target for further research (Hroudova and Fisar 2010).

$$NADH + CoQ + 6H^+_{in} \rightarrow NAD^+ + H^+_{in} + CoQH_2 + 4H^+_{out}$$

Complex II, succinate dehydrogenase, is a four subunit lipoprotein with a large soluble domain and a smaller integral-membrane domain (Hroudová and Fišar 2013, Iverson 2013). It is the smallest respiratory chain complex and is fully encoded by nuclear DNA (Grimm 2013). Complex II partly consists of covalently bound flavin adenine dinucleotide, several redox active centers, iron-sulfur clusters and quinone binding sites (Cecchini 2013). Succinate dehydrogenase enables the side entry of high energy carriers into the ECT, specifically reduced $FADH_2$, which is formed in the Krebs cycle during the oxidation of succinate to fumarate, which occurs in the soluble domain of complex II (Grimm 2013, Iverson 2013). Complex II has a role in OXPHOS by participating in the reversible oxidoreduction of the quinol and quinone (Grimm 2013). Succinate dehydrogenase is directly involved in the Krebs cycle: two electrons are released during succinate-fumarate oxidation are transferred *via* NAD^+ through

iron-sulfur cluster to CoQ10 (ubiquinone), reducing it to ubiquinol (Fig. 1) (Lodish *et al.* 2013).

$$Succ + CoQ \rightarrow Fum + CoQH_2$$
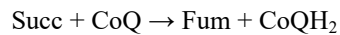
First, a partially reduced semiquinone radical is formed, which is immediately stabilized after the second electron is transferred. This mechanism most likely serves prevents excessive electron leakage (Grimm 2013). All reactions catalyzed *via* succinate dehydrogenase are reversible, although they are more efficient in their preferred catalytic direction. However, this enzyme reversibility may link complex II with some metabolic diseases (Cecchini 2013). CoQ10 is the main transporter of electrons from complex I and II to complex III (Rodriguez-Hernandez *et al.* 2009). Energy released during this step is not sufficient to pump H^+ into the IMS because part of the energy is absorbed during the reduction of CoQ10; thus, the PMF is not generated by this reaction (Lodish *et al.* 2013). Recent studies have suggested that the subunits of complex II might have tumor-suppressor gene function. Complex II can be then involved in apoptosis, thereby acting as a pro-apoptotic sensor and transducer of apoptotic signals (Grimm 2013).

Complex III, CoQ : cyt *c* oxidoreductase, is a transmembrane enzyme complex consists of two centers, Q_i facing the matrix and Q_o oriented toward to IMS, and three main subunits: cyt c_1, the Rieske center and cyt *b* (Iwata *et al.* 1998, Hroudová and Fišar 2013). Complex III catalyzes the oxidation of one molecule of reduced coenzyme Q (CoQH_2) and the reduction of two molecules of cyt *c*. It pumps $4 H^+$ into the IMS and absorbs $2 H^+$ from the matrix in a two-step process called the Q cycle (Speijer 2018).

$$CoQH_2 + 2cyt\ c^{3+} + 2H^+ \rightarrow CoQ + 4H^+ + 2cyt\ c^{2+}$$
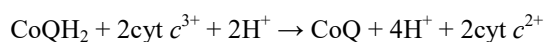
One molecule of CoQH_2 is oxidized at the Q_o center, two protons are released into the IMS, two electrons are released and CoQ dissociates from complex III. However, each cyt *c* is can carry only one electron, which is the reason that the Q cycle is a two-step reaction. The first electron travels *via* the high-potential chain through the Rieske center (iron-sulfur clusters) and cyt c_1 and finally reduces cyt *c*. The second electron travels *via* a low-potential chain (Q_i center) through cyt b_L and b_H to partially reduce CoQ and create a stable semiquinone radical. The second step of the Q cycle is exactly the same as that of a new CoQH_2

binding to complex III, and the second electron completes the reduction of semiquinone. Complex III consumes $2 H^+$ protons from the matrix, and the reduced CoQH_2 is recycled (Fig. 1). Altogether, a normally operating complex III both produces and consumes CoQH_2 (Lodish *et al.* 2013, Speijer 2018).

Complex IV, cytochrome *c* oxidase, consists of 13 subunits, of which only three form the catalytic core of the complex. Complex IV enables the terminal reduction of oxygen to H_2O (Hroudová and Fišar 2013, Lodish *et al.* 2013).

$$4cyt\ c^{2+} + 8H^+_{in} + O_2 \rightarrow 4cyt\ c^{3+} + 2H_2O + 4H^+_{out}$$
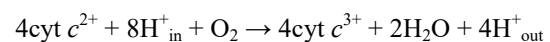
Reduction proceeds partially when 4 molecules of reduced cyt *c* bind sequentially to complex IV and transfer the electron from its heme first to the Cu_a^{2+} ions, then to the heme in cyt *a*, next to the Cu_b^{2+} ions and finally to the heme of cyt a_3. All together, these results create the oxygen reduction center, creating four molecules of H_2O (Fig. 1). During this process, another four H^+ are translocated (2 per every ½ of O_2) across the membrane (Lodish *et al.* 2013). The important regulator of this complex is the protein kinase A/cyclic adenosine monophosphate (PKA/cAMP) signaling pathway, which stimulates the phosphorylation of subunit IV and increases the activity of complex IV (Bouchez and Devin 2019).

Complex V, ATP synthase, is the fifth and the last enzyme of the OXPHOS process and contains two functional domains: F_O and F_1. F_O is a domain with three types of integral membrane proteins – *a*, *b* and *c*. Protein *a* serves as an ion channel and is rigidly connected to *b* and protein *c* forms a "*c* ring". F_1 is a hydrophilic catalytic domain containing five polypeptides with the composition $\alpha_3\beta_3\gamma\delta\epsilon$ that are strongly bound to the F_O at the surface of the membrane. F_1 contains the catalytic machinery for both, ATP synthesis and hydrolysis. The domains are connected *via* two stalks: subunit γ of the F_1, which is firmly bound to the rotating cavity of the F_O "*c* ring", and subunit *b* of F_O, which serves as a stator and prevents the $\alpha_3\beta_3$ hexamer situated on the top of subunit γ from rotating (Fig. 1) (Jonckheere *et al.* 2011, Lodish *et al.* 2013, Neupane *et al.* 2019). Complex V exists as both a monomer and a dimer supercomplex, which optimizes cristae shape and proton flow (Barca *et al.* 2018). ATP synthase is the smallest biological nanomotor and is responsible for ATP creation, which it generates using a proton gradient with membrane potential as a battery.

This battery is powered by decreased pH and a higher concentration of H$^+$ ions in the IMS and increased pH and a lower concentration of H$^+$ ions in the mitochondrial matrix. This situation is a result of H$^+$ pumping across the IMM during electron movement through the ETC. The electrochemical energy that is thus generated is translated to the PMF: H$^+$ ions return to the matrix through the *a* subunit of the F$_O$ domain and power ATP synthesis. The binding-change mechanism is describes the rotation mechanism of ATP synthase during the synthesis of ATP (Neupane *et al.* 2019). All three β subunits are able to bind adenosine diphosphate and phosphate to create ATP during indirect coupling with the proton flow of the exoplasmic medium. The PMF is used for the rotation of the "*c* ring" with subunit γ to induce cyclical changes in the β subunits during the 360° turnover. There are three conformational states of subunit β: open, loose and tight, all of which have a different affinity for substrates and products. At least two protons must past through the

membrane for synthesis of one molecule of ATP. Synthesis and hydrolysis of ATP depend only on the direction of the rotation (Lodish *et al.* 2013, Neupane *et al.* 2019). When the IMM is not sufficiently polarized, complex V acts as an ATP hydrolase and uses released energy from the hydrolyzed ATP to move the H$^+$ protons uphill and restore the Δp (Nesci *et al.* 2016). However, Liu *et al.* (2016) disagree with the conventional model that indicates reliance on the rotating "*c* ring". In their opinion, the model is defective because the number of c subunits (8-15) is indivisible by the number of rotations (3x120° = 360°). They propose an alternative rotary model, inspired by the mechanism of a retractable click ballpoint pen, in which the α$_3$β$_3$ hexamer turns instead of the "*c* ring" (Liu *et al.* 2016). Complex V is able to undergo dimerization and oligomerization, which facilitates ATP synthesis and is beneficial for the cell (Jonckheere *et al.* 2012).
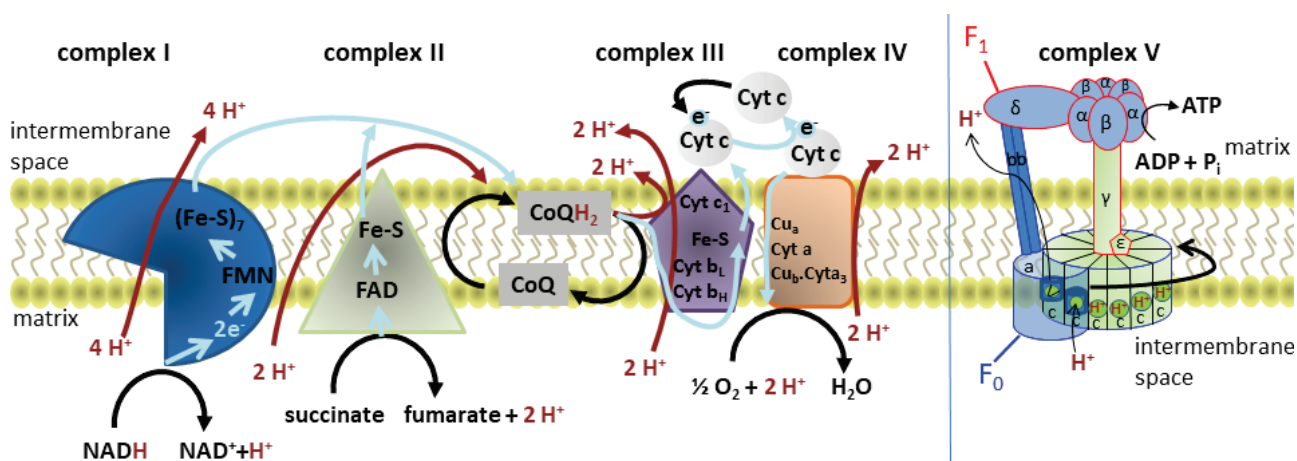

Fig. 1. The electron transport chain and structure of ATP synthase (adapted from Lodish *et al.* 2013). Electrons (blue arrows) from reduced nicotine adenine dinucleotide (NADH) move through **complex I** *via* flavin mononucleotide (FMN) and iron-sulfur clusters (Fe-S) and together with 2 protons, they bind oxidized coenzyme Q (CoQ) to form reduced coenzyme Q (CoQH$_2$). The electron flow enables 4 H$^+$ (red arrows) to be pumped into the intermembrane space. **Complex II** enables electron side entry and the electrons move from succinate through oxidized flavin adenine dinucleotide (FAD$^+$) and Fe-S form CoQH$_2$. Electrons flow from CoQH$_2$ to **complex III** and then *via* cytochrome *c* (Cyt *c*) to **complex IV**. In total, 10 H$^+$ per one NADH or 6 H$^+$ per one FADH$_2$ are translocated into the intermembrane space. **Complex V** is formed from the stator (blue) and rotor (green). The F$_0$ domain of ATP synthase consists of 3 **a** and 3 **b** subunits, and 10 **c** subunits, which form the c-ring. Subunit **a** contains the H$^+$ ion half-channel the mediates proton movement across the membrane. The subunits **α** and **β** of F$_1$ form a hexamer on the top of the **γ** subunit that is inserted into the c-ring.

Mitochondrial ROS production

ROS are highly unstable molecules which can damage different cellular structures, e.g. lipids, proteins and nucleic acids. The most common forms of ROS are superoxide anion, hydrogen peroxide and hydroxyl radical. The physiological concentration of ROS is important for maintaining homeostasis and transducing signals, whereas massive ROS production is connected

with the induction of apoptosis, necrotic cell death, and pathophysiological consequences (Lanciano *et al.* 2013).

In mitochondria, ROS are byproducts of OXPHOS, which couple substrate with adenosine diphosphate phosphorylation. This coupling is not complete because some protons are able to return to the matrix *via* other pathways that enable them to bypass ATP synthase. This process is known as a basal proton

leak (Jastroch *et al.* 2010). Electron leakage occurs when electrons avoid some part of the ETC and partially reduce oxygen to create superoxide, which is superoxide anion in aqueous environments. Superoxide anion may be converted to hydrogen peroxide, catalyzed by superoxide dismutase, which is transformed into the most damaging product: hydroxyl radical (Jastroch *et al.* 2010, Lanciano *et al.* 2013). In OXPHOS superoxide is generated mostly by complex I and complex III. Complex I releases it into the matrix, and complex III releases it on both sides of the IMM (Hroudová and Fišar 2013). There are several ways in which ROS escape out of the mitochondrial matrix. Hydrogen peroxide is able to cross phospholipid barriers, but membrane pores such as mitochondrial permeability transition pore (mPTP), aquaporins and anion channels play crucial roles (Daiber *et al.* 2017).

There are also other sources of mitochondrial ROS, such as monoamine oxidase, catabolizes monoamines and produce hydrogen peroxide. Another mitochondrial enzyme, α-ketoglutarate dehydrogenase, produces H_2O_2, especially when the ratio of NADH and NAD^+ is high (Hroudová and Fišar 2013). Mitochondria can also stimulate neighboring mitochondria to release more ROS in a process called ROS-induced ROS release. ROS are able to activate inner membrane anion channels, the mPTP, and ATP-sensitive K^+ channels to disrupt mitochondrial membrane potential. High amounts of NADH and $FADH_2$ must be consumed to compensate for the activation of these channels, which causes even greater production of ROS (Bertero and Maack 2018). Interestingly, the production of ROS is lower when complex I and complex III assemble to form a supercomplex (Bolanos *et al.* 2016).

Under physiological conditions, ROS are neutralized by and antioxidant system consisting of different enzymes, such as superoxide dismutase, catalase, glutathione peroxidase and glutathione transferase. The superoxide is converted to hydrogen peroxide by superoxide dismutase and is then eliminated by glutathione peroxidase or peroxiredoxin. This system, together with other antioxidant molecules, such as coenzyme Q10, creatine and tocopherol, protects tissues from oxidative damage, but its efficiency might be decreased under pathophysiological conditions (Wang 2007, de Sousa *et al.* 2014, Bertero and Maack 2018).

Increased production of ROS occurs when the membrane potential is low, mitochondria are depolarized or a response is mounted based on hypoxia or calcium signaling (Angelova and Abramov 2018).

Overproduction of ROS or dysregulation in the antioxidant system damages lipids, proteins and nucleic acids and the structures of which they are part (Bolisetty and Jaimes 2013). Prolonged overproduction causes oxidative stress and induce cell death, which is associated with many pathologies, including neurodegeneration, obesity or diabetes (Mailloux and Harper 2012). Mitochondrial permeability is largely increased under inflammatory conditions, which enables even more ROS to escape to the cytosol (Daiber *et al.* 2017). Complex I generates a significant amount of superoxide anions during reverse electron transfer, during which electrons are transferred backwards, from quinone to NAD^+ (Dubouchaud *et al.* 2018). These superoxides are especially likely to be produced under hypoxic conditions. During hypoxia, electron flow stops, and the mitochondrial membrane potential drops. ATP is then taken up by mitochondria from the cytosol and hydrolyzed by ATP synthase, and the mitochondrial membrane potential is restored. However, the impaired electron flow leads to only partial oxygen reduction and contributes to increased ROS production (Bernardi *et al.* 2015). Complex II is considered to be an important regulator of the ROS production by complexes I and III and may be a major source of ROS only during heart failure (De Giusti *et al.* 2013).

The mitochondrial dysfunction and the increased ROS production are probably one of the main factors in brain aging processes. During the aging, the number of defective mitochondria that produce more ROS is increased and the antioxidant system is also less effective. Decreased OXPHOS capacity and mitochondrial DNA damage is also described (Hroudová and Fišar 2013, Cedikova *et al.* 2016). Because the brain is the greatest oxygen consumer in the body, brain cells are the most vulnerable to oxidative damage (Wang 2007). In addition, ROS and reactive nitrogen species are also considered key factors in cardiovascular and inflammatory diseases. Superoxide acts as a direct antagonist of nitric oxide, which is endogenous vasodilator. Their reaction produces peroxynitrite which leads to endothelial dysfunction of vessels (Daiber *et al.* 2017).

Mitochondrial ROS and signaling

The initial studies conducted in 1998 revealed that mitochondria release hydrogen peroxide under hypoxic conditions. Increased levels of hydrogen peroxide activate hypoxia-inducible factor, which is important transcription factor for the metabolic

adaptation to low oxygen levels (Chandel *et al.* 1998). Currently, ROS are considered the secondary signaling messengers; that is, they change the redox state of the signal transduction proteins (Lenaz 2012). The signaling tasks of ROS in mitochondria are both short-term (redox signaling) and long-term (redox regulation of transcription). They influence several different systems: bridge energy metabolism to inflammatory responses *via* redox-sensitive molecules such as nuclear factor erythroid 2-related factor 2 (Nrf2) and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB); link bioenergetics, autophagy and circadian control; participate in phospholipase activation; associate with oxygen sensing in astrocytes and breathing regulation; and regulate cellular signaling in proliferating cells (Bolanos *et al.* 2016). A mild increase in ROS generation is associated with the separation of the Nrf2 protein from Keap1 (marker for ubiquitin-dependent proteasomal degradation) and the translocation of Nrf2 to the nucleus and its binding with the antioxidant response element (ARE). The Nrf2-ARE pathway is a very important component of cellular antioxidant, stress adaptation and anti-inflammatory defense systems. Another oxidative stress-responding transcription factor is NFκB, which is activated by hydrogen peroxide. Although mild oxidative stress is increased upon activation of NFκB, higher concentrations of ROS oxidize and inactivate NFκB (Bolisetty and Jaimes 2013, Indo *et al.* 2017). ROS are markers during fuel sensing and use and also serve as important regulators of hypothalamic neuropeptide-Y and pro-opiomelanocortin neurons to regulate food intake and body weight (Gyengesi *et al.* 2012). ROS may also activate extracellular endopeptidases referred to as matrix metalloproteinases and influence cell proliferation and differentiation, transcriptional regulation, wound healing, tissue remodeling and other functions (Indo *et al.* 2017).

Mitochondria as Ca^{2+} regulators

Mitochondria play crucial roles in intracellular Ca^{2+} homeostasis by regulating Ca^{2+} uptake through the Ca^{2+} uniporter and Ca^{2+} efflux *via* Na^+/Ca^{2+} exchanger or mPTP, which is very important for synaptic plasticity and for the subsequent regulation of gene transcription (Ca^{2+} ions activate Ca^{2+}/calmodulin-dependent kinases) (Wang 2007, Srivastava *et al.* 2018). Mitochondrial Ca^{2+} also regulates ATP production, mitochondrial metabolism and cell death (Giorgi *et al.* 2018).

The outer mitochondrial membrane is permeable to Ca^{2+} through voltage-dependent anion channels, which enable Ca^{2+} to enter into the IMS. Mitochondria serve as high-capacity transient Ca^{2+} stores. There is a finite capacity for mitochondrial Ca^{2+}. In high Ca^{2+} levels, mitochondria maintain low Ca^{2+} forming calcium phosphate precipitate with inorganic phosphate (Feissner *et al.* 2009). Ca^{2+} cross the IMM *via* the Ca^{2+} uniporter (a selective Ca^{2+} channel) when the Ca^{2+} concentration falls below the submicromolar threshold (rising phase). This transport is possible due to the large negative potential across the IMM. Subsequently Ca^{2+} is released *via* a Na^+-dependent Na^+/Ca^{2+} exchanger or Na^+-independent H^+/Ca^{2+} exchanger (both inhibited by Bcl-2 proteins). This Ca^{2+} cycle is likely linked with the Ca^{2+} release channels of the endoplasmic reticulum (comprising inositol triphosphate and ryanodine receptors), which serves as a buffer for both intracellular and extracellular Ca^{2+}, enabling mitochondria to participate in Ca^{2+} signal transduction. Disruptions in mitochondrial membrane potential reduce the ability of mitochondria to maintain Ca^{2+} homeostasis and result in cell damage. The mPTP connect the outer and inner mitochondrial membrane and is composed of an adenine nucleotide translocator, a voltage-dependent anion channel and the modulatory protein cyclophilin D (Brini 2003, Camello-Almaraz *et al.* 2006, Wang 2007, D'Orsi *et al.* 2017). Some studies have suggested that the mPTP is formed from ATP synthase dimers through conformational change, but the specific mechanism of its creation remains unknown (Bernardi *et al.* 2015). Studies have proposed two gating models of mPTP: one that is irreversible and leads to permanent pore opening and ultimately to cell death and one which the opening is reversible and transient (Hou *et al.* 2014). Massive mitochondrial Ca^{2+} concentration might accelerate metabolic enzymes and activate the mPTP opening (resulting in mitochondrial membranes becoming permeable for any molecule smaller than 1.5 kDa), which permits Ca^{2+} and proapoptotic molecules, such as apoptosis-inducing factor and cyt *c* (from complex III), to cross which consequently results in cell death (Camello-Almaraz *et al.* 2006, Wang 2007, D'Orsi *et al.* 2017). Not all mitochondria are equally susceptible to Ca^{2+}-induced mPTP opening. Drahota *et al.* (2012) proved that cardiac mitochondria of neonatal rats are more resistant to the Ca^{2+} overload than adult rats. This observation was only confirmed for the cardiac, not the liver mitochondria, probably because of the higher ischemic tolerance of the neonatal heart (Drahota *et al.* 2012). The mPTP opening is under control of the Bcl-2 family of proteins. This

family consists of anti-apoptotic proteins such as Bcl-2 and Bcl-xL, which maintain the mPTP in a close state, and pro-apoptotic proteins such as Bax and Bak, which induce mPTP opening and facilitate the transfer of Ca^{2+} from the ER. The results showed that ROS are able to increase Ca^{2+} concentration by internal release and disrupt Ca^{2+}-buffering system. It could be said that, in general, mitochondrial inhibitors such as rotenone, myxothiazol or antimycin A decrease Ca^{2+} oscillation and ROS production. Additionally, any Ca^{2+} mobilization in mitochondria is a signal for metabolic enzymes to increase productivity, which leads to greater production of ROS; thus, there is a direct connection between the metabolic state and ROS production (Camello-Almaraz *et al.* 2006, Wang 2007, D'Orsi *et al.* 2017). Because Ca^{2+} is part of apoptotic cascade initiation, it is not surprising that many diseases, especially those of a neurodegenerative nature, have been associated with altered Ca^{2+} homeostasis and abnormal patterns of Ca^{2+} signals. Disturbances in Ca^{2+} signaling are very often connected with tissue dysfunction, and it has been proven, that early mitochondrial Ca^{2+} defects are involved in the pathogenesis of Huntington's disease (Duchen 2000, Brini 2003).

Mitochondrial dysfunction and psychiatric diseases

Mitochondria might play a crucial role in the pathogenesis of psychiatric disorders, such as depression, anxiety, schizophrenia and bipolar affective disorder (Hroudova and Fisar 2011). The impaired function of OXPHOS and decreased energy production could easily endanger the brain, very dependent on energy supplies. The brain represents around 3 % of body mass but use around 20 % of the oxygen and 25 % of the glucose. Alterations in mitochondrial functions could have the negative impact on the energy consumption of the brain, and increase the vulnerability to psychiatric disorders (Filiou and Sandi 2019).

In brief, wide range of mitochondrial dysfunctions was observed in patients with psychiatric diseases. Polymorphisms and mutations in mitochondrial and nuclear DNA leading to dysregulations of Ca^{2+}, the abnormal cellular energy and metabolism, the decreased pH and ATP formation, the impaired function of respiratory complexes and enzymes, and increased levels of ROS. The *post-mortem* examination of patients' brains revealed also anatomical and neuroanatomical

abnormalities. More data could be found in the topic-related literature (Jou *et al.* 2009, Hroudova and Fisar 2011, Manji *et al.* 2012, Toker and Agam 2015).

Several studies suggest the possibility that damaged bioenergetics in circulating platelets might project impaired mitochondrial functions in metabolically active organs and help monitor the treatment in patients with Alzheimer´s disease or depression. In platelets of depressive patients, the decreased mitochondrial respiration and the drop in maximal capacity of ETC was described. In patients with Alzheimer´s disease, the decreased activity of the enzymes of citric acid cycle, the complex III and IV, the increased levels of nitric oxide which form peroxynitrite in reaction with superoxide, and the decreased maximal capacity of ETC was described (Fisar *et al.* 2019, Petrus *et al.* 2019). Fisar *et al.* (2019) observed reduced activity of the citrate synthase and increased activity of the complex I in patients with Alzheimer´s disease, and increased activity of the complex II in patients with the Alzheimer´s disease and depression.

Effects of psychopharmaca on mitochondrial functions

Disrupted mitochondrial functions, manifesting as increased oxidative stress, decreased energy production and Ca^{2+} imbalance have been observed across the whole spectrum of psychiatric disorders (Quiroz *et al.* 2008, Srivastava *et al.* 2018). Therefore, how psychopharmaca affect mitochondrial functions is a very interesting phenomenon (Clay *et al.* 2011). Generally, changes due to mood stabilizers, such as decreased intracellular pH, globally upregulated or downregulated mitochondrial genes, increased expression of the antiapoptotic gene *BCL2* and increased Ca^{2+} storage capacity in the ER have been observed in the brains of patients. Several studies have hypothesized that mood stabilizers induce mitochondrial migration to synaptic terminals, which influences mitochondrial functions and neurotransmitter release and uptake (Scaini *et al.* 2016). This review is focused on drugs mainly or potentially used in bipolar affective disorder therapy.

Lithium

Lithium (Li) has protective functions in human cells. It blocks tyrosine phosphorylation of the 2B subtype of the N-methyl-D-aspartate receptor and prevents massive Ca^{2+} influx and excitotoxicity. Li levels

in patients with bipolar affective disorder during depressive episodes and complex I activity are positively correlated. Study results also suggest that Li enhances mitochondrial respiration, decreases the proapoptotic enzyme glycogen synthase kinase-3 and inhibits the expression of proapoptotic genes Bax and p53 while simultaneously stimulating antiapoptotic Bcl-2 gene expression (Machado-Vieira *et al.* 2009, Cikankova *et al.* 2017). Interesting connection also exists between Li, Ca^{2+} and the mPTP. Li is able to augment the mitochondrial Ca^{2+} capacity, desensitize mitochondria against Ca^{2+}, inhibit calcium-mediated formation of mPTP to suppress membrane depolarization, swelling and the release of cyt *c* from the mitochondria of rat brain and liver and mitochondria isolated from heart tissue. It also prevents the release of Ca^{2+} from the ER by blocking the inositol monophosphatase pathway (Shalbuyeva *et al.* 2007). The same protective effect against Ca^{2+} overload was also observed in rat brain mitochondria. In homogenates of human prefrontal cortex cells, Li increased the activity of mitochondrial complexes I, II and III. Li also promoted the expression of the scavenger glutathione transferase (Clay *et al.* 2011). In the rat mania model, Li stimulated the activity of complex I in the prefrontal cortex (Valvassori *et al.* 2010). In *post-mortem* brain tissue, Li dose-dependently increases complex I activity (Maurer *et al.* 2009). Some studies have demonstrated the inhibition of ROS formation and increased glutathione levels after Li application in rat cerebral cells (Machado-Vieira *et al.* 2009). Li also had a cytoprotective effect. Li treatment inhibited aluminum-induced cyt *c* translocation, prevented Bcl-2 activity from decreasing and inhibited pro-caspase-3 cleavage in rabbits (Ghribi *et al.* 2002). Li also attenuated rotenone-induced proapoptotic caspase-3 activation (King *et al.* 2001). In another rotenone-Li experiment, Li reduced complex I dysfunction and suppressed ATP production, cellular mortality and apoptosis, and DNA methylation and hydroxymethylation in rat neurons (Scola *et al.* 2014).

However, not all the articles claim only a positive effect of Li on mitochondria and cells. Li lowered complex IV activity in mitochondria isolated from pig brain (Hroudova and Fisar 2010). Because of complex I activity stimulation, it came as no surprise that Li enhanced ROS formation such that mitochondrial structures were damaged. The results showed a decrease in antioxidants and a drop in mitochondrial membrane potential in rat hepatocytes after Li treatment (Eskandari *et al.* 2012). In mitochondria isolated from rat heart, Li

concentrations from 75-1,000 µM inhibited complex II activity and ATP formation, enhanced ROS generation and the activity of proapoptotic caspase-3, caused swelling, and abrogated the mitochondrial membrane potential (Salimi *et al.* 2017). Similar to the action of VPA, the effect of Li likely depends on many factors.

Mood stabilizing anticonvulsants

Valproate (VPA) is often associated with the disruption of mitochondrial functions. It has been established, that VPA blocks the entry of long-chain fatty acid into mitochondria (and β-oxidation) by lowering cofactors such as carnitine and CoA. It also enhances ROS formation, mostly by inhibiting complex II activity and inducing mPTP opening. Higher ROS levels and enhanced mPTP formation lead to a decrease in membrane potential, swelling and release of the cyt *c* and apoptosis. In rat digitonin-permeabilized hepatocytes, VPA notably inhibited ATP synthesis and pyruvate oxidation when pyruvate was used as a substrate for respiratory reactions. This effect was not observed when succinate or glutamate/malate was used as a substrate gradient (Silva *et al.* 1997). These results presumed an interaction between VPA and pyruvate, which was confirmed by Aires *et al.* (2008). VPA and its metabolites inhibited pyruvate uptake in inverted submitochondrial vesicles, which impaired the mitochondria as described above (Aires *et al.* 2008). Inhibition of 2-oxoglutarate and glutamate-driven OXPHOS has been described in rat liver mitochondria (Luis *et al.* 2007). Structural abnormalities in the ETC proteins and VPA inhibit complex I and IV activity and decrease superoxide dismutase (Finsterer and Zarrouk Mahjoub 2012, Cikankova *et al.* 2017, Finsterer and Scorza 2017, Costa *et al.* 2018). VPA decreased complex I and IV activity in mitochondria isolated from pig brain and facilitated mitochondrial cholesterol transport in Y1 adrenocortical cells (Hroudova and Fisar 2010, Brion *et al.* 2011).

In contrast, some studies confirmed the inhibition of cyt *c* release, increased Bcl-2 gene expression and reduced apoptosis *via* inhibition of the proapoptotic enzyme glycogen synthase kinase-3. Cell protection from glutamate-induced Ca^{2+} overload and excitotoxicity was also observed (Kazuno *et al.* 2008, Bachmann *et al.* 2009, Kato 2011, Cikankova *et al.* 2017). A similar mitochondria-stabilizing effect was observed in a rat mania model study. Rats pretreated with VPA, in addition to the same results found for LIT, showed lower amphetamine-induced citrate synthase and

succinate dehydrogenase inhibition (Correa *et al.* 2007, Feier *et al.* 2013). VPA also reversed ouabain-induced alterations to the Krebs cycle and mitochondrial enzymes and protected mitochondria from ouabain-induced lipid peroxidation and superoxide formation (Lopes-Borges *et al.* 2015, Valvassori *et al.* 2015). Chronic treatment with therapeutic doses of VPA and Li doubled Bcl-2 levels in the frontal cortex of rats (Quiroz *et al.* 2008). This gene expression was likely mediated *via* the inhibition of histone deacetylase because deacetylated histones inhibit transcription (Clay *et al.* 2011). The influence on Bcl-2 seems to be crucial for the beneficial effect of VPA on mitochondria (Bachmann *et al.* 2009).

The effect of VPA on mitochondrial functions likely depends on several factors, such as the specific type of cell population, presence of mitochondrial pathophysiology, cytotoxic stimulus and, of course, the concentration and duration of VPA treatment (Lai *et al.* 2006). It seems that VPA confers its cytoprotective effects mostly in the presence of another cytotoxic signal, whereas VPA alone tends to damage mitochondrial functions.

Carbamazepine decreases mitochondrial respiration, ATP production and membrane potential and inhibits the Ca^{2+}-induced swelling of rat liver cells (Cikankova *et al.* 2017, Finsterer and Scorza 2017).

Lamotrigine effectively inhibits the cytotoxic effect of rotenone and 1-methyl-4-phenypyridinium on PC12 cells, mostly by maintaining the mitochondrial membrane potential, preventing the opening of mPTP and increasing the levels of glutathione (Kim *et al.* 2007). The possible neuroprotective effect of lamotrigine may be mediated by respiratory complex I inhibition (Hroudova and Fisar 2011).

Conclusions

Mitochondria produce ATP supplies using substrates from proteins, lipids and carbohydrate metabolism. In addition to ATP synthesis, mitochondria participate on buffering of free Ca^{2+} concentration, maintaining of physiological levels of Ca^{2+}, and produce and regulate ROS, trigger intrinsic apoptotic pathway and participate on thermogenesis. These molecules serve as signaling molecules, are involved in the overproduction of ROS or the decreased activity of the antioxidant system damage cellular structure, leading to apoptosis or necrosis and are connected with aging and the pathophysiology of many diseases, including mood disorders.

Altered mitochondrial functions, e.g. suppressed ATP formation, reduced mitochondrial respiratory complex activity, overproduction of ROS or/and insufficient activity of the antioxidant system, and impaired Ca^{2+} balance have been observed in affected neurons in people with mood disorders and/or being treated with mood stabilizers. The dysfunctional mitochondrial hypothesis is one of current hypotheses attempts to explain the origin of mood disorders. Many studies have confirmed that mood stabilizers affect mitochondrial functions, even though the exact mechanism or localization of action is unknown. Both inhibition and stimulation of mitochondrial functions was both observed as a result of psychopharmaca treatment. Therefore, changes in mitochondrial parameters induced by mood-stabilizing drugs support the suggestion that mitochondrial dysfunction could be a primary feature of mood disorders. Further knowledge requires the investigation of other psychopharmaca used in bipolar disorder treatment, e.g. antidepressants, benzodiazepines and antipsychotics. The identification of the mechanism(s) of psychopharmaca action, new drug that target mitochondria, and measurable markers of therapy effectiveness is the focus of current biological psychiatry research.

Conflict of Interest
There is no conflict of interest.

Abbreviations
ARE – antioxidant response element, ATP – adenosine triphosphate, CoA – coenzyme A, CoQ – oxidized coenzyme Q10, $CoQH_2$ – reduced coenzyme Q10, cyt *c* – cytochrome *c*, ETC – electron transport chain, FAD^+ – oxidized form of flavin adenine dinucleotide, $FADH_2$ – reduced form of flavin adenine dinucleotide, IMM – inner mitochondrial membrane, IMS – intermembrane space, Li – lithium, mPTP – mitochondrial permeability transition pore, NAD^+ – oxidized form of nicotinamide adenine dinucleotide, NADH – reduced form of nicotinamide adenine dinucleotide, NFκB – nuclear factor kappa-light-chain-enhancer of activated B cells, Nrf2 – nuclear factor erythroid 2-related factor 2, OXPHOS – oxidative phosphorylation, PMF – proton motive force, ROS – reactive oxygen species, VPA – valproate.

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