Common aspects of neuroplasticity, stress, mood disorders and mitochondrial functions

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Motto: **"*We are what we are thanks to the past.*"**

Abstract

Neuroplasticity is a fundamental mechanism of neuronal adaptation to external and internal stimuli. There are evidences that chronic stress and mood disorders disrupt neuroplasticity, while antidepressant treatment can enhance neuroplasticity. Mitochondria strongly affect many intracellular processes coupled to plasticity and neuron survival. Mitochondrial dysfunctions are assuming an increasingly important role in hypotheses about mood disorders, bipolar disorder mainly. Here we provide an overview of basic mechanisms of neuroplasticity, molecular and cellular mechanisms accompanying chronic stress, mood disorders and mitochondrial functions. Better insight into common molecular mechanisms of stress, mood disorders, effects of antidepressants and mitochondrial functions is likely to lead to better understanding of pathophysiology of depression or interindividual variations in response to antidepressant treatment.

INTRODUCTION

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he principal role of the nervous system is to receive, store and process information. It was demonstrated that synaptic plasticity is necessary for storing memories. Information is stored in neural circuits through long-lasting changes in synaptic strengths. Increasing evidence demonstrates that neuronal plasticity is disrupted in mood disorders and as a result of chronic stress (Pittenger & Duman 2008). Moreover, there is an overlap between molecular changes induced by antidepressants and molecular mechanism of synaptic plasticity (Citri & Malenka 2008).

It is hypothesized that new memories are encoded as neural activity-induced changes in synaptic efficacy, and stabilization of these changes requires *de novo* protein synthesis (Miyashita et al 2008). Memory has many forms and is distributed across many brain regions. Hippocampus is required for the formation of episodic (event-related) memory; however, it remains unclear whether hippocampus itself acts as a memory store. The importance of the network of neurons that are activated during learning is emphasized at present time (Neves et al 2008).

The allocation of memory to specific cells and synapses within a neural network is modulated by many synaptic, cellular, and intercellular components and by mechanisms working at different time scales (Silva et al 2009). The transcription factor CREB (cyclic adenosine monophosphate (cAMP) responsive element binding) regulates transcription of many genes and has a well known role in the learning related synaptic plasticity (Carlezon et al 2005). CREB is also involved in antidepressant response (Chen et al 2001). Increase in CREB function can enhance memory; however, cognitive performance can be disrupted under some circumstances. CREB activity has sometimes beneficial, sometimes detrimental roles, depending on the brain region involved. So, alterations in CREB function do not produce uniform effects throughout the brain (Carlezon et al 2005; Tardito et al 2006).

Stress and stress hormones produce both adaptive and maladaptive effects in the brain (McEwen 2007). It is known that stress is important contributor to psychosocial and physical disorders. The relationship between stressful life events and development of mood disorders in vulnerable subjects has been long established (Kendler et al 1999; Johnson 2005). Adverse childhood experiences have been described as one of the major environmental risk factors for depressive disorder. Functional polymorphisms in the promoter region of the serotonin (5-HT) transporter gene and brain-derived neurotrophic factor (BDNF) gene were found to moderate the influence of stressful life events on depression (Caspi et al 2003; Aguilera et al 2009).

Processes accompanying neuroplasticity are extremely energy-consuming and interfere with different intracellular pathways included in signal transduction or in apoptosis. Thus, it seems to be useful to study the mitochondrial dysfunctions in relation to neuroplasticity, mechanisms of stress response, pathophysiology of mood disorders, and mechanisms of action of psychotropic drugs, antidepressants and mood stabilizers included. It was proposed that subtle deficits in the mitochondrial function likely play an important role in various facets of bipolar disorder, and that enhancing mitochondrial function may represent a critical component for the optimal treatment of the disorder (Quiroz et al 2008).

There are close relationships between the mechanisms of synaptic plasticity, effects of stress, mechanisms of antidepressant action, and pathophysiology of depression (Pittenger & Duman 2008). In order to explain these relationships, interactions among signal transduction pathways have been studied (Fišar & Hroudová 2010), including the role of mitochondria.

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lassic monoamine hypothesis of depression proposed that depression might be produced by a serotonin or norepinephrine deficiency at functionally important receptor sites in the brain, i.e. that brain monoamine systems have a primary direct role in depression. Soon it became evident that the monoamine hypothesis in its original form could not explain all of the effects of antidepressants (Nestler et al 2002). 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 serotonin depletion or to catecholamine depletion was found to be specific to the type of antidepressant treatment and type of depletion. Serotonin or norepinephrine/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 (Delgado et al 1999). Depletion studies failed to demonstrate a causal relation between serotonin and norepinephrine with depressive disorder (Ruhé et al 2007; Cowen 2008). The effects of acute tryptophan depletion on cognition in non-vulnerable participants are independent of mood changes (Mendelsohn et al 2009). Even simultaneous disruption of serotonin and catecholamine systems didn't significantly alter mood in unmedicated depressed subjects (Berman et al 2002). These findings forced a major revision of the classic monoamine hypothesis of depression. According to this revised monoamine theory of depression (Heninger et al 1996; aan het Rot et al 2009) monoamine systems are only modulating other brain neurobiological systems that have more primary role in depression.

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 BDNF, abnormal function of hypothalamic-pituitary-adrenal (HPA) axis and glutamatergic toxicity (Krishnan & Nestler 2008; Mathew et al 2008; aan het Rot et al 2009).

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 (Pittenger & Duman 2008). 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 (Quiroz et al 2008).

A) Neurotrophic, neuroplasticity and neurogenesis hypotheses

The most recently discussed biological hypothesis of mood disorders is **neurotrophic hypothesis of depression** (Duman et al 1997), which supposes that vulnerability to depression can arise as a result of neuronal damage, e.g. after chronic stress, long-term increased levels of glucocorticoids, hypoglycaemia, ischemia, certain viral infections, effects of neurotoxins, etc. The therapeutic effects of antidepressants consist of increased function of the noradrenergic or serotonergic system. It leads to increased activity of transcription factor CREB, higher expression of neurotrophin BDNF and its receptor trkB, and consequently to the increased neuronal plasticity and the resumption of cellular functions.

Series of studies support the hypothesis that a reduction of BDNF could contribute to depression and that antidepressants mediate their therapeutic benefit by increasing levels of this factor in the hippocampus. A polymorphism in the BDNF gene has been associated with depression and bipolar disorder. BDNF levels have been found to be reduced in post-mortem brain samples and in the blood of depressed patients, and these reductions are reversible by successful antidepressant treatment (Castrén et al 2007; Castrén & Rantamäki 2008). In addition, the regulation of other growth factors may also play a role in the pathophysiology and the treatment of depression (Duman & Monteggia 2006).

Stress produces a sustained suppression of BDNF transcription through histone methylation, whereas antidepressants restore BDNF synthesis through histone acetylation (Tsankova et al 2006). This suggests that chronic stress can cause long-lasting epigenetic changes that might be related to increased vulnerability to depression.

Local infusions of BDNF into specific brain regions showed to mimic antidepressant effects in behavioural models of depression. However, the loss of BDNF and signalling through the trkB receptor in broad forebrain regions *per se* is not sufficient to mediate depression-like behaviour (Duman & Monteggia 2006). BDNF does not produce uniform effects throughout the brain. Infusion of BDNF into the ventral tegmental area might be related to the development of a depression-like phenotype; therefore, the role of BDNF in the ventral tegmental area – nucleus accumbens (VTA-NAc) pathway is opposite to the role of BDNF in the hippocampus (Eisch et al 2003). It is hypothesized that BDNF signalling in the VTA-NAc is required for the establishment of associations with negative emotional stimuli; and under pathological conditions this signalling may establish abnormal associations leading to certain symptoms of depression (Nestler & Carlezon 2006).

Behavioural data support the hypothesis that regulation of neuronal plasticity might play an important role in expression of symptoms of bipolar disorder. Major intracellular signalling pathways in bipolar disorder and neural plasticity include protein kinase C (PKC) and extracellular signal regulated kinase (ERK) cascades, glucocorticoid receptor modulation, glycogen synthase kinase-3 (GSK-3), and antiapoptotic Bcl-2 (B-cell CLL/lymphoma 2), AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole propionic acid) receptors, and inositol homeostasis (Einat & Manji 2006). The **neuroplasticity hypothesis** of depressive disorder (Pittenger & Duman 2008) suggests that impaired mechanisms of neuroplasticity are core pathophysiological feature of the disorder, where chronic stress is an important causal factor in the development of this impairment, and where long-term treatment with antidepressants leads to modulation of impaired mechanisms of neuroplasticity. However, alterations in neuroplasticity do not produce the same effects in different brain regions.

The **neurogenesis hypothesis** of depression proposes that depression can arise from impaired hippocampal neurogenesis and that an array of antidepressants ultimately work by stimulating such neurogenesis. The first component of this hypothesis is not tenable, and the evidence for second component is conflicting (Sapolsky 2004).

B) Network hypothesis

According to the network hypothesis of depression, changes in levels of neurotrophins may not directly produce depression or an antidepressant effect, but neurotrophins may act as critical tools in the process whereby environmental conditions guide neuronal networks to better adapt to the environment (Castrén & Rantamäki 2010).

The network hypothesis (Castrén 2005) proposes that mood disorders reflect problems in information processing within particular neural networks in the brain; antidepressant drugs and other treatments, which alleviate depression, function by gradually improving information processing within these networks. Therefore, disorders of the nervous system, including depression, might represent disturbances in the activity-dependent information processing of the brain, rather than in the chemical balance of signalling molecules. However, some observations seem to be incompatible with the network hypothesis, e.g. rapid relapse of depressive symptoms in remitted patients, who have been treated with serotonin selective antidepressants, circadian variations in mood, and the effect of sleep deprivation on improvement of the mood of patients with depression. These rapid effects on mood can not be accounted for a gradual change in the structure of mood influencing neural networks.

The network hypothesis emphasizes the importance of processing of environmental information (such as social communication) in the recovery of the brain functions during treatment of mood disorders; so, treatment with psychotropic drug in itself is insufficient. Findings that psychotherapy result in detectable changes in the brain (Etkin et al 2005) and that combined use of psychotherapy and medication can lead to better treatment outcomes than the use of either mode of therapy alone (Elkin et al 1989) are consistent with the network hypothesis.

C) Inflammatory and neurodegenerative hypothesis

The central nervous system, endocrine and immune systems use neurotransmitters, cytokines and hormones to communicate among them (Haddad et al 2002; Kitzlerová & Anders 2007; Kovaru et al 2009). Now there is evidence that the activation of the immune system is associated with the symptoms of depression (Leonard & Myint 2009). **The inflammatory and neurodegenerative hypothesis** of depression (Maes et al 2009) 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.

D) Mitochondrial dysfunction hypotheses

Subtle deficits in mitochondrial function likely play an important role in various aspects of bipolar disorder, and enhancing mitochondrial function may represent a critical component for the treatment of the disorder (Quiroz et al 2008). Changes in cerebral concentrations of N-acetyl aspartate (NAA), glutamate/glutamine, choline-containing compounds, myo-inositol, lactate, phosphocreatine, phosphomonoesters, and intracellular pH in bipolar subjects were described (Yildiz-Yesiloglu & Ankerst 2006). A **hypothesis of mitochondrial dysfunction** in bipolar disorder (Stork & Renshaw 2005) was proposed and involved impaired oxidative phosphorylation, a resultant shift toward glycolytic energy production, a decrease in total energy production (decreased ATP production) and/or substrate availability, and changed concentrations of phosphomonoesters and altered phospholipid metabolism.

Neuronal calcium homeostasis and calcium signalling regulate multiple neuronal functions, including synaptic transmission, neuronal plasticity and survival. The idea that altered intracellular calcium signalling may be crucial for the molecular mechanisms leading to both schizophrenia and affective disorders was first suggested by Jimerson et al. (1979). Recently, disturbed calcium homeostasis has been studied in neurodegenerative (Wojda et al 2008) and mood disorders. Mitochondrial DNA (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 (Kato 2008). **Calcium and 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 (Kato & Kato 2000; Kato 2007, 2008).

Mitochondrial hypotheses correspond to, above mentioned, neurotrophic and neuroplasticity hypotheses because of an important role of calcium signalling pathway in the synaptic plasticity regulation.

NEUROPLASTICITY

The term neuroplasticity (brain plasticity, cortical plasticity, cortical re-mapping) is used for description of either functional or structural changes of neurons and glial cells that occur in developing brain as well as in the adult brain in order to adjust to external or internal stimuli (Mesulam 1999, Nestler et al 2002). Different aspects of neuroplasticity have been studied in the relation to learning and memory, which may happen through the change in the strength of connections among brain cells, by adding or removing connections, or by adding new cells. New findings suggest that all areas of the brain are plastic even after childhood. Neuroplasticity in the adult brain includes changes of dendritic functions, reorganization of synapses, long-term potentiation (LTP), long-term depression (LTD), branching and sprouting of axons and dendrites, synaptogenesis, and neurogenesis. Dendritic spines play an important role in neural processing. The morphology of dendritic spines is very diverse and changes in spine size and density are thought to reflect changes in the synaptic strength (von Bohlen und Halbach 2009).

There are evidences of the capacity of the human brain to achieve both functional and structural reorganization. Besides environment and learning-induced plasticity, morphological alterations in the adult brain can be caused by nervous system injury. Moreover, the reorganisation of the complex brain networks is not always beneficial for the individual. Maladaptive plasticity can be defined as behavioural loss or as development of disease symptoms resulting from plasticity changes in the adult brain (Draganski & May 2008).

Environmental changes could alter behaviour and cognition by adapting connections between neurons, and neurogenesis may be included in these processes. It is possible that there is a link between neurogenesis and learning-related changes in the brain. Adult neurogenesis in mammals is mainly restricted to the hippocampus and olfactory bulb, but current research has revealed that other parts of the brain, the cerebellum included, may be involved as well (Ponti et al 2008).

A) Gliotransmitters

Glial cells, especially astrocytes, provide not only structural and nutritional support for neurons, but also provide signal processing support via chemicals known as gliotransmitters (Páv et al 2008; Kovaru et al 2009; Halassa & Haydon 2010). Astrocytes are stimulated by synaptically released neurotransmitters, which increase the astrocyte calcium levels and stimulate the release of gliotransmitters that regulate synaptic efficacy and plasticity (Perera & Araque 2009).

The criteria for gliotransmitter have been defined (Parpura & Zorec 2009): (i) synthesis by and/or storage in glia; (ii) regulated release triggered by physiological and/or pathological stimuli; (iii) activation of rapid responses in neighbouring cells; and (iv) a role in physiological or pathophysiological processes. Gliotransmitters include amino acids (e.g. glutamate and D-serine), nucleotides (e.g. ATP), and peptides (e.g. BDNF, and atrial natriuretic peptide). D-serine serves as a ligand in the glycine site of N-methyl-D-aspartic acid (NMDA) receptors; so, D-serine is an essential ligand for the proper function of the NMDA receptors (Billard 2008).

Consequently, synaptic function includes also the bidirectional signalling between neurons and astrocytes. One of the most consistent neuropathological findings in major depressive disorder is a reduction in the number of glia (Rajkowska & Miguel-Hidalgo 2007).

B) Synaptic plasticity

The development of new synapses, the activity dependent changes in the strength of existing synapses and the elimination of synapses have been proposed to form basis of **synaptic plasticity**. The synaptic plasticity could be the cellular basis of certain forms of learning and memory (Citri & Malenka 2008). Synaptic plasticity has been studied in many brain regions, most frequently in the hippocampus.

The original theory of plasticity is called Hebbian plasticity: "cells that fire together, wire together". Hebbian plasticity involves two mechanisms: LTP and LTD (Bliss & Lømo 1973). LTP is the increase and LTD is the decrease in synaptic strength that occurs in a response to brief, repetitive stimulation of neuron. LTP and LTD are considered as crucial for information storage in the cell.

Recently, the concept was modified that synapse-specific forms of LTP and LTD at excitatory synapse can fully explain learning and experience-dependent plasticity. Intrinsic, inhibitory, and homeostatic plasticity were documented as additional forms of plasticity (Nelson & Turrigiano 2008). Activity-dependent modulation of intrinsic excitability that alters the input-output function of a neuron (e.g. ion channel phosphorylation or non-random distribution in neuron) is attributed to **intrinsic plasticity** (Marder & Goaillard 2006). Existence and important role of **inhibitory plasticity** result from the facts that inhibition is essential in information processing, and inhibitory GABAergic neurons form a significant part of cortical and hippocampal neurons. Finally, neuronal activity is subject to classic homeostatic negative feedback control that serves to stabilize neuron and circuit function following their activity-dependent modifications. New form of synaptic plasticity, **homeostatic plasticity**, was described that increases or decreases the strength of all of a neuron's synaptic inputs as a function activity (Turrigiano et al 1998).

Recently, it has become clear that the prior history of synaptic activity is an additional variable that influences the synaptic state. A novel form of persistent synaptic plasticity was called **metaplasticity** (the plasticity of synaptic plasticity). Metaplasticity is induced by synaptic or cellular activity, but is not necessarily expressed as a change in the efficacy of normal synaptic transmission. Instead, it is manifested as a change in the ability to induce subsequent synaptic plasticity, such as LTP or LTD. Thus, metaplasticity is a higher-order form of synaptic plasticity (Abraham & Bear 1996).

C) Presynaptic plasticity

There is both postsynaptic and presynaptic plasticity. Postsynaptic plasticity involves changes in the number or sensitivity of postsynaptic receptors without any changes in the amount of neurotransmitter release. **Presynaptic plasticity** generally translates into an increase or a decrease of neurotransmitter release (García-Junco-Clemente et al 2005). Presynaptic plasticity has the potential to greatly influence all of the neurotransmitters release sites within a given axon, such that changes in the output of one inhibitory interneuron could modify the activity of many of its downstream target neurons (Tóth & McBain 2000). Mechanisms of presynaptic LTP or LTD may be independent on NMDA receptors. It is hypothesized that various forms of presynaptic plasticity can operate in a manner fundamentally distinct from most postsynaptic forms of plasticity (García-Junco-Clemente et al 2005; McBain & Kauer 2009).

A new class of presynaptic plasticity that requires signalling by endocannabinoids has been identified in several brain structures (Chevaleyre et al 2006). The endocannabinoids are a family of lipid neurotransmitters that mediate retrograde signal from postsynaptic neurons to presynaptic ones. They are synthesized *de novo* from membrane phospholipids and released in response to postsynaptic depolarization or activation of metabotropic glutamate receptors. The endocannabinoids are widely distributed in the brain and throughout the body. *sn*-2-Arachidonoylglycerol is the most prevalent endogenous ligand of cannabinoid receptors in mammals, and anandamide (*N*-arachidonoylethanolamide) became the most explored (Fišar 2009). Once bound to presynaptic cannabinoid receptor type 1 (CB_1) endocannabinoids suppress neurotransmitter release.

While mechanisms underlying short-term depression have been identified, the molecular mechanisms linking activation of CB_1 receptors to LTD are little known. In the hippocampus the long-term endocannabinoid-dependent depression of inhibitory transmission requires presynaptic cAMP/protein kinase A (PKA) signalling. By LTD of inhibitory synapses endocannabinoids facilitate subsequent induction of LTP at nearby excitatory synapses (Chevaleyre et al 2007). Therefore, endocannabinoid system is emerging as an important compound of synaptic plasticity and its role is metaplastic in nature. At many of these synapses presynaptically expressed forms of LTD can coexist with postsynaptic forms of LTD mediated by internalization of AMPA receptors (Nelson & Turrigiano 2008).

D) Discrete synaptic states

In a **continuum model**, information is coded solely in the current strength of the synapse; e.g. synapses undergo changes in efficacy by adjusting their strength by continual changes in the rate of AMPA receptor movement into and out of the synaptic membrane. In a **state model**, synapses might exist in different states that represent and underlie different levels of efficacy.

The second model, which considers the history of the synapse, is most likely; i.e. there are discrete states that synapses move between. These states are named as active, potentiated, depressed, silent and recently silent (Montgomery & Madison 2004). In the **active state**, synapses display both AMPA receptor and NMDA receptor mediated responses; they can move to either potentiated or depressed via LTP or LTD, respectively. The **potentiated state** is defined as a plasticity state in that synaptic depression (depotentiation) occurs via activation of metabotropic glutamate receptors rather then via NMDA receptors. Potentiated synapses transmit stronger signal, because more AMPA receptors are inserted into postsynaptic membrane. **Silent synapses** are characterized by the deficiency of AMPA receptors in the postsynaptic membrane; they have no synaptic response at normal postsynaptic membrane potentials due to failing of AMPA receptor response. Their unsilencing appears to be a major mechanism of LTP. The potentiation of silent synapses leads to the **recently silent state**, in which synapses have both AMPA receptor and NMDA receptor mediated responses. The recently silent synapses differ from active synapses in that they can undergo neither LTD nor depotentiation until 30 min after synapse unsilencing.

A model for state-dependent synaptic plasticity (Montgomery & Madison, 2004) is based on the hypothesis that synaptic plasticity is determined by the AMPA receptors that are trafficked into and out of the synaptic membrane, whereas AMPA receptors are fully mobile, reluctant or immobile (due to their subunit composition, phosphorylation, interactions with specific proteins, or other factors). The finding that synapses exist in different plastic states means that the capacity of a synapse to carry information is greater than previously recognized.

E) Mechanisms of synaptic plasticity

Learning induces long-lasting changes in the synaptic strength of central glutamatergic synapses. E.g. the majority of receptors at the synapses of the hippocampus use glutamate as a neurotransmitter. Glutamate has two main receptor types: 1. excitatory ionotropic AMPA, NMDA and kainate receptors, and 2. excitatory metabotropic receptors (mGlu$_{1-8}$). The AMPA receptors are responsible for sufficient depolarization in the membrane that will abolish the magnesium cation blockade in the NMDA receptors, thus allowing calcium influx into the cell. It is important in mechanisms of synaptic plasticity that ligand-gated ion channel receptors are a class of receptor that may occur both at the cell-surface and intracellulary.

Basic mechanisms of postsynaptic plasticity are connected with activation of postsynaptic NMDA receptors followed by Ca^{2+} influx; calcium triggers four main mechanisms contributing to synaptic plasticity in spines: 1. the regulation (by kinases and phosphatises) of channels and proteins involved in trafficking, cytoskeletal organization and protein synthesis; 2. alterations of synaptic AMPA receptor properties, subunit composition and trafficking; 3. actin reorganization and modulation of spine morphology; and 4. initiation of local protein synthesis in spines and dendrites (Derkach et al 2007).

F) Short-term synaptic plasticity

Short-term synaptic plasticity changes happen as potentiation or depression of synaptic responses lasting for tenths of seconds to a few minutes. Molecular triggers of short-term plasticity inducing mechanisms are first of all intrasynaptic calcium and cAMP. Local elevation in calcium intrasynaptic concentration may be induced by input of extracellular Ca^{2+} or by release of Ca^{2+} from intracellular stores in endoplasmic reticulum or mitochondria. Ca^{2+} enters neurons through NMDA receptors, Ca^{2+}-permeable AMPA receptors and voltage-gated Ca^{2+}-channels. Ca^{2+} entry through NMDA receptors is crucial for inducing synaptic plasticity and for activation of intracellular signalling pathways leading to phosphorylation of transcription factors (such as CREB) and gene expression.

Activation of the calcium-calmodulin-dependent kinase II (CaMKII) is critical for early LTP, whereas calcium-calmodulin-dependent kinase IV (CaMKIV) participates on the long-lasting LTP. CaMKII and other kinases phosphorylate AMPA receptors and associated proteins, which leads both to increasing of the number of AMPA receptors in the postsynaptic membrane and to enhancing function of those receptors already inserted. Insertion of AMPA receptors results in the activation of silent synapses (unsilencing). Short-term increase in synaptic strength is mediated by these mechanisms (Pittenger & Duman 2008).

G) Long-term synaptic plasticity

Learning and memory depend on long-lasting changes in synaptic strength. **Long-term synaptic plasticity** changes last from hours to weeks. These changes require induction of gene expression, production and insertion of new proteins. Activation of β-adrenoceptors can enhance LTP and facilitate long-term memory storage. Cyclic AMP/PKA and extracellular signal-regulated protein kinase cascades are important to express the long-lasting LTP in hippocampus, amygdala, and cortex (Pittenger & Duman 2008; O'Dell et al 2010). Transcription factor CREB is particularly important in modulation of synaptic plasticity. CREB is activated (phosphorylated) by PKA and other kinases upon synaptic stimulation during learning (Carlezon et al 2005). CREB and other transcription factors induce gene expression of many proteins, including BDNF and series of transcription factors (Barco et al 2006).

AMPA receptors are thought to be responsible for the expression of synaptic plasticity, whereas NMDA receptors are responsible for its control. AMPA receptors are thought to be more mobile at synapses than NMDA receptors. Under basal conditions AMPA receptors cycle to and from the synaptic membrane. In response to LTP-inducing stimuli, intracellulary located AMPA receptors are rapidly inserted into the synaptic membrane, followed by lateral diffusion into postsynaptic density. NMDA receptors may be as dynamic as AMPA receptors following the induction of LTD. In response to LTD-inducing stimuli, both AMPA and NMDA receptors are thought to be removed from the synaptic membrane (Genoux & Montgomery 2007). NMDA receptors activate Ca^{2+}-dependent signalling pathways as well as MAPK cascade through Ca^{2+}-independent pathway that involves metabotropic glutamate receptors. AMPA receptors are regarded as passive conducts for current flux across the membrane; however, evidences indicate that AMPA receptors participate also on signal transduction. AMPA receptors, similar to NMDA receptors, function as signal transducers that mediate long-term, activity dependent synaptic changes (Rao & Finkbeiner 2007).

Long-lasting LTP (late-phase LTP) requires gene expression and *de novo* protein synthesis. Persistence of LTP depends on local events during its induction, as well as on the prior activity of the neuron. Plasticity changes are specific to activated synapses. A mechanism, termed **synaptic tagging**, must exist to capture newly expressed plasticity related mRNAs or proteins specifically at activated synapses. E.g. when new receptors, ion channels and other membrane proteins are being synthesized, they must also be transported to the synaptic membrane, and some sort of chemical messaging is required for this. Frey & Morris (1997) first provided evidence for the synaptic tag theory, which proposes that gene products can only be captured and utilized at synapses that have been tagged by previous activity. The PKA is critical for synaptic tagging and for input-specific late-phase LTP (Young et al 2006). It was even shown that simple pharmacological activation of cAMP/PKA pathways was sufficient for the synapse to be tagged, completely independent of any sort of activity.

STRESS IN NEUROPLASTICITY

S

tress may be defined as any environmental change, whether internal or external, that disturbs homeostasis (Leonard & Myint 2009). Stress system is located in both the central nervous system and peripheral organs. Central functions of the stress response include facilitation of arousal, alertness, cognition, attention and aggression, inhibition of vegetative functions, and activation of counter-regulator feedback loops. Peripheral functions include increase of oxygenation, nutrition of the brain, hearth and skeletal muscles, increase of cardiovascular tone and respiration, increase of metabolism and detoxification, and activation of counter-regulatory feedback loops (Chrousos 2009).

Stress activates both HPA axis and the sympathetic nervous system. The main central effectors of stress system include corticotrophin-releasing factor (CRF), arginine vasopressin (AVP) and norepinephrine. Chronic stress, as a result of the hypersecretion of cortisol, causes a decrease in serotonin turnover partly as a consequence of increased metabolism of tryptophan (Leonard & Myint 2009). Increased activity of the HPA axis has been reported in pregnancy and in many diseases, such as Cushing syndrome, depression, anorexia nervosa, obsessive-compulsive disorder, panic disorder, alcoholism, diabetes melitus, metabolic syndrome, hyperthyroidism, etc. (Chrousos 2009).

Stressors provoke the secretion of epinephrine and norepinephrine by the sympathetic nervous system, to induce the flight-or-fight response, and of the glucocorticoids by the adrenal gland. Catecholamine action involves activation of β-adrenoceptors and initiation of second messenger cascades in target cells within seconds; whereas, glucocorticoid's effects can take hours to emerge, as they involve transcriptional events. Brain areas involved in the stress response include the prefrontal cortex, the hippocampus, and the amygdala; they undergo stress-induced remodelling, which alters behavioural and physiological responses (McEwen 2007). Many central aspects of stress response are modulated, and in some cases mediated, by glutamate neurotransmission in the prefrontal cortex (Moghaddam 2002).

Acute and chronic stress can have quite different effects on neuroplasticity. The mild stress for a few hours can enhance cognition by facilitating aspects of synaptic plasticity in the hippocampus; these effects are mediated by high-affinity corticosteroid receptors. In contrast, excessive glucocorticoid exposure in the hippocampus as a result of major and prolonged stress can be directly toxic to neurons, or can increase the neurotoxicity of various hippocampal insults (McEwen & Sapolsky 1995; Sapolsky 1996; Lee et al 2002).

A) Glucocorticoids

Stress and glucocorticoids can influence neuroplasticity. Glucocorticoids regulate gene expression via binding of ligand-activated glucocorticoid receptor to glucocorticoid-responsive elements. Glucocorticoids can have a broad range of deleterious effects in the brain. The action of glucocorticoids occurs predominantly in the hippocampus, a brain region with abundant levels of corticosteroid receptors. The glucocorticoids can cause damage of neurons in the hippocampus and the medial prefrontal cortex, and these produce impairments in memory and can cause damage to a physical and mental health (Sapolsky 2003). Anxiety, depression and psychotic disorders may result from such changes in the HPA axis activity.

Inhibition of glucose uptake into neurons, participation in glutamatergic neurotoxicity, elevation of free cytosolic calcium concentrations, and oxygen radical generation, all account for the deleterious effects of glucocorticoids. However, glucocorticoid action involves many additional components, including disruption of the mobilization of neurotrophins (Sapolsky 1996).

B) Stress effects on neuroplasticity in brain structures

Stress can alter signalling pathways implicated in synaptic plasticity (Pittenger & Duman 2008). Another way whereby stress hormones modulate brain functions is by changing the structure of neurons; synaptogenesis, neurogenesis, and dendritic remodelling are included in these structural changes (McEwen 2007). Elevated activity and volume loss of the hippocampus, the orbital and the ventral prefrontal cortex in bipolar disorder and major depressive disorder are recurrently described in literature. Reduced volume might mean reduced neuronal complexity and connectivity. In contrast, dorsal aspects of the prefrontal cortex tend to display hypometabolism (Savitz & Drevets 2009).

The **hippocampus** plays a vital role in learning and memory, contextual fear conditioning and neuroendocrine regulation. Various neurotransmitter systems in the hippocampus are involved in these processes. Neurons in the hippocampus were found to be extremely sensitive to damage resulting from the global ischemia and hypoglycaemia. Prolonged stress or prolonged exposure to glucocorticoids can have adverse effects on the neuron survival in the hippocampus (Lee et al 2002). A disruption of hippocampal function may contribute to the deficits in executive performance, learning and emotion-mediated memory formation observed in mood disorders (Savitz & Drevets 2009).

Hippocampal atrophy was observed in recurrent and major depression (Campbell et al 2004) and posttraumatic stress disorder (Bremner 2006; Bremner et al 2008), when there have been multiple reports of elevated levels of glucocorticoids. Abnormal membrane turnover in the hippocampus was found greater in depressive patients with highly recurrent illness, and provided the support for the hypothesis that there are neuronal changes in this region over the course of illness (Milne et al 2009).

A meta-analysis examining data from magnetic resonance imaging studies of hippocampal volume in patients with major depressive disorder confirmed that hippocampal volume reduction generally occurs after disease onset (McKinnon et al 2009). These findings indicate that hippocampal atrophy probably does not represent a trait marker of vulnerability for disease; however, longitudinal studies that track patients over disease onset and through follow-up are needed to confirm this conclusion. Dysregulation of the HPA axis in patients with major depressive disorder is likely to have these specific and long-lasting effects on the hippocampus (Leonard & Myint 2009). Increased neurodegeneration, reduced neuroprotection and neuronal repair are common pathological features of major depression and dementia (Leonard 2007).

Stress has similar effects on neuroplasticity in the **prefrontal cortex** (Liston et al 2006). The **ventral striatum**, including nucleus accumbens, is other important structure, which participate in relationships between neuroplasticity, stress and mood disorders. Impaired striatal function may explain the anhedonia and reduction in goal-seeking behaviour that is observed in some depressive patients (Nestler & Carlezon 2006; Savitz & Drevets 2009).

The effects of stress on brain morphology and function are region and circuit dependent, which could be illustrated by the stress-induced effects on the **amygdala**. The amygdala participates in the modulation of monoamine and corticosteroid release in the response to aversive or novel stimuli. Thus, the amygdala could play an important role in the regulation of mood and affect and has been implicated in the pathophysiology of mood disorders (Savitz & Drevets 2009). Studies of amygdala volumes in mood disorders have been conflicting. A meta-analysis of these results showed that the volumes of the amygdala in patients with bipolar or unipolar disorder are comparable to controls and the amygdala volume abnormalities may not be associated with mood disorders *per se* (Hajek et al 2009).

C) Glutamatergic neurotoxicity

Stress produces a rapid increase in glutamate efflux in the prefrontal cortex and the hippocampus (Bagley & Moghaddam 1997; Moghaddam 2002). An excess of glutamate in the synapse leads to excess of cytosolic calcium, which produce overactivity of calcium-dependent enzymes and it leads to cytoskeletal degradation, protein malformation and oxygen radical generation. These processes can lead to atrophy or death of neurons (Lipton 1999; Atlante et al 2001). Different insults, such as hypoxia-ischemia, seizure and hypoglycaemia, all of them activate this pathway. It cannot be neglected that the cytoplasm of a neuron is not randomly filled with enzymes and organelles; thus, there are differing likelihoods of neurotoxicity as a function of whether the excess of calcium is derived from the extracellular space, mitochondria or endoplasmic reticulum. Moreover, glutamatergic neurotoxicity does not require an excess of glutamate during a period when neuronal energetic is disturbed.

Neurons mobilize a variety of defences when are challenged with glutamatergic insults, e.g. removal of glutamate from the synapse, and of calcium from the cytoplasm, production of heat shock proteins (HSP), protective hyperpolarisation, and protective upregulation of antioxidant enzymes (Lee et al 2002). The glia cells account for the majority of glutamate uptake.

ANTIDEPRESSANTS AND MOOD STABILIZERS IN NEUROPLASTICITY

A

ntidepressants may be classified according to their acute pharmacological effects. The first antidepressants were monoamine oxidase inhibitors and nonselective serotonin and/or norepinephrine reuptake inhibitors. 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 (NDRIs), selective serotonin reuptake enhancer (SSRE), melatonergic agonists etc.

Antidepressants affect learning and memory in animal models and enhance structural plasticity and hippocampal neurogenesis (Warner-Schmidt & Duman 2006; Kasper & McEwen 2008; Drzyzga et al 2009). Antidepressants can directly modulate glutamatergic neurotransmission through NMDA or AMPA receptors; it is likely that an intimate relationship exists between regulation of monoaminergic and glutamatergic neurotransmission and antidepressant effects (Paul & Skolnick 2003). Converging lines of evidences demonstrate action of tianeptine on the glutamatergic system. Tianeptine prevents or reverses stress-associated structural and cellular changes in the brain and normalizes disrupted glutamatergic neurotransmission in the hippocampus, the amygdala, and the cortex (Kasper & McEwen 2008; McEwen et al 2010). An inhibition of an excessive release of glutamate appears to be important to lamotrigine and riluzole mechanisms of action (Zarate et al 2006a). Robust and rapid antidepressant effect on individuals with treatment-resistant depression resulted from a single intravenous dose of ketamine (a non-competitive NMDA receptor antagonist and psychomimetic) (Zarate et al 2006b). These effects suggest that depressive symptoms can be improved by altering the action of glutamate (Krishnan & Nestler 2008).

There are many evidences that antidepressants increase signalling pathways related to neuroplasticity by upregulation of cAMP/PKA/CREB cascade, by regulation of CaMKII activity and by upregulation of the MAPK cascade (Pittenger & Duman 2008). The hypothesis that long-term antidepressant treatment enhances neuroplasticity is based on upregulation of expression of many neurotrophic factors, especially of BDNF, in the hippocampus and the prefrontal cortex (Duman & Monteggia 2006).

Mood stabilizers are psychiatric medication used in treatment of mood disorders, which are characterized by intense and sustained mood shifts (e.g. bipolar affective disorder). Most of mood stabilizers are anticonvulsants, with an important exception of lithium, which is the oldest and the best known mood stabilizing drug. Some atypical antipsychotics have mood stabilizing effects as well. Mood stabilizers affect multiple sites in intracellular signalling pathways. 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 (protein kinase C, cyclic AMP, arachidonic acid) (Gould et al 2004). 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 (BDNF, HSP, Bcl-2). Lithium protects against DNA damage, caspases activation, and apoptosis of neurons (Chuang 2005).

If a deficit in neuroplasticity is included in pathophysiology of depression, then it can be supposed that effects of stress on the mechanisms of neuroplasticity contribute to the genesis of depression and long-term antidepressant treatment affects the same mechanisms (Pittenger & Duman 2008). Recent studies have analysed the neurotrophic effects of antidepressants and mood stabilizers on hippocampal and other neural tissue (Duman & Monteggia 2006). However, there is not any large longitudinal study that might prove the ability of antidepressants to reverse atrophy of brain structures and prevent it.

MITOCHONDRIA IN NEUROPLASTICITY

M itochondria have well-known function in cellular energy production through the citric acid cycle and oxidative phosphorylation (OXPHOS). Mitochondrial OXPHOS supplies more then 92% of the total energy requirement in the cells. Brain functions are coupled to highly energy-demanding processes. Although the human brain represents only 2% of the body weight, it receives 20% of total body oxygen consumption, and 25% of total body glucose utilization. Mitochondrial electron transport chain generates ATP that is essential for the survival of neurons and other cells. Additional important roles of mitochondria include thermogenesis, production of reactive oxygen species (ROS), regulation of intracellular Ca^{2+}, cytoprotection, developmental and synaptic plasticity, and arbitration of neuronal cell death (Quiroz et al 2008; Mattson et al 2008). Mitochondrial dysfunction could lead to cell death by maintaining low ATP levels, overproduction of free radicals, initiation of apoptosis or other damage caused by leakage of macromolecules, and by decreased ability to buffer Ca^{2+} loads. There may be other, unknown effects of mitochondrial damage (Lipton 1999).

Mitochondria are the major source of cellular ROS. It is currently believed that the majority of ROS are generated by complex I and complex III of electron transport chain. ROS is potentially highly damaging, but is also involved in signal transduction pathways. During energy production 1–2% of the O_2 is reduced incompletely to give the radical superoxide ($O_2^{-\cdot}$). Much of the free $O_2^{-\cdot}$ generated during mitochondrial respiration is converted to hydrogen peroxide (H_2O_2) by the matrix manganese superoxide dismutase. Mitochondrial H_2O_2 can diffuse to the cytosol and nucleus and can be converted either to water by glutathione peroxidase and catalase, or to highly reactive hydroxyl radical (OH^-), which can cause neuronal damage and death and may account for associated health-related problems (Youdim & Bakhle 2006; Sas et al 2007). Mitochondria contain several antioxidants to protect against oxidative damage (e.g. coenzyme Q_{10}, creatine, nicotinamide). H_2O_2 is also generated during metabolism of monoamine neurotransmitters and other monoamines by mitochondrial monoamine oxidase (MAO).

Mitochondria are dynamic organelles. Their function is modulated by fission of individual mitochondria and fusion of different mitochondria (Berman et al 2008). The imbalance of mitochondrial fission/fusion can influence synaptic transmission and plasticity, and affect neuronal survival (Lu 2009; Su 2010).

The regulation of synaptic plasticity is extremely energetically expensive. Mitochondria are transported to regions with high metabolic demands such as presynaptic terminals. ATP-dependent motor proteins move mitochondria along microtubules; anterograde transport is mediated by kinesins, retrograde transport by dynein (Hollenbeck & Saxon 2005). Extension or movement of mitochondria into the dendritic protrusions correlates with the development and morphological plasticity of spines. Thus, the dendritic distribution of mitochondria is essential and limiting for the support of synapses. Reciprocally, synaptic activity modulates the motility and fusion/fission balance of mitochondria and controls mitochondrial distribution in dendrites (Li et al 2004).

Cytoplasmic Ca^{2+} is sequestered in the mitochondria and endoplasmic reticulum. The outer mitochondrial membrane is permeable to Ca^{2+} and the inner membrane contains Ca^{2+} uniporter that transfers Ca^{2+} into the mitochondrial matrix and Na^+/Ca^{2+} and H^+/Ca^{2+} antiporters that move Ca^{2+} out of the mitochondria (Mattson et al 2008). Even multiple, relatively small, Ca^{2+} additions result in repetitive partial mitochondrial depolarisations and bioenergetic demands. A large uptake of Ca^{2+} into the mitochondrion exerts a depolarizing effect and it may lead to the cessation of ATP synthesis and activation of the permeability transition pores (PTPs) that causes mitochondria membranes to become permeable to molecules smaller than 1.5 kDa (Chalmers & Nichols 2003).

Mitochondria undergo two major alterations during apoptosis. The first is the mitochondrial outer membrane permeabilisation (MOMP) by the proapoptotic members of Bcl-2 family (Bax, Bak). MOMP allows the release of apoptogenic factors such as cytochrome *c*, second mitochondria-derived activator of caspases and other apoptosis-inducing factors into the cytosol. The release of cytochrome *c* leads to the activation of caspases, proteases that cleave many cellular proteins (Brunelle & Letai 2009). The second alteration is the loss of mitochondrial membrane potential ($\Delta\psi_m$) that is normally present across the inner mitochondrial membrane (and is formed by the action of the enzymes of the electron transport chain); the event is sometimes mediated by PTP. Therefore, opening of the PTP participate in mechanisms of learning and synaptic plasticity as well as in the apoptosis. The free radicals damage electron transport and sensitize the mitochondrial PTP to calcium.

Mitochondrial apoptotic cascades can be activated locally in synapses and dendrites (synaptic apoptosis) and suggest a role for such local apoptotic signals cascades in synapse loss and neuronal death in neurodegenerative disorders that involve excessive activation of ionotropic glutamate receptors (Mattson et al 1998; Culmsee & Mattson 2005).

Mitochondria may be integrally involved in the general processes of synaptic plasticity (Yang et al 2003) both postsynaptic and presynaptic. A complex signalling network enables mitochondria to sense internal milieu or environmental changes and to adjust their responses to restoration of homeostasis; e.g. the adaptive response to stressors involves important changes in mitochondrial function. Acute stress is associated with increases in mitochondrial biogenesis and the enzymatic activity of selected subunits of the respiratory chain complexes, to meet the increased energy demands of the cell. Chronic stress leads to abnormally increased or decreased mitochondrial biogenesis, respiratory chain dysfunction, decreased ATP production, increased ROS generation, lipid peroxidation, mitochondrial and nuclear DNA damage, and increased cell apoptosis and/or necrosis (Manoli et al 2007).

D

isturbed energy metabolism and glutamate may be involved in neuronal death leading to neurodegenerative disorders (Ikonomidou & Turski 1996). Damage to mitochondria is caused primarily by ROS produced by the mitochondria themselves. Mitochondrial dysfunctions may contribute to pathogenesis of Alzheimer's, Parkinson's and Huntington's diseases, stroke, amyotropic lateral sclerosis and psychiatric disorders such as schizophrenia, depression and bipolar disorder (Orth & Schapira 2001; Kato et al 2003; Stork & Renshaw 2005; Mattson et al 2008; Quiroz et al 2008; Neustadt & Pieczenik 2008). Mitochondrial dysfunction leads to oxidative stress, damage to mitochondrial DNA, mitochondrial DNA deletions, perturbed Ca^{2+} homeostasis, altered mitochondrial morphology, alterations in mitochondrial fission and fusion and ultimately neuronal death. Several bioenergetic agents have improved mitochondrial function; creatine, coenzyme Q_{10}, nicotinamide, riboflavin and lipoic acid are being tested for their neuroprotective efficacy in neurodegenerative disorders (Chaturvedi & Beal 2008; Beal 2009).

Evidences have been reviewed recently that mitochondrial dysfunctions are included in pathophysiology of psychiatric disorders (Shao et al 2008; Rezin et al 2009a; Jou et al 2009). They include disturbances in activity of mitochondrial enzymes, impaired calcium signalling and energy metabolism, increased mtDNA deletions, mutations or polymorphisms, and effects of psychotropic drugs on mitochondria. Comorbidity of mitochondrial diseases and psychiatric disorders was reported, whereas most of patients have psychiatric presentations that preceded the diagnosis of mitochondrial disease (Kato & Kato 2000; Fattal et al 2006). It seems that a mitochondrial deficit is sufficient to trigger different psychiatric disorders; however, it remains to be determined whether the mitochondrial dysfunctions contribute to the disease development or are epiphenomena, i.e. how nonspecific mitochondrial dysfunction may cause specific symptoms.

A) Monoamine oxidase (MAO)

MAO is the most studied mitochondrial enzyme in psychiatric disorders. MAO is localized on the outer mitochondrial membrane and catalyzes oxidative deamination of biogenic and xenobiotic monoamines, including monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine. In presynaptic terminals of monoaminergic neurons MAO activity creates negative feedback to the neurotransmitters synthesis and sustains cytosolic monoamine concentrations very low. Metabolism of monoamines by MAO is the major source of H_2O_2 in the brain; therefore, excessive MAO activity is accompanied by oxygen radical generation and can lead to oxidative damage of the cell.

Two isoforms of MAO, type A (MAO-A) and type B (MAO-B), were recognized differing in pharmacological specificity to substrates and inhibitors. Inhibitors of MAO-A are used in treatment of patients with depression (Stahl & Felker 2008), selective inhibitors of MAO-B may be efficacious in treatment of some neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease (Riederer et al 2004; Horstink et al 2006; Youdim & Bakhle 2006; Youdim et al 2006).

MAO activity was proposed as biological marker of depression or predictor of the response to treatment with antidepressants (Fišar & Raboch 2008). However, this parameter did not show sufficient specificity for mood disorders because MAO activity is strongly dependent on aging and many insults, including effects of nicotine and caffeine. The interest in a role of MAO in depression has reappeared recently thanks to the finding that elevated MAO-A density is the primary monoamine-lowering process during major depression (Meyer et al 2006) and thanks to the hypotheses of mitochondrial dysfunction (Stork & Renshaw 2005; Kato 2008). Previous research and meta-analyses of genetic studies showed significant association of a MAO-A gene promoter polymorphism with major depressive disorder (López-León et al 2008), antidepressant response (Yu et al 2005), or vulnerability to environmental stress (Kim-Cohen et al 2006).

B) Mitochondrial DNA deletions/mutations/polymorphisms

Mitochondrion is the only organelle containing nonnuclear genetic information. MtDNA encodes two ribosomal RNAs, twenty two transfer RNAs, and thirteen of the electron transport chain proteins. The remaining proteins in mitochondria are encoded by nuclear genes and at least 1000 nuclear-encoded proteins are translocated to the mitochondria. Nevertheless, mtDNA defects can cause an energy crisis and bioenergetics provides the interface between the environment and the epigenome.

MtDNA is more susceptible to somatic deletions than nuclear DNA because mtDNA is not protected by histones and has a poor DNA repair system. The symptoms of many mitochondrial diseases correspond to those attributed to epigenomic changes (Wallace & Fan 2010). Mood disorder shows several features consistent with an epigenetic contribution to the disease (Mil & Petronis 2007; Feinberg 2010).

Variations both in mtDNA and nuclear DNA impact on mitochondrial-related gene expression reported in schizophrenia, bipolar disorder, and major depressive disorder (Shao et al 2008). Regulatory factors, which determine whether mitochondrial DNA molecules are maintained or lost, potentially play a more important role in these disorders than till now recognised. Candidates include ROS and the tumour suppressor p53 (Holt 2010). DNA microarray technology was used to analyze gene-expression profiles in the post-mortem frontal cortex of subjects with bipolar disorder, and downregulation of mitochondrial electron transport chain complex I, complex IV and complex V were verified by real-time polymerase chain reaction (Sun et al 2006). 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 (Kato et al 2007; Kato 2008).

C) Intracellular calcium

Mitochondria can directly influence cytoplasmic calcium concentrations by uptake of Ca^{2+} via the mitochondrial Ca^{2+} uniporter or transporting of accumulated Ca^{2+} from mitochondria into cytosol by means of mitochondrial Na^+/Ca^{2+} or H^+/Ca^{2+} exchangers. The endoplasmic reticulum is the major intracellular Ca^{2+} store, whereas mitochondria regulate calcium signalling by uptake followed by releasing of Ca^{2+}; i.e. mitochondria serve as cytosolic Ca^{2+} buffer. Indirect mitochondrial action on calcium signalling is possible by changes of concentrations of ATP, NADH, pyruvate and ROS (Walsh et al 2009).

The mitochondrial uniporter is an inward rectifying, highly Ca^{2+} selective ion channel located in the inner mitochondrial membrane (Kirichok et al 2004) and passes Ca^{2+} down the electrochemical gradient maintained across this membrane. Uptake of Ca^{2+} catalyzed by the mitochondrial uniporter occurs at high (>10 µmol/l) cytosolic Ca^{2+} concentrations that are only reached transiently in cells, near the Ca^{2+} channels. It was revealed that mitochondria are located very close Ca^{2+} release or Ca^{2+} entry channels, i.e. mitochondria are in close contacts with the endoplasmic reticulum and with plasma membrane channels (Giorgi et al 2009). However, mitochondria can also uptake Ca^{2+} at nanomolar concentrations by still not well characterized mechanism. It implies that localization of mitochondria near to the sources of Ca^{2+} might not be absolutely required for mitochondrial Ca^{2+} uptake (Santo-Domingo & Demaurex 2010).

Ca^{2+} enters mitochondria not only during pathological but also during physiological Ca^{2+} responses. Moreover, mitochondria not only passively buffer excessive Ca^{2+} but utilize Ca^{2+} signals to stimulate dehydrogenases involved in the citric acid cycle, i.e. mitochondrial Ca^{2+} transport is linked with the regulation of cellular bioenergetics (McCormack et al 1990; Rizzuto & Pozzan 2006; Walsh et al 2009). Prolonged increases in mitochondrial Ca^{2+} can induce the opening of the PTP leading to mitochondrial swelling, cytochrome *c* release, and apoptosis activation (Demaurex & Distelhorst 2003).

An elevation in basal intracellular Ca^{2+} concentrations was revealed in platelets, lymphocytes, or neutrophiles of patients with bipolar disorder (Quiroz et al 2008). It was suggested that Ca^{2+} release or sequestration may represent a site of dysfunction in bipolar disorder and that mitochondrial Ca^{2+} regulation contributes to these abnormalities (Kato & Kato 2000; Kato et al 2003). It is hypothesized that mitochondrial dysfunction contribute to the pathophysiology of mood disorders both by defective energy metabolism and by participation on altered intracellular calcium signalling (Kato 2008; Jou et al 2009).

D) Energy metabolism

Structural and functional neuroimaging studies have identified regional volumetric reductions and alterations of function in the brain of patients with bipolar disorder (Manji et al 2003). Impairments of cellular plasticity and resilience could be associated with mitochondrial dysfunctions. It was documented by decreased levels of cerebral concentrations of NAA (the compound related to neuronal viability, which is synthesized in mitochondria), decreased phosphocreatine levels (Iosifescu & Renshaw 2003), decreased pH, and increased lactate (i.e. shift away from oxidative phosphorylation towards glycolysis) (Stork & Renshaw 2005). It is possible that the mitochondrial dysfunctions suggested by neuroimaging research are directly related to those previously observed alterations in calcium signalling in patients with bipolar disorder. These observations led to the postulation that at least bipolar disorder may be associated with regional and global hypometabolism and with mitochondrial dysfunctions.

E) Electron transport chain

Additional evidence of mitochondrial dysfunction in bipolar disorder was presented in study, where abnormal gene expression of key mitochondrial proteins was found in the human brain. Extensive decrease in the expression of genes regulating oxidative phosphorylation was found in the hippocampus of subjects with bipolar disorder compared to those with schizophrenia (Konradi et al 2004).

Damage of the mitochondrial electron transport chain has been suggested to participate in the pathogenesis of a range of neurodegenerative disorders. Chronic stress induces an overproduction of nitric oxide, which regulates mitochondrial function by inhibition of respiratory chain. Chronic stress has been used as an animal model of depression. In this model, it was found that stress inhibits complexes I-III and II-III, without affecting complex IV activity (Madrigal et al 2001). Recently, it was found that mild chronic stress inhibits activities of complexes I, III and IV only in cerebral cortex and cerebellum, but complex II and creatine kinase are not affected (Rezin et al 2008). Interestingly, administration of NMDA receptor antagonist ketamine reverses the inhibition of mitochondrial respiratory chain (complexes I, III, and IV) (Rezin et al 2009b).

It seems that complex I plays a major role in controlling oxidative phosphorylation and its abnormal activity can lead to defects in energy metabolism and thereby to changes in neuronal activity (Pathak & Davey 2008). Neuroanatomical pattern of complex I pathology parallels the diversity and similarities in clinical symptoms of schizophrenia, major depressive disorder and bipolar disorder (Ben-Shachar &Karry 2008).

F) Effects of antidepressants on mitochondria

There are evidences that mitochondrial dysfunctions are implicated in the aetiology of drug-induced toxicities, and mitochondrial toxicity testing may help to indentify the most toxic drugs during the preapproval process for new medications (Scatena et al 2007; Neustadt & Pieczenik 2008). But there is relatively little information about relation of antidepressants-induced changes of mitochondrial functions to therapeutic or side effects of these drugs.

Inhibition of mitochondrial MAO is the best known effect of antidepressants on mitochondrial functions. The observation that iproniazid, a drug that irreversibly blocked MAO activity, had antidepressant effects (Fagervall & Ross 1986) led to the discovery of other compounds with similar mechanisms of action. Generally, selective inhibitors of MAO-A and nonselective MAO inhibitors seem to be effective in the treatment of patients with depression, panic disorder, and other anxiety disorders (Stahl & Felker 2008). The selective reversible MAO-A inhibitors, such as moclobemide, are used nowadays as antidepressants (Youdim & Bakhle 2006; Youdim et al 2006). Antidepressants, which act primarily as serotonin and/or norepinephrine reuptake inhibitors, show inhibitory activity towards MAO as well (Reyes & Lisansky 1984; Egashira et al 1996; Gnerre et al 2001; Fišar et al 2010). Mood stabilizers do not inhibit MAO activity.

Both direct and indirect actions of antidepressants and mood stabilizers on mitochondrial functions have been studied. Tricyclic antidepressants have anti-inflammatory and neuroprotective effects by modulating glial activation due to decreased production of nitric oxide and proinflammatory cytokines (Hwang et al 2008), and mitochondria are well-known target of nitric oxide. Recently, very different effects of three antidepressants, nefazodone, trazodone, and buspirone, on the induction of mitochondrial dysfunction and cytotoxicity were described (Dykens et al 2008). Complex I, and to a lesser amount complex IV, were identified as the targets of nefazodone toxicity. No inhibition was found for trazodone, and buspirone showed much lesser inhibition than nefazodone.

Mood stabilizers exert major effects on the regulation of mitochondrial functions, e.g. chronic administration of lithium increases concentration of antiapoptotic protein Bcl-2, reduces levels of the proapoptotic protein p53 and inhibits GSK-3 (Gould & Manji 2005). GSK-3 is kinase that is known for inhibition of the mitochondrial complex pyruvate dehydrogenase (Hoshi et al 1996); thus, GSK-3 inhibition may lead to an increase in maximal metabolic rate in the brain. Lithium induces also changes in activity of the respiratory chain complexes. Activities of complexes I + III and complexes II + III were increased by lithium, activity of succinate dehydrogenase remained unchanged, and activity of complex IV was not affected or decreased (Lambert et al 1999; Maurer et al 2009). Lithium, likely through its effect on mitochondrial functioning, produces a reversal of illness-related atrophy (Quiroz et al 2004, 2008). It can be hypothesised that the mitochondria-controlled process of oxidative damage could be a significant therapeutic target for treatment of bipolar disorder with mood-stabilizing drugs (Wang 2007).

The unique structural and functional characteristics of mitochondria enable the selective intracellular targeting of drugs designed to modulate mitochondrial functions (including electron transport chain, ROS production, mitochondrial PTP, Bcl-2, and mtDNA) for therapeutic gain (Armstrong 2007). E.g. folate supplementation and homocysteine reduction may have roles as an augmentation to antidepressant pharmacotherapy, because low folate status and elevated homocysteine increase the generation of ROSs and contribute to mitochondrial dysfunction, which may lead to apoptosis (Kronenberg et al 2009). Pharmacological targeting of mitochondria in mood disorder is in the developmental stage, because there is insufficient information about side effects of various regulators of mitochondrial functions and it is difficult to affect only the brain regions of interest.

CONCLUSIONS

Signal transduction is an amount of processes by which a cell converts one kind of signal into another. Neuronal signal transduction pathways involve neurotransmitter release, receptor activation and ordered sequence of biochemical reactions inside the cell. These processes can be rapid in the case of ion-channels opening (milliseconds), slower in the case of the activation of second messenger systems (minutes), and slow in the case of gene expression (hours, and even days). As signal propagates from a relatively small initial stimulus to a final large response, the signal cascade involves increasing number of proteins and other molecules (Fišar & Hroudová 2010). Many feedbacks and cross reactions are included in this amplification of the signal. Determining factors in signal transduction are input signals and concentration, activity and subcellular localization of participating molecules. All these factors are determined by previous history of the brain, and it is probable that participate in interindividual differences in response to the same stimuli.

It is assumed that information in the brain is stored both in chemical and structural forms. Chemical form includes changes in expression of cellular molecules and modifications of their properties. Structural form includes neurogenesis and selective neural elimination, formation, destruction or changes of axons, synapses, dendrites (branching, pruning, sprouting) and dendritic spines. Information processing, whether received from surroundings or kept in memory, is based on complex interactions of brain cells and strongly depends on previous history.

Regulation of critical intracellular signalling pathways plays a critical role in higher-order brain functions, which are altered in mood disorders, suggesting the involvement of dysfunctions of signalling pathways in the pathophysiology and the treatment of mood disorders (Gould et al 2007). It can be concluded that both some structural deviations in neural networks and disturbances of signal transduction in certain neurons participate in development of mood disorders. It is assumed that novel biomarkers of mood disorders and/or predictors of efficiency of pharmacotherapy may be discovered on the basis of this research.

It is suggested that environmental stress and genetic risk variants interact with each other in a complex manner to alter neural circuitry and evoke illness. Considering the existence of very rapid distinct shifts of mood (e.g. ultra-ultra-rapid cycling in bipolar affective disorder) (Kramlinger & Post 1996), developmental and structural changes in neural networks could be considered as necessary condition for vulnerability to the development of pathological states of mood, whereas disturbances in signal transduction pathways in chemical synapses could be related to the onset of specific symptoms of mood disorder. Distinct shifts in mood and activity occur both in "normal" and "disordered" man and can be induced both by endogenous and external stimuli. Therefore, occurrence of several symptoms, their severity and time duration depend on the proportion of dysfunction of brain homeostatic mechanisms in various brain areas. It may be supposed that both normal and pathological shifts of mood (e.g. ultradian cycling or rapid switching from episode of depression to mania) are associated with changes in expression or activity of specific compounds of signal transduction pathways related to monoaminergic and glutamatergic systems. Identification of compounds of signal transduction that is primarily responsible for shifts of mood remains incomplete. We suppose that mild dysfunction of some mitochondrial functions might be basis for homeostatic imbalance in synapses during episodes of depression, hypomania, mania or the appearance of mixed states.

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