Beyond the serotonin hypothesis: Mitochondria, inflammation and neurodegeneration in major depression and affective spectrum disorders

Ann Gardner a,⁎, Richard G. Boles b,1

a Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden
b Division of Medical Genetics, Saban Research Institute, Childrens Hospital Los Angeles, Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA 90027, USA

A R T I C L E   I N F O

Article history:
Received 31 January 2010
Received in revised form 2 July 2010
Accepted 28 July 2010
Available online 5 August 2010

Keywords:
ATP
Inflammation
Major depression
Mitochondrial
mtDNA
Unipolar depression

A B S T R A C T

For many years, a deficiency of monoamines including serotonin has been the prevailing hypothesis on depression, yet research has failed to confirm consistent relations between brain serotonin and depression. High degrees of overlapping comorbidities and common drug efficacies suggest that depression is one of a family of related conditions sometimes referred to as the “affective spectrum disorders”, and variably including migraine, irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia and generalized anxiety disorder, among many others. Herein, we present data from many different experimental modalities that strongly suggest components of mitochondrial dysfunction and inflammation in the pathogenesis of depression and other affective spectrum disorders. The three concepts of monoamines, energy metabolism and inflammatory pathways are inter-related in many complex manners. For example, the major categories of drugs used to treat depression have been demonstrated to exert effects on mitochondria and inflammation, as well as on monoamines. Furthermore, commonly-used mitochondrial-targeted treatments exert effects on mitochondria and inflammation, and are increasingly being shown to demonstrate efficacy in the affective spectrum disorders. We propose that interactions among monoamines, mitochondrial dysfunction and inflammation can inspire explanatory, rather than mere descriptive, models of these disorders.

© 2010 Elsevier Inc. All rights reserved.

1. Introduction

1.1. Depression and affective spectrum disorders

For many years, the prevailing hypothesis on depression has been that depression is caused by an absolute or relative deficiency of monoamines. The serotonin hypothesis of depression arise due to the observation that reserpine, an antihypertensive drug that depletes the brain of monoamine neurotransmitters including serotonin, inadvertently caused depression. Studies on the mode of action of tricyclic antidepressants also suggested that serotonin is primarily involved in the control of mood. A causal relationship was suggested between disturbances in monoamine metabolism and depression (Coppen, 1967; Schildkraut, 1965). In a review of serotonin and psychiatric disorders, it was pointed out that the relation between disturbances in monoamine metabolism and depression between disturbances in monoamine metabolism and depression have been displayed interactions with environmental factors, and in some cases even opposite directions between the genders (Nordquist and Oreland, 2010).

We believe that the literature does not support the hypothesis that the pathogenesis of depression is predominately a function of monoamines alone. After a lifetime investigating mood disorders, Winokur proposed that unipolar depression is clinically homogeneous but etiologically heterogeneous (Judd et al., 1998; Winokur, 1997). In this review we will present the “mitochondrial psychiatry” model of depression in Sections 2 and 3, and the “inflammatory hypothesis” model of depression in Section 4.
can shed some light on pathogenesis, we begin the review by the presentation of major depression in the context of the family of affective spectrum disorders.

1.2. The concept of major depression

Depression is a relatively recent word in the history of the English language, and was first coined by Samuel Johnson who used it in the 1750s to describe low spirits (Rousseau, 2000). The historical origins of the present-day concept of major depression are presented in a recent essay. Fatigue and loss of energy were recognized as common symptoms in depression in the 1950–70s (Kendler et al., 2010) and are included as the A6 criterion in DSM-IV for Major Depressive Episode. Pain (e.g., headaches or joint, abdominal, or other pains) is mentioned as a frequent associated feature in the introductory chapter (American Psychiatric Association, 1994) and multiple somatic symptoms have been suggested to be a core component of depression (Simon et al., 1999).

Chronic pain, leden paralysis (a heavy, leden feeling in the limbs) and hypersomnia are common features in atypical depression, a depression subtype which has been a subject of nosological debate since its inception in the late 1950s. Atypical depression has been reported in 31–62% of those with major depressive episodes. Clinical studies have showed that 64–72% of those with atypical depression have bipolar II or subthreshold bipolar II. Atypical depression may occupy an intermediate nosological position in the unipolar–bipolar spectrum of mood disorders (Lee et al., 2009). Bipolar II patients were recently reported to experience more depressive episodes and more leden paralysis than bipolar I patients suggesting that these groups may not represent a continuum. Clinical variables other than the intensity of hypomanic/manic symptoms may differentiate these groups (Janowsky, 2009). It is difficult to clinically differentiate recurrent major depression from bipolar II, which was reported in 21% of depressive outpatients in a study (Malik, 2009), since patients may not consider hypomanic episodes as ego-dystonic (Cassano et al., 1999).

For the above-mentioned reasons, studies of major depression may contain variable proportions of patients with atypical depression and bipolar II. Other confounding factors are comorbidity with ADHD, as ADHD may be common in individuals with major depression (Goodman and Thase, 2009), that atypical depression may be common in ADHD (Asherson, 2005), and that lifetime ADHD is a frequent comorbid condition in adults with bipolar disorder (Nierenberg et al., 2005). Among patients with ADHD plus bipolar disorder in one study, 88% had bipolar II (Wilsen et al., 2003).

Episodes of major depression may be the most severe state of illness representing only the tip of the iceberg of a common, chronic and disabling disease with alternating symptom severity. A conceptual shift has occurred in the understanding of depression and it is now seen as a chronic medical disease (Angst, 1999; Judd et al., 1998). Cognitive impairment affecting the domains of executive functioning, attention, memory, visuo-spatial processing and psychomotor function, is a feature of major depression. Lasting cognitive impairment in immediate memory and attention has been reported in subjects with previous depression (Baune et al., 2010).

1.3. Common physical/medical comorbidities in major depression

In a study of depressed inpatients, 92% reported pain, headache and/or myalgia at admission (Corruble and Guelfi, 2000). Major depression has been reported to increase the risk for migraine, and migraine to increase the risk for major depression (Breslau et al., 2003). Tinnitus has been reported in 48% of unmedicated depressed patients, while it was only present in 12% of the controls (Mathew et al., 1981). Irritable bowel syndrome (IBS) has been demonstrated to co-associate with depression in numerous studies (Garakani et al., 2003; Gros et al., 2009). The presence of a functional state of insulin resistance during major depression, with serum glucose concentrations remaining elevated for a longer time than in controls, suggests impaired glucose utilization and thus that major depression represents a more generalized biological disturbance in some patients. The results from those patients were similar to type 2 diabetes in which the most important site of insulin resistance is in the muscle tissue (Winokur et al., 1988). A meta-analysis revealed that depression is associated with a 60% increased risk of type 2 diabetes, while type 2 diabetes is associated with only a modest increased risk of depression (Mezuk et al., 2008).

1.4. The concept of affective spectrum disorders

The term “affective spectrum disorders” has been proposed for a group of psychiatric and medical disorders suggested to share specific but unknown pathogenic factors — because each disorder has been shown to respond to three or more chemically unrelated classes of antidepressant medications (Hudson et al., 2004). As such, it has been proposed that the affective spectrum disorders include the conditions of major depression, ADHD, bulimia nervosa, dysthymic disorder, generalized anxiety disorder (GAD), obsessive–compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder, social phobia, fibromyalgia, IBS, migraine, and cataplexy (attacks of muscular weakness triggered by strong emotions) (Hudson et al., 2004). Chronic fatigue syndrome (CFS, or ME/CFS) is common in patients with fibromyalgia (Hudson et al., 2004), was included in the “affective-sensory model” of functional somatic syndromes in a twin study (Kato et al., 2009), and has a high co-occurrence with major depression (Ciccone and Natelson, 2003). For these reasons we include ME/CFS in this review although the inclusion of ME/CFS into the affective spectrum disorder group is controversial.

1.5. The nosology of the major depression diagnosis

Sullivan and Kendler have suggested that the scale of the co-occurrence between major depression and other conditions is not consistent with an orthodox conceptualization of major depression as a discrete nosological entity. Psychiatric nosology, as in the DSM-IV, does not adequately capture the “natural” tendency to health-related as well as psychiatric comorbidity (Sullivan and Kendler, 1998). Klein has suggested that the shift from conceptualizing mood disorders as episodic or remitting conditions ought to be replaced by a two-dimensional system assessing severity and chronicity in the classification of depressive disorders in the upcoming DSM-V (Klein, 2008). Zimmerman et al. have reported that at omission of the four somatic criteria of major depression in the DSM-IV (weight loss, weight gain, sleep disturbance, and fatigue, which may be sequelae of medical illnesses) and only assessing three of five mood and cognitive symptoms (low mood, loss of interest, guilt or worthlessness, impaired concentration or indecisiveness, and death wishes or suicidal thoughts), a high level of concordance with the original DSM-IV classification was found between this simpler definition of major depression in three patient samples. The authors comment that an unintended consequence of the elimination of the somatic items from the criteria may be the reduced appreciation of the somatic expression of psychiatric illness, and that the elimination might interfere with clinicians recognizing depression in patients who present with somatic complaints, thus overlooking symptoms that are important to assess in depressed patients (Zimmerman et al., 2010).

2. Mitochondrial disorders

2.1. The pathophysiology of mitochondrial disorders

Mitochondria are cytoplasmic–located cellular organelles whose most fundamental function is the production of adenosine triphosphate (ATP)
in the respiratory chain. Tissues and organs that are heavily dependent upon ATP production, predominantly nerve and muscle, are affected first and foremost in mitochondrial disorders. However, variability in terms of clinical manifestations and severity is extremely broad. Mitochondrial disorders, because of the widespread cellular distribution of mitochondria, in fact may lead to all kinds of clinical signs and symptoms ranging from mild myopathic complaints to neonatal death and virtually everything in between (Smelink, 2003).

Mitochondrial disorders may arise due to mutations in two distinct genetic systems: the nuclear DNA (nDNA) within the chromosomes and the mitochondrial DNA (mtDNA). Some patients appear to be sporadic cases, whereas others are clearly familial. The first pathogenic mtDNA mutations that could be linked to specific disorders were reported in 1988 (Holt et al., 1988; Lestienne and Ponsot, 1988; Wallace et al., 1988; Zeviani et al., 1988). mtDNA is inherited only from the ova, and hence is transmitted in the maternal line. A maternal inheritance pattern has been established for some mtDNA mutations, including most point mutations and duplications. Paternal inheritance of mtDNA in a human has been reported only once (Schwartz and Vissing, 2003). The concept “Mitochondrial Medicine” was coined in 1994 by Rolf Luft who in 1962 reported the first case of a mitochondrial disorder in a female patient investigated at Karolinska Hospital in Stockholm (Luft, 1994; Luft et al., 1962). This patient later committed suicide (personal communication 2005, A.G. and Rolf Luft).

Most people have a single dominant mtDNA sequence throughout their tissues, although individual tissues harbour sequence variations, a condition known as “homoplasy”. By contrast, patients harbouring pathogenic mtDNA defects often have a mixture of two different mtDNA sequences throughout their tissues, which is known as “heteroplasy”. The percentage of the mutated mtDNA sequence can vary widely among different members of the same maternal line, as well as from tissue to tissue within the same individual, and even between individual cells in a tissue. Various nuclear genes have also been identified that are fundamentally important for mtDNA homeostasis, and when these genes are disrupted, they cause autosomal-inherited (dominant or recessive) mitochondrial disease. Some such disorders cause secondary mtDNA abnormalities (deletions and/or copy number depletion), and are considered as defects in intergenicom communication (Spinazzola and Zeviani, 2009). In recent years, disease-causing mechanisms affecting the import of proteins into mitochondria, and mitochondrial dynamics (fission, fusion, and intracellular transport) have been described (DiMauro and Schon, 2008).

While most human cells contain two copies of nDNA, they contain many more copies of mtDNA (from 100 to 100,000, depending on the cell type). The expression of over 90% of the whole mtDNA consisting of a ~16,569 base pair (bp) circle of double stranded DNA is essential for mitochondrial bioenergetic function, whereas only ~7% of the nuclear genome of ~10^9 bp has been proposed to be expressed at any particular differentiated stage (Ozawa, 1997).

The proportions of mutated mtDNA in individual tissues may change during development and throughout adult life, potentially influencing the phenotype within an individual. Two mechanisms contribute to this process: relaxed replication and mitotic segregation. mtDNA replication is independent of the cell cycle, i.e., it is relaxed. Unlike nDNA which replicates only once during each cell cycle, mtDNA is continuously recycled, even in nondividing tissues such as skeletal muscle and brain. In a heteroplasmic cell, mutated and wild-type mtDNA can replicate at subtly different rates — either by chance or because of a subtle selective effect in favour of one particular type. This mechanism can lead to changes in the proportions of mutated mtDNA in patients with mtDNA disease, providing an explanation for the late onset and progression of some mtDNA disorders. When a heteroplasmic cell divides, subtle differences in the proportion of mutated mtDNA may be passed on to the daughter cells, leading to changes in the level of mutated mtDNA within a dividing tissue. Presumed shifts due to functional selection against the mutant mtDNA explain why the level of some pathogenic mtDNA mutations decreases in some rapidly-dividing tissues, such as blood, during life. Clinical expression of mitochondrial disorders is influenced by the heteroplasmic proportions, mtDNA background, nuclear background, and their interaction with the environment (Chinnery and Schon, 2003).

The overall process in which ATP is produced is schematically presented in Fig. 1. Nuclear genes code for the majority of mitochondrial respiratory chain polypeptides which make up the five mitochondrial respiratory chain enzyme complexes, see the bottom line in the figure. These polypeptides are synthesised in the cytoplasm with a mitochondrial targeting sequence that directs them through the translocation machinery spanning the outer and inner membranes of mitochondria which are depicted in Fig. 2. ATP is the high energy source used for most active metabolic processes within the cell, and it must be released from the mitochondrion in exchange for cytosolic ADP. Thus the respiratory chain is an elaborate system that must

---

**Fig. 1.** The picture (modified and used with permission by Ben-Shachar (2002)) shows the respiratory chain complexes, with their rough spatial configurations, embedded in the mitochondrial inner membrane (see Fig. 2). Reduced cofactors (NADH and FADH2) generated from the intermediary metabolism of carbohydrates, proteins, and fats, donate electrons to complexes I and II. These electrons flow between the complexes down an electrochemical gradient, shuttled by complexes III and IV and by two mobile electron carriers, ubiquinone (co-enzyme Q10) and cytochrome c (Cyt c). The liberated energy is used by complexes I, III, and IV to pump protons (H^+) out of the matrix, the mitochondrial center, into the intermembrane space, the space between the outer and inner membranes. This proton gradient, which generates the bulk of the mitochondrial membrane potential, is harnessed by complex V to synthesise ATP from adenosine diphosphate (ADP) and inorganic phosphate (Pi).
Mitochondrial dysfunction can arise due to deficiencies of cofactors necessary for the function of the mitochondrial respiratory chain. Coenzyme Q10 (CoQ10) transfers electrons from complexes I and II to complex III in the respiratory chain. Mutations in two CoQ10 biosynthetic enzymes causing mitochondrial dysfunction have been identified in cases of encephalomyopathy and nephrotic syndrome. From its scientific importance, knowledge of CoQ10 deficiency syndromes is important for physicians because most patients improve with CoQ10 supplementation (DiMauro and Schon, 2008). Among other deficiencies that may contribute to disease-related mitochondrial dysfunction are deficiencies of selenium (Jeffree et al., 2007), B-vitamins (Depeint et al., 2006), and carnitine, the latter of which is involved in the lipid transport across the mitochondrial membranes (Parikh et al., 2008; Scholte et al., 1987).

2.2. Common physical comorbidities, depression and other affective spectrum disorders in mitochondrial disorders

Many symptoms in mitochondrial disorders are non-specific. The symptoms may also show an episodic course, with periodic exacerbations. The episodic condition of migraine, as well as myalgia, gastrointestinal symptoms, tinnitus, depression, chronic fatigue, and diabetes, are mentioned among the various manifestations of mitochondrial disorders in review papers on mitochondrial medicine (Chinnery and Turnbull, 1997; Finsterer, 2004). Cognitive features of mitochondrial disorders in patients without general cognitive decline are impairments of memory, executive functioning, attention, visuo-spatial processing and psychomotor function (Bosbach et al., 2003; Turconi et al., 1999). In patients with mitochondrial disorders, clinical symptomatology typically occur at times of higher energy demand associated with physiological stressors such as illness, fasting, over-exercise, and environmental temperature extremes. Furthermore, psychological stressors also frequently trigger symptomatology, presumably due to higher brain energy demands for which the patient is unable to match with sufficient ATP production. In a patient with mitochondrial dysfunction, episodes of severe depression occurred after long-term work-related stress (Gardner et al., 2003a). It is unknown if such deterioration at increased cellular work load is linked to a further increase of the oxidative stress contributing to the pathology associated with the mitochondrial defect (Mckenzie et al., 2004).

The concept “Mitochondrial Psychiatry” has been used in the title of a review about psychiatric symptoms in mitochondrial disorder and of mitochondrial alterations in psychiatric disorders (Gardner and Boles, 2005), and as chapter titles in a book and a review about mitochondrial medicine (DiMauro et al., 2006; DiMauro and Schon, 2008). The authors of the book provided the chapter on mitochondrial psychiatry because it deserves, in their stated view, more attention both for clinical and therapeutic reasons and because it offers a window on the pathogenic mechanisms of affective and behavioral disorders (Rosenberg, 2006). Depression is not infrequent, and sometimes the sole clinical manifestation, in mitochondrial patients (DiMauro and Schon, 2008).

In another study, major depression was found in 5 out of 35 children and adolescents (14%) with various mitochondrial disorders. It was suggested that abnormal central nervous system energy metabolism may be an important contributing factor in the development of depression in the patients with mitochondrial disorders (Koene et al., 2009). Paediatric depression in general varies between 3 and 4% in children and adolescents (Merikangas et al., 2010).

Two studies revealed that a several-fold increased likelihood of developing depression can be maternally inherited along with the mtDNA, which strongly argues that mtDNA sequence variants may induce mitochondrial dysfunction that can predispose individuals towards the development of depression (Boles et al., 2005; Burnett et al., 2005).

3. Mitochondrial dysfunction in depression and other affective spectrum disorders

3.1. Mitochondrial dysfunction in depression

The relationship between mitochondrial dysfunction and unipolar depression has been explored in several studies. In studies of postmortem brain from subjects with probable or diagnosed major depression, of whom most subjects were (probably) medicated, no increase of the common 5 kb mtDNA deletion could be detected (Kato et al., 1997; Sabunciyian et al., 2007; Shao et al., 2008, Stine et al., 1993). Alterations of translational products linked to mitochondrial function were found in the frontal, prefrontal and tertiary visual cortices (Karry et al., 2004; Whatley et al., 1996). Alterations of four mitochondrial-located proteins in the anterior cingulate cortex have been reported (Karry et al., 2004). Decreased gene expression for 6 of 13 mtDNA-encoded transcripts in frontal cortex tissue (Brommann areas (BA) 9 and 46) (Shao et al., 2008), and of nDNA-encoded mitochondrial mRNA and proteins in the cerebellum, have also been reported in major depression (Ben-Shachar and Karry, 2008). Levels of an electron transport chain complex I subunit (NDUFS7), and complex I activity, in postmortem prefrontal cortex were found to be below or at the lowest range of the normal controls in half of the cases of major depressive disorder in a recent study (Andreazza et al., 2010). In the two latter studies, the authors were unable to detect any effect of medication on the results.
subject with very high degrees of somatic complaints demonstrated low ATP production rates in biopsied muscle suggested clinical relevance (Gardner and Boles, 2008a). Six specific questions related to dysautonomia, muscle symptoms, and mental fatigue resulted in near-perfect separation between depressed subjects with high degrees of such somatic complaints and low muscle ATP production rates, and depressed subjects with normal degrees of somatic complaints and normal muscle ATP production rates (Gardner and Boles, 2008b).

3.2. Mitochondrial dysfunction in other affective spectrum disorders

Mitochondrial abnormalities in muscle with ragged red fibers (RRF, collections of abnormal mitochondria oftentimes considered to be an informative light microscopic alteration of mitochondrial disorders) and reduction of the number and shape of mitochondria have been reported in fibromyalgia (reviewed in Le Goff, 2006). In migraine, RRFs and cytochrome c-oxidase (COX) negative fibers (considered “the histochecmical signature” of most mitochondrial encephalomyopathies) have been found in muscle in some patients, as well as biochemical alterations indicating mitochondrial dysfunction (reviewed in Sparaco et al., 2006). In ME/CFS, several differentially expressed genes affect mitochondrial functions, including fatty acid metabolism (Vernon et al., 2006). Anticardiolipin antibodies in the sera of ME/CFS patients indicate alterations of mitochondrial inner membranes (Hokama et al., 2009). In a study of the degree of dysfunction of ATP production in neutrophils in ME/CFS patients and healthy controls, dysfunction was strongly correlated with the severity of illness. The authors concluded that mitochondrial dysfunction is the immediate cause of ME/CFS symptoms (Myhill et al., 2009).

3.3. Mitochondrial dysfunction in bipolar disorder

The association between mitochondrial function and bipolar disorder has been explored in many studies and will not be reviewed here. The authors of a perspective paper on the topic concluded that “accumulating evidence from microarray studies, biochemical studies, neuroimaging, and postmortem brain studies all support the role of mitochondrial dysfunction in the pathophysiology of bipolar disorder. We propose that although bipolar disorder is not a classic mitochondrial disease, subtle deficits in mitochondrial function likely play an important role in various facets of bipolar disorder” (Quiroz et al., 2008). Impairment of complex I was seen in prefrontal cortex in all patients with bipolar disorder (Andreazza et al., 2010), and abnormalities of mitochondrial structure in the prefrontal cortex, fibroblasts and lymphocytes in another recent study (Cataldo et al., 2010). A mouse model with multiple mtDNA deletions in brain demonstrates mood disorder-like phenotypes which resemble bipolar disorder (Kasahara et al., 2006, 2008). Altered levels and/or turnover of (several) monoamines compared to control littermates including substantially decreased serotonin levels in the hippocampus and amygdala were demonstrated in one of these studies (Kasahara et al., 2006). This model is intriguing, linking mitochondrial dysfunction and secondary monoamine depletion with the phenotype of a mood disorder.

4. Inflammation and neurodegeneration in depression, other affective spectrum disorders, and mitochondrial disorders

4.1. The concept of inflammation

Inflammation is the term for the complex biological response of tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is a protective attempt by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue. Inflammation is normally closely regulated by the body. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. A possible explanation for the parallel and overlap between the pathways activated during immunity and those controlling apoptosis (programmed cell death, death of a cell in any form mediated by an intracellular program that may be stimulated due to injury or disease) and cell survival indicate co-evolution of these pathways/effectors under pressure imposed by infections. Bacteria, and mitochondria (that are reminiscent of bacteria), sit on top of the signaling pathway. Low-level caspase-1 activation does not only result in inflammation, which alarms the system without killing the cell, but also favours cell survival through regulation of lipid biogenesis and membrane repair. Bcl-2 proteins that control mitochondrial cell death appear to additionally regulate caspase-1 activation (Yeretssian et al., 2008).

Caspases are a family of cysteine proteases, which play essential roles in inflammation, apoptosis, and necrosis and have been termed “executioner” proteins for their roles in the cell. Caspase-1 is required in the immune system for the maturation of inflammatory cytokines. Cytokines are produced by macrophages, T cells, platelets and vascular wall cells and exert their biological effect by binding to specific receptors on the surface of target cells. Cytokines also interact with mitochondria to increase the production of reactive oxygen species (ROS). Mitochondria also generate ROS as byproducts during ATP production. ROS at low concentrations may function as signaling molecules and participate in the regulation of cell activities such as cell growth. In contrast, ROS at high concentrations may cause cellular injury and death. ROS in turn increase cytokine expression, which closes vicious circle of inflammation (Sprague and Khalil, 2009).

4.2. The concept of neurodegeneration

Neurodegeneration is the umbrella term for the progressive death and loss of neurons. Neurodegeneration can be found in many different levels of neuronal circuitry ranging from molecular to systemic (Bredesen et al., 2006; Rubinsztein, 2006; Thompson, 2008). The most common form of cell death in neurodegeneration is through the intrinsic mitochondrial apoptotic pathway. This pathway controls the activation of caspase-9 by regulating the release of cytochrome c from the mitochondrial intermembrane space. The concentration of ROS, normal byproducts of mitochondrial respiratory chain activity, is mediated in part by mitochondrial antioxidants. Over production of ROS (oxidative stress) is a central feature of all neurodegenerative disorders. In addition to the generation of ROS, mitochondria are also involved with life-sustaining functions including calcium homeostasis, mitochondrial fission and fusion, the lipid concentration of the mitochondrial membranes, and the mitochondrial permeability transition (MPT). Mitochondrial disease leading to neurodegeneration is likely, at least on some level, to involve all of these functions (DiMauro and Schon, 2008).

Palace has pointed out that in multiple sclerosis (MS), the conventional hypothesis is that an autoimmune process and subsequent inflammation lead to neurodegeneration. However, data have shown that neurodegeneration occurs early in the disease. Neurodegeneration can itself lead to inflammation, and laboratory and clinical observations suggest that inflammation can be neuroprotective (Hohlfeld et al., 2006). Thus, powerful immunomodulation at onset may not only be ineffective but harmful. Alternative anti-inflammatory treatments need to be developed if there is a low-grade inflammation in MS, as suggested (Palace, 2007).

4.3. Inflammation and neurodegeneration in depression

Signs indicative of immune activation in major depression have been reported since 1990–1991 (Maes et al., 1990–1991). The presence of an inflammatory response in major depression has since then been reported several times and is evidenced by, amongst other
things, increased plasma levels of pro-inflammatory cytokines and acute phase reactants, oxidative damage to red blood cell membranes and serum phospholipids, and lowered serum zinc (Maes et al., 1995; Maes et al., 2009a). In a recent review of the immunity hypothesis of depression, Miller remarks that “it has been heartening for me to see the tremendous progress that has been made in terms of understanding [—] how the immune system interacts with pathophysiologic pathways relevant to depression” (Miller, 2010). In a recent meta-analysis of 24 studies involving unstimulated measurements of cytokines in patients with major depression, the result was interpreted to strengthen the evidence that depression is accompanied by activation of the immune response system (Dowlati et al., 2010).

A support for the role of pro-inflammatory cytokines in depression is the observation that they can induce depression in up to 70% of patients treated with such agents (Maes et al., 2009a). While there is considerable overlap in symptom expression between cytokine-induced depression and idiopathic depression, including general somatic symptoms (muscle aches and fatigue) being increased to a comparable degree in both groups, differences suggest that cytokines may preferentially target neurocircuits relevant to psychomotor activity (e.g. basal ganglia) while having a limited effect on cognitive distortions regarding self-appraisal (Capuron, 2009a).

Depression is also associated with neurodegeneration and reduced neurogenesis. Decreases of synaptic “products” indicative of spine loss, and of prefrontal inhibitory local circuit neurons, alterations in the packing density and size of cortical neurons in frontolimbic brain regions, and reduced cortical glial cell numbers, have been described in depression (reviewed in Gardner and Pagani, 2003). Decreased volumes of various brain regions in major depression have been reported using magnetic-resonance morphometry (Campbell et al., 2004; Campbell and MacQueen, 2006; Parashos et al., 1998; Steingard et al., 2002; Vasic et al., 2008; Zou et al., 2010). A significant reduction in neuropil detected by decreased pyramidal neuron soma size may account for the decreased hippocampal volume seen by neuroimaging in major depression (Stockmeier et al., 2004).

4.4. Inflammation and neurodegeneration in the other affective spectrum disorders

Elevations of cytokines have been reported in fibromyalgia (Gür et al., 2002; Wallace et al., 2001; Zhang et al., 2008a). In a search for a candidate gene affecting inflammatory pathways in fibromyalgia, rare missense variants of the MEVF gene were found in 15% of the patients which, on average, had higher levels of IL-1β (a pro-inflammatory cytokine) compared to controls (Feng et al., 2009). Various mutations in MEVF lead to Familial Mediterranean Fever (FMF), the most common inherited autoinflammatory disease in the world. Mitochondrial abnormalities in kidney (Kiliçaslan et al., 2007) and increased depression scores (Makay et al., 2010) have been reported in FMF. Other manifestations of MEVF mutations other than FMF have recently been described (Ben-Chetrit et al., 2009).

Furthermore, decreased volumes of various brain regions in fibromyalgia have been reported using magnetic-resonance morphometry (Burgmer et al., 2009; Kuchina et al., 2007; Lutz et al., 2008; Schmidt-Wilcke et al., 2007). However, when another group of fibromyalgia patients was investigated, volume decreases were only observed in those patients with concurrent major depression, bipolar disorder, dysthymia, or general anxiety disorder (Hsu et al., 2009).

Elevations of cytokines have also been reported in migraine (Ba et al., 2009; Koçer et al., 2009; Perini et al., 2005; Sarchielli et al., 2006) and IBS (Dinan et al., 2006; Langhorst et al., 2009; Liebregts et al., 2007; Öhman et al., 2009). Decreased volumes of various brain regions in migraine have been reported using magnetic-resonance morphometry (Kim et al., 2008). Morphological alterations indicating enteric neuropathy have been reported in the gut in IBS (Lindberg et al., 2009; Törnblom et al., 2002; Veress et al., 2009).

Numerous studies have shown that ME/CFS is characterized by aberrations in inflammatory pathways including cytokine abnormalities (Fletcher et al., 2009; Gupta et al., 1997; Patarca, 2001). Larger cerebral ventricles and decreased volumes of various brain regions in ME/CFS have been reported using magnetic-resonance morphometry (de Lange et al., 2005; Lange et al., 2001).

4.5. Cellular degeneration in inflammation and mitochondrial disorders

It has been suggested that, as a general rule, muscle cells in mitochondrial myopathies are disabled, but often do not die. Inflammatory reaction, connective tissue infiltration, and muscle necrosis, are usually absent (Schon et al., 1997). However, remarkable atrophy with variation in size and form of muscle fibers with unclear margins and prominent nuclei may be observed (Mizukami et al., 1992).

Neuropathological examinations of the brain in patients who died due to severe mitochondrial disorders have revealed prominent neuronal degeneration, gliosis in both the grey and white matter, total loss of regional nerve cells, and demyelination (Filosto et al., 2007; Mizukami et al., 1992; Oldfors et al., 1990; Sparaco et al., 1993; Tanahashi et al., 2000). Macrophage infiltration has been observed in a few cases (Piao et al., 2006; Sparaco et al., 2003).

Recent findings in MS, generally considered to be an inflammatory disease (Palace, 2007), suggest mitochondrial dysfunction in the pathogenesis of disease progression (Mao and Reddy, 2010; Regenold et al., 2008; Su et al., 2008). The inflammatory infiltrates in MS consist of macrophages/microglial cells, T cells, plasma cells and B cells with macrophages/microglia as the dominant cell population in newly formed lesions. So-called chronic active lesions show a rim of inflammatory cells (microglial cells and T cells) at the border to the normal-appearing white matter (Kuhlmann et al., 2009). Remyelination and inflammatory infiltrates apart from occasional macrophage infiltration were not observed in brain of patients with primary mitochondrial disorders (Filosto et al., 2007; Mizukami et al., 1992; Oldfors et al., 1990; Sparaco et al., 1993; Tanahashi et al., 2000) except in cases of Leber’s Hereditary Optic Neuropathy (LHON), an mtDNA disorder that presents clinically overwhelmingly in males, but can be associated with an MS-like illness mainly in females (Palace, 2009; Perez et al., 2009). Neuropathological lesions in LHON with demyelinating plaques in white matter, presence of macrophages and lymphocytes within lesions, and T cells in the frontal lobe, were described in a case. It was suggested that mtDNA mutations may affect the nervous system on a common metabolic basis and occasionally may aggravate or initiate autoimmune pathology (Kovác et al., 2005).

It has been proposed that the over-expression of the Class I major histocompatibility complex (MHC I) detected in fibroblasts from patients with the mtDNA-mutation disorder Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like episode (MELAS) provides a mechanism by which the immune system can recognize and eliminate cells containing mtDNA mutations (Gu et al., 2003). The MCH in humans is oftentimes referred to as the human leukocyte antigen system (HLA), and these molecules are found on every nucleated cell of the body with the function to display fragments of proteins from within the cell to T cells; thus healthy cells are ignored while cells containing foreign proteins such as those infected by a bacterium or virus will be attacked by the immune system. HLA types are inherited and people with certain HLA antigens are more likely to develop some autoimmune diseases such as type 1 diabetes. HLA typing in autoimmune is being increasingly used as a tool in diagnosis.

Diabetes mellitus is common in the mitochondrial disorder MELAS. HLA typing in a MELAS patient with diabetes revealed DR3 and DR4 types that are linked to diabetes, and positive anti-GAD antibody. The findings were interpreted to suggest that autoimmunity may have contributed to diabetes in this patient (Huang et al., 1998). Ilet cell antibodies were found in three members of a family with MELAS and diabetes indicating that mitochondrial diabetes may involve beta cell
damage (Oexle et al., 1996). In a patient with Kearns–Sayre syndrome (KSS) with a large-scale mtDNA deletion, and diabetes and hypoparathyroidism, HLA typing showed the presence of HLA-A24 and CW3 antigen. A genetic linkage, as well as mitochondrial dysfunction, was considered as responsible for the co-occurrence of the disease states (Isohani et al., 1996). Patients with mitochondrial gene mutations and diabetes are usually autoantibody-negative (Zhang et al., 2004). One of four LHON patients in a study also had an HLA haplotype associated with MS. The disease progression was not more severe in this patients compared to the other LHON patients (Morrissy et al., 1995). Some mitochondrial disease patients are noted to have decreased CSF folate levels, and treatment with folic acid (which delivers folate to brain independent of that receptor) appears efficacious in some. In one such patient, folate receptor-blocking antibodies were found (Hasselmann et al., 2010), demonstrating another mechanism in which immune activation may result in clinical disease in these patients.

Systemic juvenile idiopathic arthritis (sJIA) is a rheumatic disease in childhood characterized by systemic symptoms and a relatively poor prognosis. An increase of foremost depressive disorder and somatiform disorder has been reported (Mullick et al., 2005). Peripheral leukocytes are thought to play a pathological role, and overproduction of pro-inflammatory cytokines is reportedly involved in the disease. These soluble factors may affect the peripheral leukocytes and alter the gene expression profiles in the cells. In a study of the gene expression profile in peripheral leukocytes, genes involved in mitochondrial ATP production were downregulated, suggesting mitochondrial dysfunction. Expression of mtDNA-encoded genes were suppressed in patients with sJIA, while the investigated nDNA-encoded mitochondrial genes were intact. Molecules constituting tumor necrosis factor (TNF) network cascades were upregulated. TNFα is a pro-inflammatory cytokine. The findings were interpreted to suggest that sJIA is not only an immunological disease but also a metabolic disease involving mitochondrial dysfunction. The mitochondrial dysfunction may be secondary to overproduction of TNF since TNF induces mitochondrial damage (Ishikawa et al., 2009).

Cytokines play a role in the regulation of chondrocyte function, and pro-inflammatory cytokines are considered to be important in cartilage destruction. In addition, multiple studies have implicated a decrease in mitochondrial bioenergetic reserve as a pathogenic factor. In a study of pro-inflammatory cytokine exposure, breaks in the mtDNA and decreased ATP levels were found at increasing exposure in osteoarthritic, but also in normal, human cartilage cells. Treatment with a vector-delivered DNA-repair enzyme protected the chondrocytes from accumulation of mtDNA breaks and preserved ATP levels. The authors conclude that the mitochondrion is an important target for chondrocyte damage induced by pro-inflammatory cytokines. Protection from this damage ameliorates mitochondrial dysfunction and diminishes cell death induced by cytokines (Kim et al., 2010).

At reinterpretation of the previously mentioned study of mitochondrial biochemistry and small mtDNA deletions in muscle from patients with a lifetime diagnosis of major depression (Gardner et al., 2003b) with “immunological vision”, it cannot be excluded that the origin of the small mtDNA deletions was the result of an inflammatory process. No deletions were found in the investigated mtDNA regions in four of 25 investigated patients, one of whom was shown to have a primary mtDNA disorder. An mtDNA duplication producing several mtDNA deletions in this patient was described by another laboratory (Houshmand et al., 2004). In the 22 controls, deletions were found in all elderly subjects. Chronic low-grade inflammation is a characteristic of ageing (Capuron et al., 2009b), and breaks in the mtDNA with pro-inflammatory cytokine exposure were found in the above-mentioned study (Kim et al., 2010).

5. Diagnostic problems and promises in mitochondrial disorders

This section is included in order to give the reader a perspective of the kinds of analyses that can be applied to searching for mitochondrial disease, and mitochondrial dysfunction, on a clinical basis in individuals with depression thought to possibly have a mitochondrial disorder, as well as in studies of depression and other psychiatric disorders.

There is no one single test that will prove or disprove whether a patient has a mitochondrial disorder (Chinnery and Schon, 2003; Haas et al., 2008; Mancuso et al., 2009). The diagnosis is generally suspected based upon the clinical presentation, including the presence of multiple idopathic, and generally intermittent, manifestations of nerve and muscle disease. However, the range of known clinical manifestations is so broad such that a large proportion of all patients in general have consistent presentations. A family history of a high prevalence of disorders among the matrilineal relatives can be helpful when present, but such a history is often absent (autosomal recessive disease and new mtDNA mutations), and when present the clinical manifestations are generally radically different in each affected relative. Thus, biomarkers for laboratory screening of at risk patients are needed, as well as definitive testing at the protein or gene levels.

The first line of laboratory screening in most expert centres consists of analyses of body fluid metabolites (blood and urine, sometimes CSF) for markers of disturbed energy metabolism. Usually this consists of screening for elevated intermediates of lipid and carbohydrate metabolism, including assays of lactate, pyruvate, ketones, dicarboxylic acids, and/or acylcarnitines, as well as for amino acid-derived intermediates of the Krebs cycle. However, such testing is often normal in the stable/fed state in all but the most severely-affected patients. Serum markers of cell death, including transaminases and creatine kinase, may be increased, but are often normal.

More sophisticated investigations are generally performed at specialist centres, often including measurements of the individual respiratory chain complexes in a sample obtained on muscle biopsy. However, the muscle may be both morphologically and histochemically normal, and not surprisingly especially in individuals whereas clinical manifestations are more encephalopathic, and less myopathic. Respiratory chain enzymes in patients with mtDNA mutations may be within the normal range as a mitochondrial disorder may result in a functional defect that is not detectable in the laboratory (Chinnery and Turnbull, 1997; Chinnery and Schon, 2003; Sciacco et al., 2001). Furthermore, interference of such highly transient cellular events as mitochondrial calcium-handling affecting the membrane potential may be one of the main effects of some mtDNA mutations (Brini et al., 1999).

Identifying the causative primary gene mutation is becoming feasible in a rapidly growing subset of mitochondrial disease patients, yet this is still a minority. Sequencing of the entire mtDNA genome and many nuclear-encoded mitochondrial genes is now commercially available. Also commercially available is sequencing of the POLG gene whose protein, gamma polymerase, both replicates and proof reads mtDNA, in which mutations can result in a wide variety of disease manifestations, including migraine and depression (DiMauro and Schon, 2008; Hudson and Chinnery, 2006; Komulainen et al., 2010). Chip technology allows for the evaluation of the entire nuclear genome at high density for single nucleotide polymorphisms that indicate the presence of copy number variations (deletion and duplications) and areas that are identical by descent, which can lead to investigations of the mitochondrial-targeted genes within the affected coding. However, powerful in research for identifying new mitochondrial disorders, the above approaches are expensive, and generally produce several sequence variants of unknown relationship to the patients’ disease for every frank mutation identified.

6. Treatment of mitochondrial disorders

Treatment of mitochondrial disorders focuses on symptom-based management, mitigating worsening during physiologic or psychologic stress, and avoidance of drugs impairing mitochondrial functions (Finsterer and Segall, 2010). Nutraceuticals acting on the pathogenic cascade, “mitochondrial cocktail”, are often employed.
6.1. The mitochondrial cocktail

The mitochondrial cocktail targets the final common pathways of mitochondrial dysfunction. There may be synergistic apart from additive effects of the components (Parikh et al., 2009; Tarnopolsky, 2008). The components most frequently employed by experts in mitochondrial medicine are CoQ10, riboflavin, and at least one additional antioxidant (vitamin C, E, and/or α–lipoic acid). L-carnitine is generally given when blood carnitine levels are low or low-normal. Some evidence supports using antioxidants since ROS are produced in increased amounts in mitochondrial disorders. A randomized double-blind trial in which CoQ10, creatine monohydrate, and α-lipoic acid were used showed reduced lactate and markers of oxidative stress in patients with mitochondrial cytopathies (Rodriguez et al., 2007). Commonly-used components are presented in Table 1 along with effects in depression and other affective spectrum disorders, and in inflammation.

According to the experiences of both authors, we believe that the cocktail often demonstrates effects with the somatic symptoms in depression and possibly in depression itself. Efficacy usually does not occur for several months before there is an obvious improvement. Gold and Cohen suggest that “providing [mitochondrial cocktail] as part of an individual trial in which the patient serves as their own control seems to be a reasonable approach” (Gold and Cohen, 2001).

7. Effects of psychopharmacological agents and ECT on mitochondria and inflammation

7.1. Tricyclic antidepressants

The tricyclic drugs imipramine and chlorimipramine exhibit some characteristics of classical mitochondrial uncouplers, i.e. they release respiratory control, hinder ATP synthesis, and enhance ATPase activity of isolated rat liver mitochondria. Unlike classical uncouplers, however, both drugs only weakly stimulate proton uptake in intact mitochondria (Weinbach et al., 1986). The effects of long-term intraperitoneal administration of the tricyclic imipramine on energy metabolism of rat brain mitochondria were examined in a study. Stimulation of the state 3 respiration rates was seen with various substrates. The effect was evident within a week of imipramine administration and was sustained through the second week of the drug treatment. State 4 respiration rates were also found to be increased in general. Respiration decreased with substrates that are electron donors for complex IV. The intramitochondrial content of some respiratory chain subunits increased in the rats that received several shocks (Búrigo et al., 2006). In a more recent study of the tricyclic nortriptyline, which has been identified as a strong inhibitor of MPT (which leads to mitochondrial dysfunction and is implicated in acute neuronal death), the effects of nortriptyline were studied in primary cerebrocortical neurons and in a mouse model. Nortriptyline was found to inhibit oxygen/glucose deprivation-induced cell death, loss of mitochondrial membrane potential, and downstream release of mitochondrial factors. The authors concluded that the results indicate that nortriptyline is neuroprotective (Zhang et al., 2008b).

7.2. SSRI antidepressants

The exact nature (agonist or antagonist) of the action of SSRI agents is not known, and the effects of them on mitochondria are largely untested. Fluoxetine has been found to exert multiple effects on the energy metabolism of rat liver mitochondria, being potentially toxic in high doses (Souza et al., 1994), and to affect electron transport and ATPase activity inhibiting ATP production in isolated rat brain mitochondria (Curti et al., 1999). In a study, fluoxetine was demonstrated to inhibit MPT and to interact with a MPT pore component, thus protecting against induced apoptotic cell death ( Nahon et al., 2005).

7.3. Lithium

Lithium has several uses in medicine apart from its classical role, the treatment of bipolar disorder. Some cases of treatment-resistant presumably unipolar depression may respond remarkably well to lithium (A.G., personal observation). However, it cannot be excluded that such cases in fact have bipolar II for which lithium is the only preventive treatment for both depression and hypomania that is supported by several controlled studies (Benazzi, 2007). Lithium is also in use in the treatment of cluster headache (Steiner et al., 1997; Van Alboom et al., 2009).

The activities of the mitochondrial respiratory chain complexes I + III, complexes II + III and complex IV were measured in postmortem human brain cortex homogenates following exposure to lithium. An increase in complex I and complex II activities was shown to be induced by lithium, thus suggesting a potential of lithium to enhance ATP production. The authors write that the results raise the intriguing possibility that the use of lithium may be considered in the prevention or treatment of disorders associated with defects of the mitochondrial respiratory chain (Maurer et al., 2009). Using multiple measures, a robust enhancement of mitochondrial function by long-term treatment with lithium at therapeutically-relevant concentrations was found in a study using a cell line of human origin, neuronal phenotype, and rats with methamphetamine-induced mitochondrionally mediated toxicity in the brain. The authors write that, taken together, the evidence suggests that lithium has an effect on the regulation of mitochondrial functions in vitro and in the CNS and that lithium may have potential clinical utility in the treatment of other diseases associated with impaired mitochondrial function (Bachmann et al., 2009).

7.4. ECT

Little progress has been made in understanding the mechanism of action of electroconvulsive therapy (ECT), a treatment for depression. The activities of mitochondrial respiratory chain complexes II and IV were increased for up to 30 days after one single shock in the hippocampus, striatum and cortex in rats. Several shocks presented lesser effects when compared to a single shock, but complex II activity in cortex was increased in the rats that received several shocks (Búrigo et al., 2006).

7.5. Effects of antidepressants and lithium on inflammation

Antidepressant medications including tricyclics, SSRIs, the atypical antidepressant tianeptine, and lithium, have been found to have anti-inflammatory effects. Studies in animal models demonstrate that antidepressants attenuate inflammation-induced brain cytokine production and prevent the development of depression induced by high-dose IFNα (reviewed in Kenis and Maes, 2002; Maes et al., 2009a).

In a study in which whole blood from healthy volunteers was diluted with various antidepressants and examined for ability to promote an anti-inflammatory cytokine phenotype in human blood, all of the antidepressants suppressed production of a pro-inflammatory cytokine irrespective of their preference for serotonin or noradrenaline transporters. The results provide evidence questioning the relationship between the monoaminergic reuptake properties of antidepressants and their immunomodulatory effects (Diamond et al., 2006).

However, in another study, the impact of antidepressive medications of several classes for at least six months on the expression of pro-inflammatory cytokines was investigated in patients with heart failure with and without major depression. No differences were observed for the pro-inflammatory cytokines between patients with depression under treatment and those without depression. However, the level of one pro-inflammatory cytokine and CRP levels were significantly lower in patients receiving tricyclics or serotonin/norepinephrine reuptake inhibitors (SNRI) compared to patients receiving SSRIs or those without depression. The results showed that the type of antidepressive
Table 1
Components of the mitochondrial cocktail, findings in depression, other affective spectrum disorders, and inflammation.

<table>
<thead>
<tr>
<th>Components of the mitochondrial cocktail</th>
<th>Suggested dosages for adults</th>
<th>Effects on mitochondrial metabolism</th>
<th>Findings in depression</th>
<th>Findings in other affective spectrum disorders</th>
<th>Findings in inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoQ10 as ubiquinol (preferred) or ubiquinone</td>
<td>Ubiquinol: 50–600 mg daily; ubiquinone: 300–2400 mg daily</td>
<td>Transports electrons across complexes within the respiratory chain and has antioxidant effects</td>
<td>Decreased mean plasma level in treatment-resistant depression: 51% of patients below the lowest values detected in controls (Maes et al., 2009b).</td>
<td>Fibromyalgia: increased plasma and decreased mononuclear cell level (Cordero et al., 2009).</td>
<td>Lowers the production of pro-inflammatory cytokines (Schmelzer et al., 2007a; 2007b; 2008).</td>
</tr>
<tr>
<td>Riboflavin (vitamin B2)</td>
<td>50–400 mg daily</td>
<td>A key component in respiratory chain complexes I–II–III and in several other key enzymatic reactions in energy metabolism</td>
<td>Deficiency in functional red blood cell enzyme assay in a subset (Bell et al., 1991; 1992).</td>
<td>Migraine: efficacy in prophylaxis in both open and randomized, placebo-controlled trials (Boehnke et al., 2004; Condò et al., 2009; Schoenen et al., 1998). No effect in another trial (MacLennan et al., 2008). Efficacy greater in subjects with non-H mtDNA haplotypes (Di Lorenzo et al., 2009).</td>
<td>Suppressive effect on production of tissue inflammatory mediators in endotoxin-induced shock in mice (Kodama et al., 2005). Prevented cytokine upregulation and cytokine-induced alterations in iol beta-cells (Cobianchi et al., 2008). Increase of plasma levels and heart expression of cytokines in hypertensive rats reversed (Miguel-Carrasco et al., 2008).</td>
</tr>
<tr>
<td>L-carnitine</td>
<td>100–1000 mg 2–3 times daily</td>
<td>A crucial role in mitochondrial β-oxidation by transferring long-chain fatty acids across the mitochondrial inner membrane</td>
<td>Antidepressant effect in geriatric depression after about four or more weeks of treatment which was longer than in younger patients according to a review of nine studies. Effect equals results obtained with antidepressants (Pettegrew et al., 2000).</td>
<td>ME/CFS: effect by acetyl-L-carnitine on mental fatigue, and by propionyl-L-carnitine on general fatigue. Worsening of fatigue after cessation of either or combined l-carnitines</td>
<td></td>
</tr>
<tr>
<td>Creatine monohydrate</td>
<td>5 g in one dose or 2 dosages daily</td>
<td>Combines with phosphate to form phosphocreatine which serves as a source of high energy phosphate and acts as an intracellular buffer for ATP</td>
<td>Improved treatment-resistant depression in a small open-label study. Possible precipitation of a manic switch observed in the two bipolar patients (Roitman et al., 2007).</td>
<td>ME/CFS: beneficial in a randomized double-blind placebo-controlled trial (Magis et al., 2007).</td>
<td>Increase of plasma pro-inflammatory cytokines in athletes after competition reduced in the treated group in a double-blind trial (Basit et al., 2008).</td>
</tr>
<tr>
<td>α-lipoic acid (thioctic acid)</td>
<td>50–200 mg daily</td>
<td>An antioxidant and potentiates creatine uptake in skeletal muscle</td>
<td>Manic switch observed in the two bipolar patients (Roitman et al., 2007).</td>
<td>Migraine: beneficial in a randomized double-blind placebo-controlled trial (Magis et al., 2007).</td>
<td>Reduces various signs of inflammation in inflammation-induced mice (Jesudason et al., 2008). Lower levels in elderly subjects with increased levels of pro-inflammatory cytokines, poor physical health and poor mental health scores (Capuron et al., 2009b). Individual response at supplementation on cytokine production partly mediated by genetic factors (Belisle et al., 2009).</td>
</tr>
<tr>
<td>Vitamin E (tocopherol)</td>
<td>100–200 IU daily</td>
<td>An antioxidant</td>
<td>Significantly lower serum or plasma concentrations (Maes et al., 2000; Owen et al., 2005). Dietary intake not related to plasma level (Owen et al., 2005). Significantly increased plasma level in another study (Sarandol et al., 2007).</td>
<td>Fibromyalgia: plasma levels significantly lower than in sex-matched controls (Akkus et al., 2009). Migraine: efficacy in menstrual migraine in a placebo-controlled double-blinded trial with reduction of pain severity and functional disability. Superior effect regarding photophobia, phonophobia, and nausea (Ziaei et al., 2009).</td>
<td></td>
</tr>
<tr>
<td>Vitamin C (ascorbic acid)</td>
<td>50–200 mg daily</td>
<td>An antioxidant and co-factor in the synthesis of carnitine</td>
<td>Decrease in plasma levels (Khanzode et al., 2003).</td>
<td>ME/CFS: significantly lower serum concentrations than in age- and sex-matched controls (Miwa and Fujita, 2009).</td>
<td>Shown to inhibit cytokine production in a dose-dependent manner (Härtel et al., 2004).</td>
</tr>
</tbody>
</table>
treatment may have a significant effect on the underlying inflammatory process (Tousoulis et al., 2009).

8. Main conclusions and future perspectives

In this review, we have presented findings “beyond the serotonin hypothesis” of depression regarding the alternative mitochondrial and inflammatory models of depression. There is, however, a role for serotonin within the new models. A substantial decrease of serotonin levels was observed in hippocampus and amygdala in a mouse model of bipolar disorder with multiple mtDNA deletions in brain (Kasahara et al., 2006), testifying to the necessity of cellular energy in the production of serotonin. Serotonin depletion has also been shown to be related to neuroinflammation since inflammation depletes the availability of tryptophan resulting in reduced serotonin in brain (Maes et al., 2009a).

Brain tissue requires a high level of energy for its metabolism, including the maintenance of the transmembrane potential, signal transduction and synaptic remodeling. An increase of psychiatric symptoms and disorders, in particular depression, is likely present in patients with mitochondrial disorders. The above-mentioned similarities in cognitive impairments in major depression and mitochondrial disorders suggest that the same neurobiological substrates for the involved cognitive domains may be preferentially affected in both conditions.

Mitochondrial structure and function, measured by a variety of different techniques, have been shown to be abnormal in patients with mood disorders including major depression as well as in the other affective spectrum disorders. No definite conclusion can yet be drawn as to whether mitochondrial dysfunction plays an important etiological role in these conditions. However, many studies suggest this possibility. The studies performed to date essentially rule out the presence of “common” mtDNA mutations in most individuals with major depression. However, there may be large number of polymorphisms on both mtDNA and nDNA genes involved in energy metabolism, either alone or in combination with each other, that result in a moderately-lowered energy metabolism and that can result in major depression and/or other affective spectrum disorders in the presence of other factors. The other factors likely include polymorphic variation in genes involved with neurotransmitter and/or inflammatory pathways, as well as environmental risk factors. In recurrent early-onset depression, a modest maternal bias in the susceptibility suggest that predisposing genetic factors likely reside on the mtDNA (Bergemann and Boles, 2010).

Mitochondrial dysfunction leads to apoptosis, which primes the immune system with intracellular antigens causing inflammation, and which in susceptible individuals even may lead to autoimmune disease. Although inflammatory processes have been reported to occur in some patients with confirmed primary mitochondrial disorders as reviewed herein, very few studies have investigated inflammatory markers in such patients. Myelin pathology is common in mitochondrial diseases (Lerman-Sagie et al., 2005), and has been described in unipolar depression (Regenold et al., 2007). There is good evidence that a metabolic injury to oligodendrocytes and myelin turnover may depend on mitochondrial dysfunction (Carelli and Bellan, 2008). Signs of metabolic injury to oligodendrocytes and myelin turnover may also be demonstrated in major depression, and low mitochondrial energy metabolism and that can result in major depression and/or other affective spectrum disorders in the presence of other factors. The other factors likely include polymorphic variation in genes involved with neurotransmitter and/or inflammatory pathways, as well as environmental risk factors. In recurrent early-onset depression, a modest maternal bias in the susceptibility suggest that predisposing genetic factors likely reside on the mtDNA (Bergemann and Boles, 2010).

Disease has sneaked into me
I feel my limbs heavy
I no longer know my own body
Should the master physician come to me
My heart is not revived by his medicines.

Conflict of interests

The authors declare that they have no competing interests.

References
