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The Energy Crisis in Parkinson's Disease: A Therapeutic Target

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1. Introduction

The energy demand of the brain is very large: it accounts for 20% of the body's energy consumption, even though its weight is less than 2% of the total body mass. In the adult, brain energy comes primarily from glucose through oxidative glycolysis. The end product is acetyl-coenzyme A (acetyl-CoA), which enters the mitochondria and feeds into the tricarboxylic acid (TCA) cycle to produce energy in the form of reductants, such as NADH. The chemical energy of NADH is then used by the respiratory chain, or electron transport chain, to synthesize ATP (Fig. 1). Energy depletion is a major factor in the cascade of events culminating in dopaminergic neuronal death in Parkinson's disease (PD). There are two reasons for that. First, a frequent feature of the disease, as well as of other neurodegenerative diseases, is an alteration of glucose metabolism. Second, there is a decrease of mitochondrial respiratory chain activity due to, in particular, inhibition of the electron transport system complex I (NADH-ubiquinone oxidoreductase).

Complex I activity is redox-dependent and thiol-regulated; therefore its inhibition is associated with oxidative stress. Depletion of GSH, a major antioxidant and redox modulator, is observed in the substantia nigra of parkinsonian patients, as well as in the mouse MPTP model of the disease. Conversely, the restoration of GSH levels preserves complex I activity. Accordingly, the maintenance of cellular redox homeostasis by thiol agents protects against nigrostriatal toxicity.

In the case of the alteration of glucose metabolism, the brain has the ability to adapt its metabolism and to increase its reliance on lipids for energy production, through fatty acid β-oxidation. The process involves a mitochondrial oxido-reductase superfamily with broad substrate specificity. The penultimate step of the process is catalyzed by L-3-hydroxyacyl-CoA dehydrogenase (HADH II) (EC 1.1.1.35). HADH II overexpression protects against acute brain injury and chronic neurodegeneration. By-products of fatty acid β–oxidation are the ketone bodies β-hydroxybutyrate and acetoacetate. When injected into mice or rats, or administered in the form of a ketogenic diet, ketone bodies have a protective role in a broad spectrum of cerebral injuries and diseases.

In the present report, we examine the brain energy metabolism, its alterations associated with PD and how fatty acid β-oxidation can compensate such impairment. Energy store boosting agents have potential therapeutic properties. Pantethine, the precursor of vitamin

B5, is one of them, with the advantage of targeting multiple pathways involved in disease process. By itself or by its constituents (Fig. 2), pantethine regulates lipid metabolism, in addition to its anti-oxidant and anti-inflammatory properties, giving rise to the promise of an original therapeutic strategy against PD.
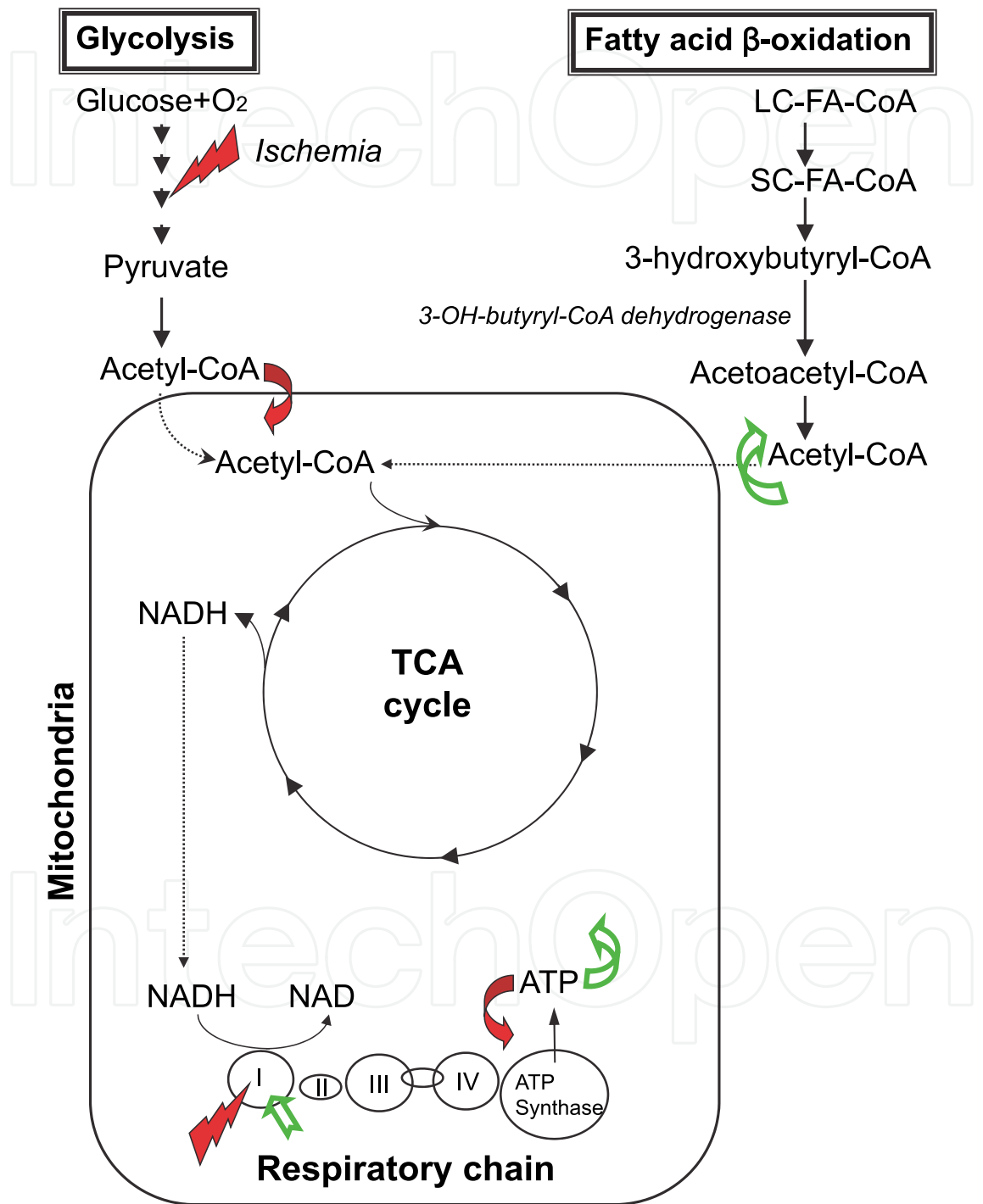

Fig. 1. The energetic pathways. Glycolysis is the major energetic pathway in the adult brain. It is impaired in Parkinson's disease, leading to an energy crisis, which is compensated by fatty acid-β–oxidation. Solid symbols (red) indicate the injuries and alterations occurring in the processes leading to the disease; open symbols (green) indicate the protective effects of pantethine.
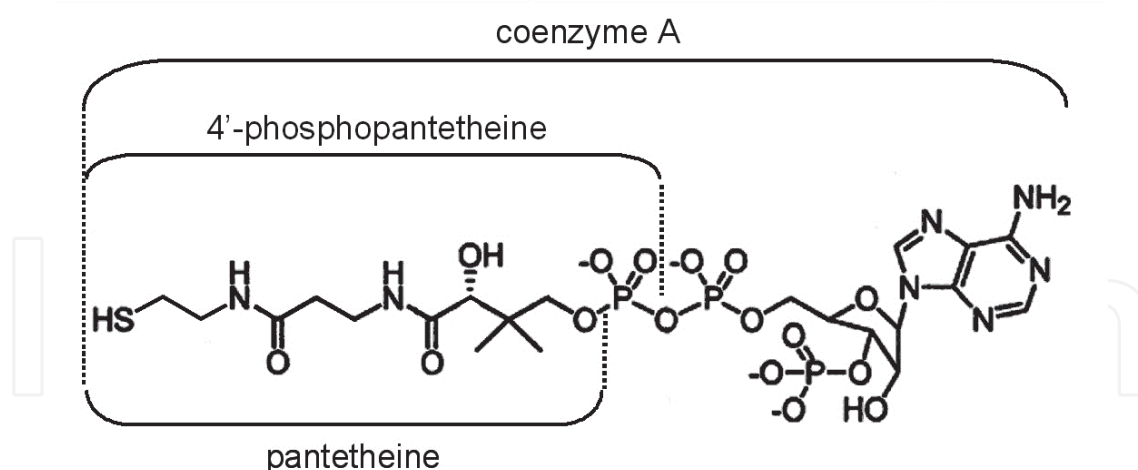
Fig. 2. Pantethine forms the active moiety of CoA. Pantetheine, the reduced form of pantethine, is first 4'-phosphorylated by pantothenate kinase and then adenylated by phosphopantetheine adenylyl transferase (CoaD) to form dephospho-CoA; finally, dephospho-CoA is phosphorylated to coenzyme A by the enzyme dephosphocoenzyme A kinase (CoaE). Lipids are metabolized as fatty acids linked to the SH group of pantetheine, in the form of acyl-CoA thioesters.

2. Brain energy metabolism

Although the brain represents only 2% of the body weight, it receives 15% of the cardiac output and accounts for 20% of total body oxygen consumption as well as 25% of total body glucose utilization. Under physiological conditions, glycolysis is, by far, the major energetic pathway in the adult brain. Glucose is broken down in the presence of oxygen, yielding pyruvate and lactate. Evidence accumulated during the past decade supports the notion that astrocytes play a pivotal role in the regulation of brain-glucose metabolism, via the so-called neuron-astrocyte lactate shuttle (Escartin et al., 2006; Hertz, 2004; Schurr, 2006). Owing to their strategic location surrounding cerebral blood capillaries, astrocytes form the first cellular barrier encountered by glucose entering the brain parenchyma, which makes them a prevalent site of glucose uptake. Blood-borne glucose crosses the vascular endothelial cells and enters brain cells through specific hexose transporters of the glucose transporter family (GLUT) (McEwen and Reagan, 2004; Vannucci et al., 1997). When the supply of oxygen therefore does not match precisely the demand, e.g. during neuronal activation or under pathological conditions, glucose may be broken down anaerobically, to produce lactate in order to supply energy faster. This process has, however, low energetic efficiency.

The following step of energy production is the conversion of pyruvate to acetyl-CoA which is used by mitochondria, the power house of living cells. Mitochondria produce the reductant NADH via the tricarboxilic acid cycle; then the chemical energy of NADH is used by the electron transport chain (ETC) to synthesize ATP. Mammalian ETC is composed of least 49 individual polypeptides which constitute a series of electron carriers organized in four enzymatic complexes plus the ATP synthase machinery. Complex I (NADH ubiquinone oxidoreductase) (EC1.6.5.3) is a very large enzymatic set catalyzing the first step of the ETC (Saraste, 1999; Schultz and Chan, 2001). The enzyme oxidizes NADH, transferring electrons to Ubiquinone (Coenzyme Q, CoQ), a lipid soluble electron carrier

embedded in the lipid bilayer of the inner mitochondrial membrane. Complex II (succinate-ubiquinone oxidoreductase) (EC1.3.5.1), bound to the inner mitochondrial membrane, catalyzes the oxidation of succinate to fumarate with the reduction of ubiquinone to ubiquinol. Complex III (ubiquinol-cytochrome C oxidoreductase; EC 1.10.2.2) is the oligomeric protein complex that transfers electrons from ubiquinol to cytochrome C and links proton translocation to this electron transfer by the proton motive Q cycle mechanism (Trumpower, 1990). Complex IV (cytochrome C oxidase (EC 1.9.3.1) is a transmembrane protein which receives electrons from cytochrome C and transfers them to one oxygen molecule, converting molecular oxygen to water. In the whole process, a transmembrane difference of proton electrochemical potential is established that the ATP synthase then uses to synthesize ATP. Mitochondrial dysfunction results in a dwindling supply of ATP, a failure in maintaining cellular homeostasis and activation of cell death pathways.

3. Energy crisis in Parkinson's disease

PD, Huntington's disease (HD) and Alzheimer's disease (AD) are age-related diseases of diverse etiologies, but energy crisis is a common factor. The link between PD and mitochondria was first established with the identification of a deficiency in the activity of complex I in the substantia nigra of PD patients (Schapira et al., 1989) and it has been then confirmed by several authors (see reviews in (Banerjee et al., 2009; Schapira, 2006)). Complex I deficiency was noticed not only in the brain but also in the peripheral tissues of PD patients (Krige et al., 1992; Wallace et al., 1992). Whether mitochondrial dysfunction is the cause or effect of PD pathogenesis is debatable. However, it is clear that dopaminergic neurons are especially susceptible to energy deficit, meaning that mitochondrial dysfunction may underlie selective dopaminergic neuro-degeneration in PD (Beal, 2005).

The seminal discovery that MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) causes PD-like symptoms in humans (Langston et al., 1983) and the ensuing rapid unraveling of the molecular mechanism of its toxicity strongly stimulated the interest of the PD research community in the role of mitochondria in PD pathology. MPTP is metabolized to its toxic form MPP[+] (1-methyl-4-phenylpyridinium ion) by mitochondrial monoamine oxidase (MAO) (Chiba et al., 1984), specifically by MAO B (Heikkila et al., 1984) and is rapidly concentrated in the mitochondria (Ramsay et al., 1986b). Once accumulated, MPP[+] specifically inhibits the oxidation of NAD–linked substrates (Nicklas et al., 1985) by blocking the electron transfer through the ETC complex I (Ramsay et al., 1986a). It also inhibits the activity of a key TCA (tricarboxylic acid) enzyme KGDHC (α-ketoglutarate dehydrogenase complex) thereby impairing the ATP synthesis and inducing "**energy crisis**" *in vivo* (Mizuno et al., 1988b) and *in vitro* (Mizuno et al., 1988a). The rather selective toxicity of MPP+ to dopaminergic neurons in SN (substantia nigra) was explained by the fact that MPP+ is selectively accumulated by the dopamine uptake system involving the dopamine transporters (DAT) (Javitch et al., 1985). Platelets which also express DAT (Frankhauser et al., 2006) have been shown to accumulate MPP+ with high efficiency and suffer from mitochondrial failure as a result of MPP+ exposure (Buckman et al., 1988). Human platelets also contain high levels of MAO B and share a number of properties with aminergic neurons including receptors, uptake sites and storage granules for amine neurotransmitters. As platelets are more available for research than PD brain samples or muscle biopsy specimens, they were a natural choice for PD tissue samples in earlier studies on the status of complex I in PD. Low complex I activities have been reported in

both PD platelet homogenates and mitochondria isolated from PD platelets, although the degree of its inhibition varied within a wide range. Other ETC complexes in PD platelets are also concerned: complex II (Yoshino et al., 1992), complex II + complex III (Haas et al., 1995), and complex IV (Benecke et al., 1993). Several studies showed impaired complex I, II+III, and IV activities in PD muscle (Bindoff et al., 1991; Blin et al., 1994; Cardellach et al., 1993); whereas no differences were observed in other studies (DiDonato et al., 1993; Mann et al., 1992; Reichmann et al., 1994). Similar conflicting results were reported in the ETC in PD lymphocytes (Martin et al., 1996; Yoshino et al., 1992). Such inconsistency in the experimental data may be explained by significant methodological differences in these studies, e.g. difficulties in obtaining the relevant tissue samples, individual variability of PD patients and many other factors, as was suggested (Parker et al., 2008).

Complex I activity is reduced in mitochondria isolated from PD frontal cortex (Keeney et al., 2006; Parker et al., 2008); it is believed to be an early pathogenic event in PD. Ample data strongly suggest that MPTP-induced ETC disruption per se is sufficient to trigger the death of nigrostriatal neurons and to cause PD-like symptoms in animals and humans. Thus, despite some conflicting results, systemic complex I deficiency might be a predominant feature in PD pathogenesis (Banerjee et al., 2009). Accordingly, ^{1}H and ^{31}P magnetic resonance spectrometry demonstrated mitochondrial dysfunction in the putamen and midbrain of both early and advanced PD subjects, with a bilateral reduction of high-energy phosphates; the changes were associated with abnormally elevated lactate levels. In contrast, low-energy metabolites such as adenosine diphophosphate and inorganic phosphate were within normal ranges. These results provide strong in vivo evidence that mitochondrial dysfunction of mesostriatal neurons is a central and persistent phenomenon in the pathogenesis cascade of PD which occurs early in the course of the disease (Hattingen et al., 2009; Henchcliffe et al., 2008).

Paraquat and rotenone are other neurotoxins that inhibit mitochondrial complex I activity, whereas there are substantial differences in their action (Richardson et al., 2005). Rotenone rat models of PD have been developed that reproduce essential biochemical and behavioral human PD features (Alam and Schmidt, 2002; Betarbet et al., 2000; Greenamyre et al., 2003; Sherer et al., 2003).

Complex I activity is redox-dependent and thiol-regulated (Annepu and Ravindranath, 2000; Sriram et al., 1998). Since PD pathogenesis consistently involve reactive oxygen and nitrogen species (Bove et al., 2005; Li et al., 2003; Przedborski, 2005; Przedborski and Ischiropoulos, 2005) this may explain, at least in part, complex I inhibition. Thus, depletion of GSH, an antioxidant and redox modulator, may be one of the early events leading to the inhibition of complex I activity and loss of mitochondrial function (Chinta and Andersen, 2006; Jha et al., 2000).

4. Mitochondrial dysfunction and the genetic causes of the disease

In the past decade, a rapidly expanding list of Mendelian-inherited gene mutations has provided great insight into the mechanisms leading to loss of the nigrostriatal dopaminergic neurons in familial PD which constitutes less than 10% of the total number of PD cases. In recent years, a plethora of studies of the multifunctional consequences of these mutations point towards the disruption of mitochondrial function culminating in neuronal dysfunction and death.

α-Synuclein was the first gene associated with familial PD. It was followed by four other genes linked conclusively to autosomal recessive (parkin, PINK-1, DJ-1) or dominant (LRRK2) Parkinsonism (Bogaerts et al., 2008; Henchcliffe and Beal, 2008).

PINK1. Mutations in phosphatase and tensin homologue (PTEN)-induced putative kinase (PINK1) cause a rare form of autosomal recessive, PD early onset Parkinsonism following the parkin mutations (Valente et al., 2004; Winklhofer and Haass, 2010). Loss of PINK1 function increases the propensity of cells to oxidative stress-induced cell death and imbalance of calcium homeostasis. The experiments suggest that the impairment of mitochondrial calcium efflux promotes ROS formation that inhibits glucose uptake, resulting in reduced substrate delivery and respiration (Gandhi et al., 2009).

Parkin is a multifaceted ubiquitin ligase (Moore, 2006)**.** Mutations in the *parkin* gene serve as the most common cause of young onset PD (Farrer et al., 2001; Lucking et al., 2000). Loss of function of E3 ligase activity has been suggested to result in accumulation of toxic substrates leading to autosomal recessive form of PD (Dawson, 2006). *Parkin* gene expression is up-regulated in various stress examples and has a wide range of neuroprotective capacities, including protection against mitochondrial dysfunction, endoplasmatic reticulum stress, exitotoxicity, proteasome inhibition, and overexpression of α-synuclein, tau, and other proteins. Future studies of the biochemical interactions between PINK1 and parkin and identification of other components in this pathway are likely to provide insight into PD pathogenesis, and might identify new therapeutic targets (Henchcliffe and Beal, 2008).

DJ-1 and **LRRK2**. DJ-1 has structural similarities with the stress-inducible Escherichia coli chaperone Hsp31 and mutations in the *DJ-1* gene are associated with rare cases of early onset autosomal recessive PD (Andersen, 2004). The loss of DJ-1 function leads to a striking sensitivity to the herbicide paraquat and the insecticide rotenone; this suggests that DJ-1 may have a role in the protection from oxidative stress caused by environmental toxins. It has been clearly demonstrated that, while overexpression of DJ-1 protects neurons from oxidative stress-induced damage, conversely DJ-1 deficiency renders cells more susceptible to oxidative injury. Mutations in leucin-rich repeat kinase 2 (*LRRK2* gene) cause autosomal dominant PD (Paisan-Ruiz et al., 2004; Zimprich et al., 2004). The precise physiological role of this protein is unknown but the presence of multiple functional domains suggests involvement in a wide variety of functions. A possible mechanism of LRRK2 action is at the mitochondrial level.

5. Lipids as an alternative carbon source for energy production

The brain has the ability to use fatty acids as an alternative carbon source. Fatty acid β-oxidation parallels glycolysis (Fig. 1). This occurs normally during embryonic development and, in adults, under conditions of inadequate glucose supply or increased energy demand, as well as under pathological conditions, such as neurodegeneration, hypoxia/ischemia and traumatic brain injury (Prins, 2008).

5.1 Lipid metabolism and regulation of mitochondrial function

Peroxisome Proliferator-Activated Receptors (PPARs) regulate development, tissue differentiation, inflammation, wound healing, mitochondrial function, lipid and glucose metabolism (Reddy et al., 2006; Reddy, 2001). PPARs are expressed in CNS neurons and astrocytes, raising the possibility of exploring the neuroprotective efficacy of PPAR agonists

in several neurodegenerative disorders (Bordet et al., 2006; Heneka and Landreth, 2007; Woods et al., 2003). Gene-knockout experiments have revealed that, consistent with their distinct expression patterns, each PPAR subtype performs a specific function in fatty acid homeostasis. PPAR-α targets genes function together to coordinate the complex metabolic changes necessary to conserve energy during fasting and feeding in cases where catabolic enzymes promote fatty acid β–oxidation.

It is now well established that damage to dopaminergic neurons involves oxidative stress, microglial activation-mediated inflammation and mitochondrial impairment, which ultimately culminate in activation of an apoptotic pathway. The PPAR-γ agonist pioglitazone was shown to exert protective effects in a mouse model of PD; it attenuated the MPTP intoxication-induced glial activation and prevented dopaminergic cell loss in the substantia nigra pars compacta (Breidert et al., 2002). These findings were paralleled by another study showing that the treatment with pioglitazone may offer an opportunity for treatment of PD to slow its progression (Dehmer et al., 2004).

PPAR-γ coactivator 1α (PGC-1α) is a master regulator of mitochondrial biogenesis and respiration (Lehman et al., 2000; Lin et al., 2002; Puigserver et al., 1998; Wu et al., 1999). It transduces many physiological stimuli into specific metabolic programs, often by stimulating mitochondrial activity. For example, PGC-1α regulates both β–oxidation of fatty acids and gluconeogenesis in liver (Herzig et al., 2001; Puigserver et al., 2003; Rhee et al., 2003; Yoon et al., 2001). The importance of PGC-1α in these metabolic programs was further revealed through the generation of PGC-1α null mice. These mice display a reduced basal expression of many mitochondrial genes in liver, brain, skeletal muscle and heart, compared with wild-type animals (Arany et al., 2005; Leone et al., 2005; Lin et al., 2004). Moreover, it has been shown that PGC-1α knockout (KO) mice displayed neurodegenerative lesions in the brain, particularly in the striatum; the animals also showed behavioral abnormalities (Leone et al., 2005; Lin et al., 2004). At present, the cause of the brain lesions is unclear, but the lesions observed in many genetic models with altered ROS levels raise the possibility that PGC-1α plays an important role in the control of ROS in vivo (St-Pierre et al., 2006). PGC-1α and PGC-1β are powerfully induced by ROS, and these coactivators, in turn, regulate a complex and multifaceted ROS defense system. In the MPTP model, PGC-1α KO mice have a greatly increased sensitivity to damage by oxidative stress in the dopaminergic cells of the substantia nigra and hippocampal neurons. Conversely, the overexpression of PGC-1α in cultured dopaminergic neurons from embryonic rat midbrain resulted in activation of electron transport genes and protection against neuronal damage induced by mutant α-synuclein (Zheng et al., 2010). The same authors found in postmortem brain tissue samples from PD patients that the gene sets with the strongest association with PD contained nuclear genes encoding subunits of the ETC proteins. These genes all showed decreased expression in substantia nigra dopaminergic neurons even in the earliest stages of PD. Furthermore, a second gene set associated with PD and also underexpressed in the earliest stages of PD encodes enzymes involved in glucose metabolism. These results are compelling because many studies have already implicated dysfunctional mitochondria and altered energy metabolism as well as defective glucose metabolism in PD. The authors realized that these gene sets had in common the master transcriptional regulator, PGC-1α and surmised that disruption of PGC-1α expression might be a root cause of PD.

5.2 Fatty acid β-oxidation

As in the case of glycolysis, the end product of fatty acid β-oxidation is acetyl-CoA (Fig. 1) which feeds into the TCA cycle to produce energy in the form of NADH and $FADH_2$. The enzymes involved in fatty acid β-oxidation all act on acyl-CoA, i.e. fatty acids linked to CoA as thioesters. They belong to an oxido-reductase superfamily with broad substrate specificity. The enzymes are subdivided into several groups, according to the substrate chain length. Each of the constituent steps of the pathway comprises three consecutive enzymatic reactions catalyzed by a trifunctional enzymatic complex: 2-enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase and 3-ketoacyl-CoA thiolase. The reactions yield acetyl-CoA plus a chain-shortened acyl-CoA (at each step, the fatty acid chain loses two carbons) (Eaton et al., 2000).

In the present review, we focus attention on the penultimate step of the process, i.e. acyl-CoA dehydrogenation. It involves four classes of enzymes: short-chain acyl-CoA dehydrogenase (SCAD, active with C_4 and C_6), medium-chain acyl-CoA dehydrogenase (MCAD, active with C_4 to C_{12}), long-chain acyl-CoA dehydrogenase (LCAD, active with C_8 to C_{20}) and very-long-chain acyl-CoA dehydrogenase (VLCAD, active with C_{12} to C_{24}). SCAD, MCAD and LCAD are homotetramers located in the mitochondrial matrix. VLCAD, however, is a homodimer and is located in the inner mitochondrial membrane. VLCAD is a constituent of the trifunctional protein described above.

Short chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD) also known as L-3-hydroxyacyl-CoA dehydrogenase/amyloid-peptide binding alcohol dehydrogenase (HADH II/ABAD) is predominantly a mitochondrial enzyme (Furuta et al., 1997; Kobayashi et al., 1996) that belongs to the short-chain dehydrogenase/reductase superfamily (Jornvall et al., 1995). It acts on a wide spectrum of substrates, including steroids, cholic acids, and fatty acids, with a preference for short chain methyl-branched acyl-CoAs. Abnormally low or high levels of SCHAD in certain brain regions may contribute to the pathogenesis of some neural disorders. The human SCHAD gene and its protein product are therefore potential targets for intervention in conditions such as PD, AD and an X-linked mental retardation, which may arise from the impaired degradation of branched fatty acid chains and of isoleucine (Yang et al., 2005; Zschocke et al., 2000).

The levels of SCHAD/HADH II are significantly reduced in the ventral midbrain of both PD patients and of a PD mouse model generated by MPTP injection (Przedborski et al., 2004). Conversely, transgenic mice with increased expression of human HADH II/ABAD are significantly more resistant to MPTP; overexpression of the enzyme mitigates MPTP-induced impairment of oxidative phosphorylation and ATP production (Tieu et al., 2004). This observation suggests that a new way to prevent PD may be to increase expression of SCHAD/HADH II in the midbrain.

6. Therapeutic strategies to target the energy crisis

6.1 Potential therapeutic compounds

Coenzyme Q (CoQ) is a component of the electron transport chain where it accepts electrons from complexes I and II (Beal, 2004). Its administration increases mitochondrial uncoupling protein (UCP) expression in the nervous system of primates, and this is associated with marked neuroprotection in both *in vitro* and *in vivo* models of MPTP, paraquat and rotenone-induced mitochondrial dysfunction. CoQ_{10} exerts significant

protection against MPTP-induced dopamine depletion and loss of tyrosine hydroxylase immunoreactive neurons in aged mice (Shults et al., 2002).

Creatine is a nitrogenous guanidine compound that helps to supply energy to muscle and nerve cells (Adhihetty and Beal, 2008). Chronic administration of creatine protects against MPTP-induced dopamine loss and improves the survival of neurons in the substantia nigra (Matthews et al., 1999).

α-Lipoic acid (ALA) is a disulfide compound found in mitochondria as a coenzyme for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. Dietary supplementation with α-lipoic acid in old rats improved ambulatory activity, decreased oxidative damage, and improved mitochondrial function (Hagen et al., 1999). *In vitro*, pre-treatment of PC12 cells with R-lipoic acid acts to prevent depletion of GSH content and preserves the mitochondrial complex I activity which normally is impaired as a consequence of GSH loss (Bharat et al., 2002).

Carnitine transports long-chain fatty acid into the mitochondrial matrix for subsequent β–oxidation (Di Lisa et al., 1985; Rosenthal et al., 1992). Carnitine also facilitates the removal of short-chain and medium chain fatty acids that accumulate in the mitochondria during normal and abnormal metabolism. Carnitine and acetyl-L-carnitine attenuate neuronal damage produced by 3-nitropropionic acid, rotenone, and MPTP *in vitro* (Snyder et al., 1990; Virmani et al., 1995).

Nicotinamide is a precursor of NADH, a substrate for Complex I (NADH-ubiquinone oxidoreductase). It is also an inhibitor of poly-ADP-ribose polymerase, which is activated by DNA damage and in turn depletes both NADH and ATP. Activation of poly-ADP-ribose polymerase plays a role in neuronal injury induced by both ischemia and MPTP (Eliasson et al., 1997; Mandir et al., 1999).

6.2 Ketone bodies

If the amounts of acetyl-CoA generated by fatty acid β-oxidation challenge the processing capacity of the TCA cycle or if activity in the TCA cycle is low, acetyl-CoA is used in the biosynthesis of ketone bodies via β–hydroxy-metylglutaryl-CoA (HMG-CoA) synthesis. The main ketone bodies are D-β-hydroxybutyrate (DβHB) and acetoacetate (ACA). They are produced by hepatocytes and are transported to the tissues, including the brain; astrocytes are also ketogenic, although to a lesser extent (Guzman and Blazquez, 2001).

DβHB and ACA have a protective role in a broad spectrum of cerebral injuries and diseases and they preserve neuronal cell integrity and stability *in vitro*. The experimental approaches used are intravenous infusion of mice or rats with DβHB (Prins, 2008) or administration of a ketogenic diet (Maalouf et al., 2009). Exogenous ketone bodies have been employed successfully in both rapidly developing pathologies (glutamate excitotoxicity, hypoxia/ischemia) and neurodegenerative conditions (PD, AD) [for review see(Prins, 2008)]. In vitro DβHB prevents neuronal damage induced by glucose deprivation (Izumi et al., 1998). Following MPP+ exposure, administration of 4 mmol/L of DβHB increased the survival of cultured neurons (Kashiwaya et al., 2000). In the rotenone *in vitro* model, application of 8 mmol/L of DβHB improved mitochondrial membrane potential and reduced cytochrome C release by mouse neuronal cultures (Imamura et al., 2006); under the same conditions, cell survival was increased by 60% in human neuroblastoma cell culture. *In vivo*, 24 h infusion of DβHB, using mini-osmotic pumps, protected SNpc dopaminergic neurons against MPTP in a dose-dependent and stereospecific manner and prevented the

development of PD-like motor abnormalities in mice (Tieu et al., 2003). Tieu's studies provide *in vivo* and *in vitro* evidence that DβHB protects not by alleviating MPTP-related complex I inhibition, but by enhancing oxidative phosphorylation via a mechanism dependent on mitochondrial complex II (succinate-ubiquinone oxidoreductase).

Therefore, modulation of DβHB levels may be a neuroprotective strategy for the treatment of neurodegenerative diseases such as PD. However, the long-term effects of the chronic use of DβHB on the cellular metabolism, and especially on mitochondrial function, are not known. DβHB has been administered orally for several months to two 6-months-old infants with hyperinsulinemic hypoglycemia (Plecko et al., 2002). The high dosage (up to 32 g/d) seemed to be tolerated by these patients. In addition, ketogenic diets have been used in humans as a treatment for refractory epilepsy. In general, patients tolerate the ketogenic diet well with mild side effects (Freeman et al., 2006). However, long-term ketone therapy will have to take into consideration possible adverse effects.

6.3 Pantethine

A promising emerging therapeutic strategy involves fatty acids combined with pantethine. CoA is central in these fields, as illustrated by pantothenate kinase-associated neurodegeneration (PKAN). Pantothenate kinase catalyzes pantetheine phosphorylation to 4'-phosphopantetheine, the first step of CoA synthesis (Fig. 2). PKAN, due to insufficient kinase activity, occurs in early adulthood and its symptoms, such as dystonia, rigidity and tremor, recall PD and it may lead to PD in late adulthood. PKAN results in a decrease of CoA levels associated with mitochondrial dysfunction. These defects can be reversed by pantethine, the oxidized form of pantetheine. Dietary pantethine increased CoA synthesis, improved mitochondrial function, rescued brain degeneration, enhanced locomotor abilities, and increased lifespan in a Drosophila model of PKAN (Rana et al., 2010). Moreover, pantethine circumvented the impairment of fatty acid β-oxidation in rat liver mitochondria and microvessels of the brain (Morisaki et al., 1983). It has been shown recently that pantethine mitigated MPTP neurotoxicity in the mouse via the enhancement of fatty acid β–oxidation, leading to increased levels of circulating ketone bodies and improved mitochondrial function (Cornille et al., 2010). In addition, pantethine attenuates MPTP-induced neuroinflammation, as shown by reduced expression of macrophage antigen-1 (MAC-1), a critical trigger of microglial activation associated with neurodegeneration (Pei et al., 2007) (Fig. 3). Ultimately, pantethine protects from MPTP-induced blood-brain barrier (BBB) leakage (Fig. 4) and significantly attenuates the clinical scores (Fig. 5).

7. Concluding remarks and future perspectives

Deficits in mitochondrial activity in combination with increased oxidative stress, and aging-associated damage to mitochondrial DNA are key biochemical abnormalities associated with the pathogenesis of not only in sporadic PD but also in familial forms of the disease. Factors that trigger these mitochondrial abnormalities are still elusive, however one may speculate that strategies aimed at correcting these biochemical abnormalities might be useful in halting or slowing down the progression of PD. In this regard some of the candidate drugs which showed great efficacy in experimental models of PD have already made it to clinical trials. Preliminary clinical trial data on Coenzyme Q10 and creatine have shown some promise. There is also a great deal of enthusiasm following the recent identification of

novel mitochondrial targets such as PGC-1α and the sirtuin family of enzymes that are known to modulate aging, mitochondrial biogenesis, metabolic homeostasis and mitochondria-dependent cell death. These observations hold promise for future development of neuroprotective strategies in PD by targeting mitochondrial dysfunction. However it is important to remember that PD is a multi-factorial disease and mitochondrial dysfunction may only be a part of this complex process. Future research should thus focus on developing neuroprotective strategies by targeting multiple pathways involved in the disease process. Therapeutic approaches targeting both mitochondrial dysfunction and oxidative damage in neurodegenerative diseases and aging have great promise (Beal, 2005). Pantethine provides an example of molecule able to restore mitochondrial function while displaying antioxidant and anti-inflammatory properties. Perhaps, this safe and effective compound of natural origin merits consideration for broader use against pathologies such as PD.
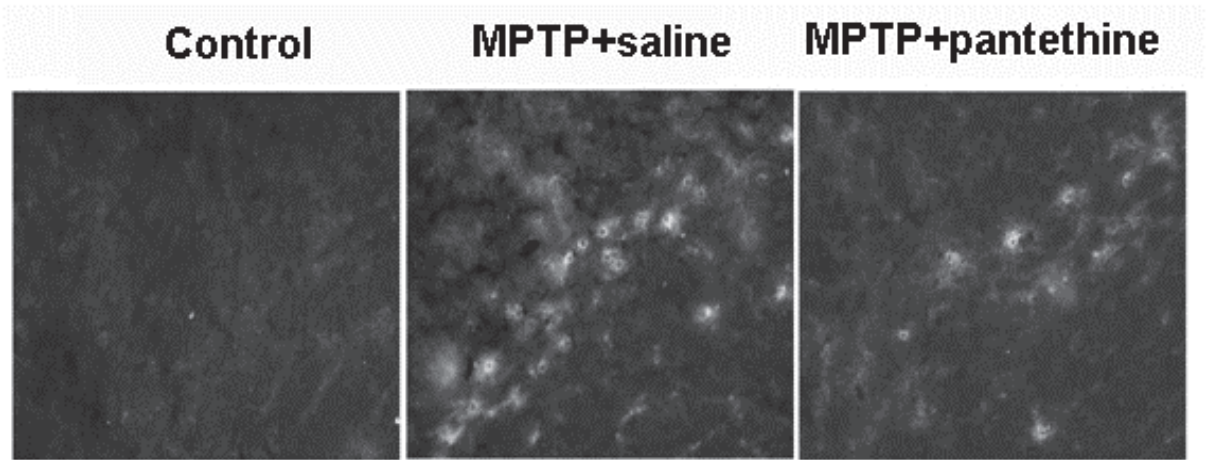

Fig. 3. Attenuation of microglial reaction by pantethine treatment in MPTP-injected mice.

The figure shows macrophage antigen-1 (Mac-1) immunostaining in SNpc, two days after MPTP injection. Microglial reaction was drastically reduced in pantethine-treated mice as compared to saline ones. No immunostaining was observed in control animals.
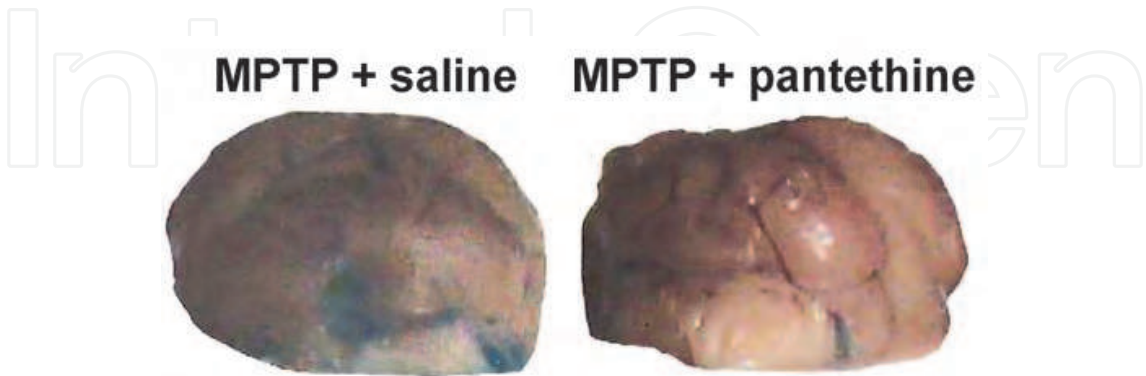

Fig. 4. Prevention of BBB leakage by pantethine treatment in MPTP-injected mice.

Evans blue was administered intravenously on day 16 after MPTP injection. The figure shows brains of saline mice with a diffuse dye leakage, and some intensively stained areas. In contrast, brains of pantethine-treated mice looked normal, with limited stained areas.
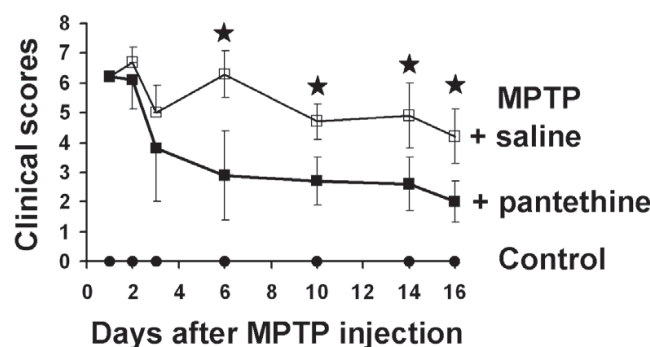
Fig. 5. Attenuation of the clinical scores by pantethine treatment in MPTP-injected mice.

Mice were injected with MPTP and then treated or not treated with pantethine. Under our experimental conditions, the scores were 6.2 in both groups 24 hours after MPTP injection and they decreased much more rapidly in the pantethine group. (*) Significant difference between the two groups, according to the Student t test ($p < 0.01$).

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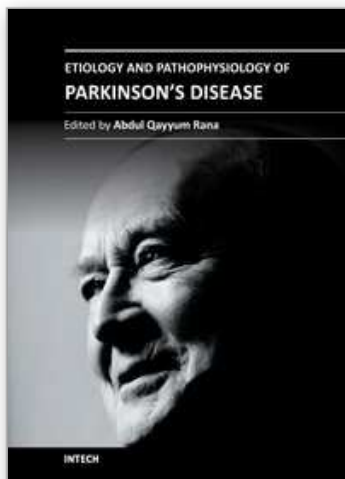
Etiology and Pathophysiology of Parkinson's Disease

Edited by Prof. Abdul Qayyum Rana

This book about Parkinson's disease provides a detailed account of etiology and pathophysiology of Parkinson's disease, a complicated neurological condition. Environmental and genetic factors involved in the causation of Parkinson's disease have been discussed in detail. This book can be used by basic scientists as well as researchers. Neuroscience fellows and life science readers can also obtain sufficient information. Beside genetic factors, other pathophysiological aspects of Parkinson's disease have been discussed in detail. Up to date information about the changes in various neurotransmitters, inflammatory responses, oxidative pathways and biomarkers has been described at length. Each section has been written by one or more faculty members of well known academic institutions. Thus, this book brings forth both clinical and basic science aspects of Parkinson's disease.

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