Review

Impaired Bioenergetics in Clinical Medicine: A Target to Tackle

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Mitochondrial energy deficit is considered a key element of different clinical pathologies - from inherited disorders of energy metabolism to drug-induced mitochondrial toxicity, to cardiometabolic and neurodegenerative diseases. However, clinical manifestations of impaired bioenergetics are not easy to recognize, with patient-reported features usually include non-pathognomonic fatigue and weakness, or exercise intolerance, while specific lab tests are missing. Although it is not clear whether poor energetics is a primary deficit or a secondary consequence of specific disorders, improving mitochondrial viability remains a challenging task in both experimental and clinical medicine. In this review, biochemical and clinical evidence of energy deficits were reviewed, along with possible therapeutic options to tackle energy failure and restore bioenergetics.

Introduction

The capacity of each cell to provide and sustain energy is essential to life. It seems that optimal energy flux mainly depends on mitochondria, subcellular structures that deliver chemical energy. Owing to their ability to produce adenosine triphosphate (ATP), a central molecular proxy for intracellular energy transfer, mitochondria became a driving force in evolution (Friedman and Nunnari 2014). Many intrinsic and extrinsic factors may affect mitochondrial capacity to furnish energy of ATP, including pre-components availability, functionality of synthetic machinery, or challenging environment (Fig. 1). Whatever damages this energy-making capacity could easily translate into clinical outcomes of impaired bioenergetics that particularly tackle energy-demanding tissues such as the brain, myocardium, skeletal muscle, pancreas or liver (Archer 2013). Here, I review biochemical and clinical evidence of energy deficits in clinical medicine, either inherited or acquired, and discuss possible therapeutic options to tackle impaired mitochondrial bioenergetics in biomedicine.

Inherited Mitochondrial Disorders of Energy Metabolism

Several relatively rare (10 to 15 cases per 100,000 persons) inherited metabolic disorders affect energy metabolism, and induce a great diversity of signs and symptoms due to a deficiency of energy production and/or utilization (Ezgu 2016). Fostered by a defect in a gene coding for a mitochondrial protein, these conditions negatively impact mitochondrial metabolism of pyruvate and fatty acids, also Krebs cycle and electron transport chain, within the central and peripheral nervous system, skeletal muscle, heart, and other organs (Mak et al. 2013; Vernon 2015). These include congenital lactic acidosis, fatty acid oxidation defects, gluconeogenesis defects, and mitochondrial respiratory chain disorders. Main characteristics of above disorders are outlined in Table 1. Many other inherited metabolic diseases can also affect cellular bioenergetics, including creatine deficiency syndromes (Mercimek-Mahmutoglu and Salomons 2009) or muscle-specific glycogen synthase deficiency (Cameron et al. 2009), but the pathophysiology and clinical characteristics of these conditions are outside of the scope of this paper.

Although above conditions are distinct in prevalence, etiology and severity, all share a common feature - an impaired cellular bioenergetic that translates into energy depletion-related signs and symptoms, including muscle weakness, exercise intolerance and neuromuscular fatigue (Mak et al. 2013). Many studies confirmed incapacitated bioenergetics in inherited mitochondrial disorders, as assessed via low levels of high-energy phosphates (HEPs) in target tissues. For example, Eleff and co-workers (1990) found that phosphocreatine-to-ATP ratios were significantly reduced, with phosphorylation potentials and percentage of maximal rate of ATP synthesis significantly altered in the brain of patients with heritable disorders of oxidative phosphorylation. Equivalent ATP depletion has been reported in
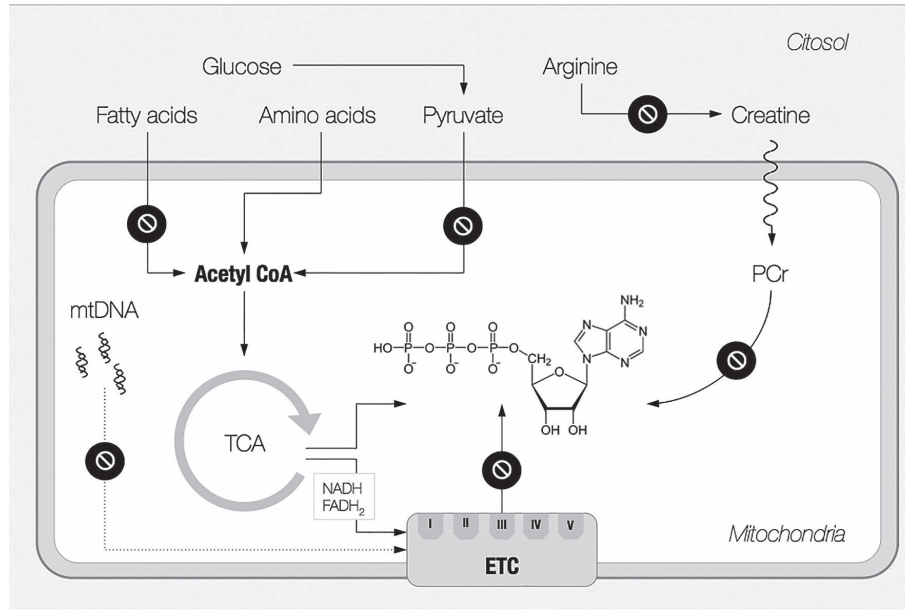
Fig. 1. Metabolic map summarizing mitochondrial bioenergetics.
mtDNA, mitochondrial DNA; TCA, tricarboxylic acid cycle; PCr, phosphocreatine; ETC, electron transport chain; NADH, reduced form of nicotine amide dinucleotide; $FADH_2$, reduced form of flavin adenine dinucleotide.
⊘ denotes possible blockages in bioenergetics pathways due to impaired gene coding or direct obstruction of energy-generating processes.

Table 1. Characteristics of inherited disorders of energy metabolism.

Disorder	Prevalence	Mutation	Pathophysiology	Clinical picture	Diagnosis	Treatment
Congenital lactic acidosis	1 : 50.000	PDHA1	Deficit of pyruvate dehydrogenase enzymatic complex that converts pyruvate into acetyl-CoA	Hypotonia, lethargy, intellectual disability, seizures; vomiting, severe breathing problems, abnormal heartbeat	↑ Lactate in blood and CSF	Ketogenic diet Dichloroacetate
Fatty-acid oxidation disorders (12+ diseases)	~ 1 : 10.000 (combined prevalence)	SLC22A5, SCL25A20, CPT1A, CPT2, ACADVL, ACADM, ACADS, ACAD9, HADHA, HADHB, DECR1	Defects in transport and utilization of fatty acids and related intermediates	Fasting hypoketotic hypoglycemia, cardiomyopathy, rhabdomyolysis, muscle weakness, myalgia, liver dysfunction, sudden death; also neuropathy and pigmentary retinopathy	↑ Acylcarnitine metabolites in blood ↑ Dicarboxylic acids and acylglycines in urine	Dietary modification Avoidance of fasting Carnitine suppl.
Gluconeogenesis defects	~ 1 : 20.000 (combined prevalence)	PC, G6PC, SLC37A4, PEPCK, FBP1, FBP2	Defects in any of the four enzymes (PC, PEPCK, FDPase, G6Pase) of the glycolytic-gluconeogenic pathway	Hypoglycemia, hyperventilation, hypotonia, moderate hepatomegaly, progressive neurodegenerative disorder, seizures	↑ Lactate in blood and CSF	Dietary modification Avoidance of fasting Vitamin suppl.
Mt respiratory chain disorders	1 : 5.000	ND1, ND2, ND3, ND4L, ND4, ND5, ND6, CytB, A6, A8, COXI, COXII, COXIII etc.	Impaired production of ATP	Psychomotor retardation, seizures, ataxia, myoclonus, dystonia, peripheral neuropathy, weakness and exercise intolerance, short stature, cardiomyopathy, liver failure	↑ Lactate in blood and CSF Ragged-red fibers on muscle biopsy	Dichloroacetate Arginine Co-enzyme Q10 Idebenone Exercise

Mt, mitochondrial; CSF, cerebrospinal fluid; CoA, coenzyme A; PC, pyruvate carboxylase; PEPCK, phosphoenolpyruvate carboxykinase; FDPase, fructose-1,6-bisphosphatase; G6Pase, glucose-6-phosphatase; ATP, adenosine triphosphate; PDHA1, pyruvate dehydrogenase E1 alpha 1 subunit gene; SLC22A, solute carrier family 22 genes (member 5 and 20); CPT, carnitine palmitoyltransferase genes (subunits 1A and 2); ACADVL, acyl-CoA dehydrogenase genes (short, medium and very long chains, and family member 9); HADHA, hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex genes (subunits alpha and beta); DECR1, 2,4-dienoyl-CoA reductase 1 gene; PC, pyruvate carboxylase gene; G6PC, glucose-6-phosphatase catalytic subunit gene; SLC37A4, solute carrier family 37 member 4 gene; PEPCK, gene encoding phosphoenolpyruvate carboxykinase; FBP, fructose-bisphosphatase genes (units 1 and 2); ND, mitochondrially encoded nicotine amide dinucleotide dehydrogenase genes (subunits 1-6); CytB, mitochondrially encoded cytochrome b gene; A6-8, gene encoding small interleukin enhancer-binding factor 3/nuclear factor 90-associated RNA A6 and 8; COX, mitochondrially encoded cytochrome c oxidase genes (subunits I-III).

the skeletal muscle and heart of patients suffering from mitochondrial cytopathies, with some tissues seem to be more vulnerable to energy deficiencies (Korzeniewski 2016).

Usually discovered during the newborn period or early infancy, inherited disorders of energy metabolism have polyvalent pathophysiology, spreading from minor muta-tions with mild phenotypic features to life-threatening multi-system defects of energy metabolism. Due to the fact that most mitochondrial disorders often manifest as minor defects with unremarkable clinical picture while well-defined syndromes are not always seen (Chinnery and Turnbull 1997), an integrated investigation of patients with suspected disease is essential. Diagnostic approaches com-

prise evaluation of clinical features and investigational laboratory tests, including blood and cerebrospinal fluid chemistry, fibroblasts culture or muscle biopsy for enzyme assay, and DNA analysis (Vernon 2015). Those disorders are also hard to tackle, with current management options (e.g. vitamins, co-factors, dietary modifications, exercise) typically prescribed to prevent or reduce severe symptomatic episodes (for review see Vernon (2015)) while no cure is available at the moment. Future advances in genomic therapies to synthesize and deliver deficient mitochondrial enzymes or protein units (Chinnery and Turnbull 1997), or novel approaches in pharmaco-nutritional science to develop mitochondria-targeted energy-rich compounds might offer a new hope for population with inherited disorders of energy metabolism.

Intoxications that Affect Energy Metabolism

Different mitochondrial uncouplers, inhibitors and toxins could jeopardize the organelle's production of cell energy (Chan et al. 2005; Kovacic et al. 2005), with many individuals might be extensively exposed to those agents in everyday life. Overall, mitochondrial toxins could affect energy flux by two means: (1) through direct obstruction or aggravation of energy-generating processes in the organelle, and (2) by provoking detrimental reactions that indirectly affect mitochondrial bioenergetics through overproduction of reactive oxygen species (ROS), mitochondrial DNA (mtDNA) damage, or impairment of mitochondrial membrane structure. For example, benzene, a widespread colorless volatile organic compound, could negatively affect mitochondrial bioenergetics, acting as a blocker of the electron chain transport in the mitochondrial matrix, ROS-generating toxicant, and mtDNA-mutagenic agent (Shen et al. 2008). The substances with mitochondrial toxicity include pharmaceuticals (including anticonvulsants, psychotropics, antibiotics or anti-arrhythmics), industrial chemicals and pesticides (e.g. carbon monoxide, polyaromatic hydrocarbons, rotenone, pentachlorophenol, paraquat), or illicit drugs or related agents (such as cocaine, methamphetamine, tobacco, or alcohol) (for detailed review see Meyer et al. (2013)). Most of these agents inhibits electron chain transport activity and uncouples oxidative phosphorylation, causing a decrease in cellular levels of ATP and cytotoxicity. Several toxic agents also attack mtDNA, with damaged mitochondrial genome causes a misexpression of the proteins involved in energy metabolism (Hargreaves et al. 2016).

No data known to author are available concerning the prevalence of intoxications that affect mitochondrial bioenergetics in clinical environment. Since mitochondrial effects are often secondary to effects of toxicants elsewhere (or perhaps too complex to recognize), it seems that most cases remain unobserved. Nevertheless, many recent reports suggested that off-targeted mitochondrial toxicity might be highly frequent, and therefore should be recognized as a critical factor to be considered by clinicians and drug developers as a possible causative factor that contributes to the adverse side effects associated with certain drug regimens or environmental exposures (Varga et al. 2015; Hargreaves et al. 2016). For example, drug-induced mitochondrial damage has been recognized as an important adverse effect of nucleoside analogue reverse transcriptase inhibitors in patients with human immunodeficiency virus infection, with many patients exhibit iatrogenic organ-specific mitochondrial damage and insufficient energy production (Gardner et al. 2014). Another well-known example is doxorubicin, a chemotherapeutic whose clinical use is limited since its off-target effects include inhibition of mitochondrial ATP production via uncoupling of oxidative phosphorylation and irreversible cardiomyopathy (Wallace 2007). Exposure to rotenone, an isoflavone-based broad-spectrum pesticide, inhibits complex I of the mitochondrial respiratory chain that could induce significant respiratory depression and respiratory arrest (Wood et al. 2005). It seems that prolonged exposure to mitochondrial toxins induce diverse clinical features that includes myopathy, cardiomyopathy, and peripheral neuropathy, also lipodystrophy, hepatosteatosis and biochemical disturbances, with lactic acidosis being a classic hallmark (Gerschenson and Brinkman 2004). Deleterious consequences of toxicant-induced mitochondrial dysfunction seem to depend on many aspects, including a level of exposure and bioaccumulation (Meyer et al. 2013), and cell type sensitivity (Brown and Borutaite 2012). Therefore, it is important to test for mitochondrial toxicity early in drug development or during environmental exposure to pollutants (Chan et al. 2005), since impairment of mitochondrial bioenergetics can induce various pathological conditions, and also to consider adjuvant strategies that target impaired bioenergetics associated with certain toxicants in clinical medicine.

Energy Deficit and Neurodegeneration

Impaired bioenergetics from mitochondrial dysfunction is at least partially causative for many neurodegenerative diseases, with the most notable being Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). In experimental models of neurodegeneration, there is a strong evidence for energy deficit, as evaluated by tissue ATP and phosphocreatine depletion, reduced glucose uptake and increased lactate concentration, and elevated lactate-to-pyruvate ratio in the brain, but also in peripheral tissues (Pathak et al. 2013). However, only a handful of *in vivo* studies evaluated energy deficit in clinical patients with neurodegenerative diseases. Kudo et al. (1997) reported impaired regional HEPs and phospholipid metabolism in the brain of patients with PD, as evaluated with ^{31}P magnetic resonance spectroscopy (MRS). Impaired brain bioenergetics in PD patients has been confirmed by ^{31}P MRS, with HEPs drop significantly (by 36%) after visual activation (Rango et al. 2006). Another MRS study with HD and PD patients detected no major changes in cerebral phospho-

creatine and ATP, yet small, systematic changes in brain creatine and alterations in other key cerebral metabolites were demonstrated in all patients individually (Hoang et al. 1998). Several *in vivo* trials confirmed impaired bioenergetics in AD patients (Longo et al. 1993; Pettegrew et al. 1994; Mandal et al. 2012). Gonzalez and co-workers (1996) reported unfluctuating brain energy stores in AD yet abnormalities in biophysical state of membrane phospholipid metabolism were found in all patients with the disease. Impaired oxidative phosphorylation, oxidative stress and incapacitated mitochondrial calcium turnover, and deregulation of mitochondrial biogenesis are suggested as biochemical means of energy deficit in neurodegeneration (Mochel and Haller 2011).

Although neurodegenerative diseases manifest with different clinical features, with symptoms and signs of neurodegeneration usually depend on the area within the brain where dysfunction takes place, all share attributes of gradual energy failure leading to neuronal death as the disease progresses (Pathak et al. 2013). Impaired bioenergetics in the brain of HD and PD patients especially affects basal ganglia (Amano et al. 2015) while energy deficit seems to commence in the precuneus and spread to other parts of the cerebral cortex in AD (Love and Miners 2016). In addition, a state of chronic energy deficit in the motor cortex has been reported in ALS (Ioannides et al. 2016). Several recent reviews described possible therapeutic advances in targeting mitochondrial bioenergetics in neurodegeneration (Yao and Brinton 2011; Yadav et al. 2014). However, it appears that many candidates that seem to potentiate brain metabolic energetics, including -lipoic acid, resveratrol and B vitamins, primarily tackle mitochondria as antioxidants or signaling modulators rather than energy-boosting compounds. On the other hand, energy-promoting agents (such as creatine) are occasionally used in neurodegenerative disease, with effectiveness and practicability rather debatable (as described below).

Cardiometabolic Diseases and Impaired Bioenergetics

Several pioneering trials from 1970-s reported smaller or dysfunctional mitochondria in the liver, muscle, or adipose tissue from obese and diabetic patients (Marubbio et al. 1976; Petersen 1977; Vondra et al. 1977), implying insufficient energy production (or excessive utilization) in different cardiometabolic disorders. Recent clinical studies confirmed above supposition using non-invasive ^{31}P MRS techniques to quantify ATP concentrations or synthesis in target tissues. Research in humans on hepatic energy metabolism under conditions of type 2 diabetes mellitus, insulin resistance and non-alcoholic fatty liver disease revealed reduced HEPs content, decreased ATP recovery and altered flux through ATP synthase (for review see Koliaki and Roden (2013)). Mitochondrial transmembrane potential, inorganic phosphate utilization (indicative of ATP synthase capacity), and the activities of respiratory chain complexes I-IV in subcutaneous white adipose tissue were all reduced in obese and type 2 diabetes mellitus patients compared to those in control subjects (Kraunsøe et al. 2010; Chattopadhyay et al. 2011). Obesity and insulin resistance were also associated with impaired bioenergetics following exercise in overweight-to-obese children (Slattery et al. 2014; Wells et al. 2017) and adults (Valkovič et al. 2013), as evaluated via slower mitochondrial oxidative capacity recovery in the skeletal muscle. Type 2 diabetes mellitus patients with apparently normal cardiac function have impaired myocardial and skeletal muscle energy metabolism, with significantly lower phosphocreatine-to-ATP ratio (1.50 ± 0.11) than the healthy volunteers (2.30 ± 0.12) (Scheuermann-Freestone et al. 2003). Compromised mitochondrial bioenergetics has also been described in patients with hypertrophied or failing human hearts, as evaluated by a decrease in HEPs and an increase in ADP concentration quantified with ^{31}P MRS on the whole heart *in vivo* (Ventura-Clapier et al. 2011). Phosphocreatine drops for 50-70% in heart failure while ATP levels are diminished by ~ 30% (Beer et al. 2002; Weiss et al. 2005). Although it is not clear is impaired mitochondrial bioenergetics accounts as a cause or a consequence of cardiometabolic dysfunction, it appears that defective oxidative metabolism in the organelle is involved in visceral fat gain and the development of insulin resistance (Affourtit 2016).

In a situation of excess energy intake that usually characterizes cardiometabolic phenotype, it appears that fatty acid cannot be used properly by mitochondria. That leads to the accumulation of fatty acid intermediates, that in turn inhibit the insulin signaling pathway and induce insulin resistance accompanied by inadequate mitochondrial ATP production (Aguer and Harper 2012). The detailed mechanism seems to involve many intracellular modulators, including peroxisome proliferator-activated receptor-γ co-activator-1α, adenosine monophosphate activated protein kinase, or estrogen-related receptors, with skeletal muscle being a major site of bioenergetic impairment (Affourtit 2016). The clinical picture of cardiometabolic disorders comprises of many well-known attributes, with patient-reported features of impaired mitochondrial bioenergetics often include reduced ability to exercise, post-exertional malaise, ongoing muscle weakness, and fatigue. To confirm the diagnosis of bioenergetic impairment with cardiometabolic background, a clinician needs to order rather non-standard tests (e.g. muscle or liver biopsy, ^{31}P MRS) since no robust and routine tests exist at the moment. Although some patients with obesity and type 2 diabetes may have an elevated blood lactate (as a consequence of altered mitochondrial oxidative phosphorylation) (Lovejoy et al. 1992) or low co-enzyme Q10 levels (due to stress-induced depletion of this component of the mitochondrial electron transport chain) (McDonnell and Archbold 1996), both tests seem to lack sensitivity and specificity to be widely used. Many management strategies are available to treat cardiometabolic disorders, however impaired mito-

chondrial bioenergetics has not been recognized so far as the primary target for pharmacological or nutritional interventions here. While recent evidence suggests some beneficial effects of co-enzyme Q10 administration in mitochondrial dysfunction with metabolic and cardiovascular background (Alam and Rahman 2014), its direct role for improved bioenergetics has never been demonstrated in clinical environment.

Other conditions with Bioenergetic Impairment

A plethora of other clinical conditions seems to be accompanied by mitochondria-related energy deficit. Levy (2007) suggested inadequate oxidative phosphorylation and defective electron-transport-chain function in the heart and other organs during sepsis, leading to cellular metabolic down-regulation and organ dysfunction syndrome. Dysfunctional mitochondrial bioenergetics has been recognized in the pathogenesis of various hepatic disorders (Auger et al. 2015), with the inactivation of crucial mitochondrial enzymes and decreased ATP levels could critically contribute to alcoholic liver disease and hepatocellular carcinoma. Emerging role of bioenergetics deregulation has been advocated in osteoarthritis, where impaired chondrocyte bioenergy might contribute to the inflammation and disease progression (Liu-Bryan and Terkeltaub 2015). Furthermore, patients with chronic fatigue syndrome had abnormally reduced phosphocreatine-to-ATP ratio and higher adenosine diphosphate (ADP) on exercise in the ^{31}P MRS of their skeletal muscles (Barnes et al. 1993; Chaudhuri and Behan 2004), suggesting that bioenergetics abnormalities could be present in patients with this perplexing medical condition. Abnormal brain and muscle energy metabolism has been also shown in patients affected by migraine with aura, with tissue ^{31}P MRS disclosed a low phosphocreatine content accompanied by high ADP concentration and a low phosphorylation potential (Barbiroli et al. 1992; Reyngoudt et al. 2011). Reduction of brain HEPs has been detected in patients with bipolar disorders (Kato et al. 1994); same group reported more decreased phosphocreatine levels in severely depressed patients compared to mild depressives (Kato et al. 1992). Impaired tissue bioenergetics was also reported in patients with thyroid disorders (Erkintalo et al. 1998; Khushu et al. 2010; Rana et al. 2012), lung cancer (Leij-Halfwerk et al. 2000), peripheral arterial disease (Schocke et al. 2008), Friedreich ataxia (Nachbauer et al. 2013), schizophrenia (Fukuzako et al. 1995), Marfan syndrome (Crilley et al. 2007), adults with Down's syndrome (Phillips et al. 2013), and college athletes after concussion (Sikoglu et al. 2015). The above inventory of clinical conditions should be kept open since pre-clinical trials suggest dysfunctional mitochondrial energetics with ATP depletion in many experimental disease models (Boczonadi and Horvath 2014), implying bioenergetic-centric context as an unfolding clinical paradigm in human medicine.

Tackling Impaired Bioenergetics

At the moment, there are no pharmaceutical cures for impaired mitochondrial bioenergetics disorders in clinical medicine. Although several mitochondria-targeted therapeutics have been developed in the past two decades, most compounds are designed as antioxidants, focused to tackle organelle-specific oxidative stress rather than energy deficit (Smith et al. 2011; Apostolova and Victor 2015). So far, only few human trials evaluated the therapeutic value of non-specific energy-boosting compounds in clinical conditions with impaired mitochondrial bioenergetics. Most studies used oral creatine and creatine analogs, or amino acid derivatives and peptides, and revealed rather ambiguous results.

Oral creatine monohydrate administration improved cellular energetics (as verified by increased muscle phosphocreatine-to-inorganic phosphate ratio by ^{31}P MRS at post-administration) and muscle strength in ambulatory Duchenne muscular dystrophy patients (Banerjee et al. 2010). Creatine corrects muscle ^{31}P spectrum in gyrate atrophy with hyperornithinaemia (Heinänen et al. 1999), improved *in vivo* ^{1}H MRS brain creatine levels in a child with guanidinoacetate methyltransferase deficiency (Leuzzi et al. 2000), and partially recovered cerebral creatine levels in a patient with arginine:glycine amidinotransferase deficiency (Ndika et al. 2012). Creatine also improved brain bioenergetics in a dose-ranging ^{31}P MRS study of adolescent females with drug-resistant depression (Kondo et al. 2016). Yet, several clinical studies reported low-to-medium therapeutic potential of creatine to positively dysfunctional energy metabolism in Huntington's disease (Bender et al. 2005) and Parkinson's disease (Bender et al. 2006), also schizophrenia (Kaptsan et al. 2007). Co-administration of creatine and ketogenic diet did not result in ^{31}P-MRS visible changes in muscle energy metabolism in patients with McArdle disease although the intervention showed some energy-independent beneficial effects (Vorgerd and Zange 2007). In addition, creatine has no beneficial effect on skeletal muscle energy metabolism in patients with single mitochondrial DNA deletions (Kornblum et al. 2005). Guanidinoacetic acid, a direct precursor of creatine, improved work capacity in women with chronic fatigue syndrome yet markers of tissue bioenergetics were not improved by the intervention (Ostojic et al. 2016), suggesting non-energy related role of this compound. Oral *L*-arginine, another precursor of creatine, positively affected energy metabolism in MELAS syndrome, an inherited disorder of mitochondrial energy metabolism (Rodan et al. 2015), while its effectiveness to improve brain bioenergetics in patients with X-linked creatine transporter defect was absent (Fons et al. 2008) or minimal (Chilosi et al. 2012). Improved muscle bioenergetics and mitochondrial function have been reported recently in children suffering from Duchenne muscular dystrophy treated with *L*-arginine and metformin for 16 weeks (Hafner et al. 2016).

Although copper-histidine therapy improved markers of brain metabolism in a boy with Menkes disease, a rare inherited disorder of copper trafficking and ATPase abnormality, the brain atrophy and severe neurological symptoms were not ameliorated by this intervention (Munakata et al. 2005). Similarly, sodium benzoate improved brain creatine in a girl with guanidinoacetate methyltransferase deficiency yet tissue bioenergetics remained below normal in the basal ganglia and white matter after 3 years of the intervention, and treatment did not improve intellectual disability (Mercimek-Mahmutoglu et al. 2014). Also, studies failed to show any significant effect of L-carnitine administration on objective measures of muscle energetics in end-stage renal disease (Vaux et al. 2004). ^{31}P MRS did not show improved mitochondrial bioenergetics after eight weeks of recombinant human erythropoietin exposition in skeletal muscle tissue of Friedreich ataxia patients (Nachbauer et al. 2013). Molecular hydrogen improved fatigability and serum lactate-to-pyruvate ratio (a surrogate marker of mitochondrial electron transport system viability) in MELAS patients, yet no markers of tissue energetics were evaluated in this study (Ito et al. 2011). In addition, an acute administration of allopurinol, a xanthine oxidase inhibitor, increased cardiac phosphocreatine-to-ATP ratio and phosphocreatine levels in patients with non-ischemic cardiomyopathy (Hirsch et al. 2012), offering preliminary evidence that myocardial energy can be pharmaceutically augmented in the failing human heart.

Although some encouraging ^{31}P MRS data exist for the treatment of specific bioenergy disorders, most studies shown low-to-mild improvement, were inadequately sized or lacked a placebo group, with technical differences among trials often complicate interpretation of tissue bioenergetics assays. In addition, no information is currently available concerning the degree of specific compound's mitochondrial uptake, and its subcellular bioenergetic behavior during intervention in clinical environment. A supreme candidate agent should have chemical properties that enable its full-off delivery to the organelle when administered via enteral or parenteral route (Avula et al. 2014). In addition, a superior ability to directly replenish cellular ATP that translates into clinical benefit is a must for such an agent.

Conclusions

Impaired mitochondrial bioenergetics disorders are becoming recognizable as clinical entities of interest in many medical disciplines, with conditions seem to be far more common than previously anticipated. Many issues on impaired bioenergetics in clinical medicine remain unresolved, including unknown prevalence and burden of those disorders in clinical environment, a debatable degree in which local bioenergetic deficit translates into systemic energy failure, a lack of gold-standard tests for energy failure diagnosis, or a dearth of effective treatments to restore tissue bioenergetics (Fig. 2). However, although it is not clear whether poor energetics is a primary deficit or a secondary consequence of the specific disease, improving mitochondrial bioenergetic status seems to emerge as a challenging task for drug manufacturers and physicians. This is particularly true for patients suffering from highly prevalent conditions that go together with bioenergetic impairment, such as obesity, type 2 diabetes, or Alzheimer's disease, that could benefit a lot from advances in bioenergetic medicine.
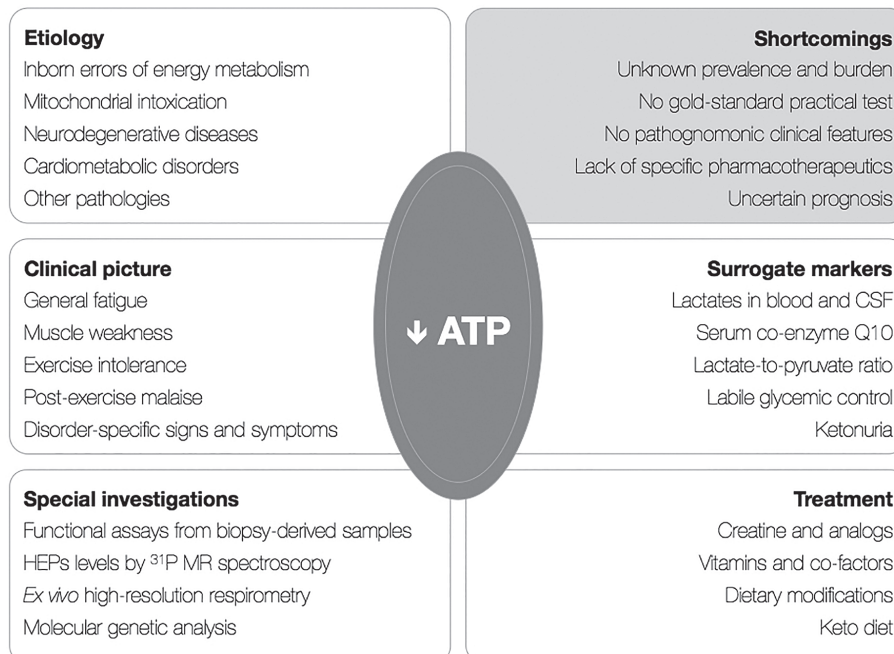

Fig. 2. Clinical overview of impaired mitochondrial bioenergetic disorders.
HEPs, high-energy phosphates; MR, magnetic resonance; CSF, cerebrospinal fluid; ATP, adenosine triphosphate.

Acknowledgments

Conflict of Interest

The author declares no conflict of interest.

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