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Themed Issue: Mitochondrial Pharmacology: Energy, Injury & Beyond

REVIEW

Bioenergetic medicine

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Here we discuss a specific therapeutic strategy we call 'bioenergetic medicine'. Bioenergetic medicine refers to the manipulation of bioenergetic fluxes to positively affect health. Bioenergetic medicine approaches rely heavily on the law of mass action, and impact systems that monitor and respond to the manipulated flux. Since classically defined energy metabolism pathways intersect and intertwine, targeting one flux also tends to change other fluxes, which complicates treatment design. Such indirect effects, fortunately, are to some extent predictable, and from a therapeutic perspective may also be desirable. Bioenergetic medicine-based interventions already exist for some diseases, and because bioenergetic medicine interventions are presently feasible, new approaches to treat certain conditions, including some neurodegenerative conditions and cancers, are beginning to transition from the laboratory to the clinic.

LINKED ARTICLES

This article is part of a themed issue on Mitochondrial Pharmacology: Energy, Injury & Beyond. To view the other articles in this issue visit http://dx.doi.org/10.1111/bph.2014.171.issue-8

Abbreviations

AChEI, acetylcholine esterase inhibitor; AD, Alzheimer's disease; AMPK, AMP kinase; CoQ, coenzyme Q; COX, cytochrome oxidase; cybrid, cytoplasmic hybrid; DM, diabetes mellitus; ER, endoplasmic reticulum; ETC, electron transport chain; FA, Friedreich's ataxia; FAD, flavin adenine dinucleotide; FDG PET, fluorodeoxyglucose PET; HD, Huntington's disease; IP3, inositol triphosphate; MCI, mild cognitive impairment; MCT, monocarboxylate transporter; mtDNA, mitochondrial DNA; mTOR, mammalian target of rapamycin; NAA, n-acetyl aspartate; OAA, oxaloacetate; PD, Parkinson's disease; PDHC, pyruvate dehydrogenase complex; PDK4, pyruvate dehydrogenase kinase 4; PGC1, peroxisome proliferator-activated receptor γ-complex 1; SERCA, sarcoendoplasmic reticulum calcium ATPase

Bioenergetics refers to the chemistry and molecular physiology of energy metabolism. It is most often considered at the individual cell level, with a cell's bioenergetic status typically summarized as the amount of energy-yielding intermediates, such as ATP, it contains. The balance between a cell's rate of energy intermediate production and consumption determine this parameter.

Multiple biochemical pathways contribute to a cell's bioenergetic state. Within cells, these pathways are variably compartmentalized or span compartments, and bioenergetic pathways are ultimately characterized by the passage of carbon that starts as part of one molecule and ends as another. Bioenergetic pathways, therefore, are characterized by movement through the pathway, or as a 'flux'.

Bioenergetic changes occur in many diseases, including the mitochondrial encephalomyopathies, neurodegenerative diseases and cancer (Swerdlow, 2009b; Vander Heiden *et al.*, 2009; Chaturvedi and Beal, 2013). In some disorders, bioenergetic perturbations are etiologically relevant. In others, bioenergetic changes induced by upstream pathologies mediate or amplify a particular phenotype or pathology. Mitochondrial dysfunction is frequently seen, and diseases in which mitochondria appear to play particularly upstream roles are sometimes considered 'mitochondriopathies' (Swerdlow, 2009a; Swerdlow, 2009b). Mitochondrial and bioenergetic dysfunctions often coincide, as mitochondrial dysfunction tends to cause bioenergetic dysfunction.

'Mitochondrial medicine' refers to the art and science of correcting mitochondrial dysfunction or minimizing the consequences of mitochondrial dysfunction (Luft, 1994; Swerdlow, 2009a; Swerdlow, 2011b). Data increasingly indicate one can manipulate mitochondria indirectly, or mitigate the impact of mitochondrial failure, by manipulating bioenergetic pathways that lie external to the mitochondria or, for pathways that traverse the mitochondria, at steps that lie outside the mitochondria themselves. This currently feasible overall strategy also impacts non-mitochondrial bioenergetic parameters, as well as the expression of genes that monitor and respond to a cell's overall bioenergetic state. These effects can fundamentally affect cell health and viability. This review considers the complexities and potential of bioenergetic flux manipulation or, to introduce a term, 'bioenergetic medicine', for the treatment of various disorders and conditions.

Bioenergetic fluxes: A brief overview

This section briefly reviews several major bioenergetic pathways, some of which are summarized in Figure 1. The glycolysis, Krebs and oxidative phosphorylation pathways facilitate carbohydrate-based energy production. Glycolysis allows for anaerobic ATP generation, and occurs in the cytosol. Within the mitochondria, conversion of pyruvate to acetyl CoA, followed by a full turn of the Krebs cycle, reduces NAD+ to NADH and FAD to FADH2. Cytosolic NADH, which is generated during glycolysis, can also supplement this by using shuttle systems to transfer 'reducing equivalents' to

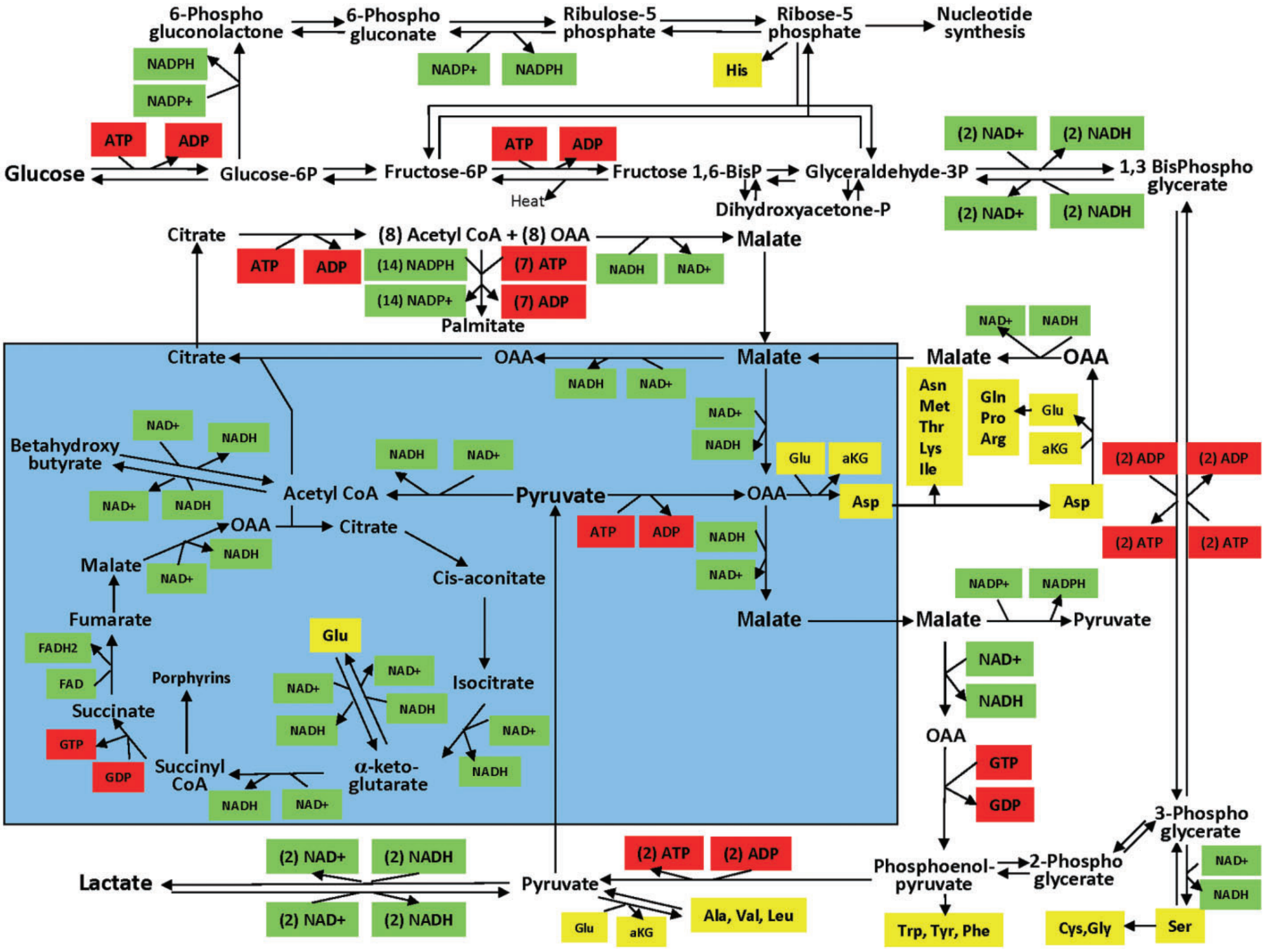

Figure 1

Some of the major bioenergetic pathways. Glycolysis, the pentose phosphate shunt, the Krebs cycle and gluconeogenesis are illustrated. The large blue box indicates the mitochondrial compartment; the cytosol is the area outside of this blue box. Redox (green text boxes) and energy storage (red text boxes) intermediates are indicated. Relationships between these pathways and some amino acids (yellow text boxes, with standard abbreviations used) are shown. To give a better overall feel for the connectivity between these pathways, some critical shuttles such as the malate-aspartate shuttle and citrate-malate shuttle are superficially (but incompletely) indicated. High-energy electrons from NADH and FADH2 feed into the respiratory pathway, and combine with O_2 to form H_2O (not shown). Fatty acid β-oxidation, which produces large amounts of NADH and acetyl CoA is not shown, although entry of D-β-hydroxybutyrate (a ketone body) carbon into the Krebs cycle is incompletely summarized in order to show its associated contribution to the mitochondrial redox balance.

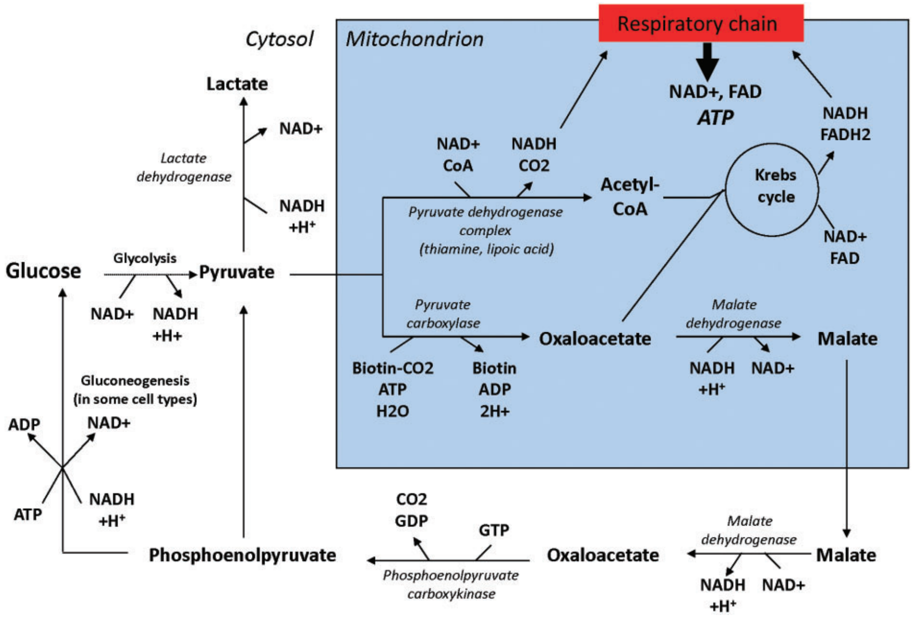

Figure 2

Pyruvate flux is influenced by redox states. Upon entering the mitochondrion (shown as a blue box), pyruvate carbon can proceed to acetyl CoA and the Krebs cycle, or ultimately return to the cytosol. NAD+/NADH ratios influence this branch point, with a high ratio favouring the PDHC-catalysed reaction. If acetyl CoA accumulates, biotin decarboxylation occurs and pyruvate carboxylase converts pyruvate to OAA. If the NAD+/NADH ratio remains relatively elevated and ATP levels are low, OAA enters the Krebs cycle (an anaplerotic reaction). If the NAD+/NADH ratio falls and ATP levels are high, OAA is reduced and the pyruvate carbon returns to the cytosol as malate. In tissues that perform gluconeogenesis, if the cytosol is adequately reduced and contains adequate ATP, the original pyruvate carbon can proceed through that pathway.

the mitochondrial matrix. The oxidative phosphorylation pathway, or respiratory chain, oxidizes these reduced dinucleotides, using molecular oxygen as the final electron acceptor.

Fatty acid catabolism proceeds via β-oxidation, a series of reactions that occur within mitochondria. This process reduces NAD+ to NADH, FAD to FADH2 and generates acetyl CoA. These acetyl groups can enter the Krebs cycle or, under conditions of excess or low insulin levels, divert towards ketone body formation.

A number of branch points exist that facilitate conservation of carbon and its conversion towards or incorporation into other molecules. For example, the pentose phosphate shunt diverts glucose towards the production of 5-carbon sugars that are used to generate nucleic acids and nucleotides, as well as aromatic amino acid precursor carbons. Also, although forward flow through these major bioenergetic fluxes is generally considered from the energy-producing, catabolic perspective, the case of gluconeogenesis emphasizes that reverse fluxes occur.

The law of mass action influences bioenergetic fluxes and flux patterns. Increasing concentrations of upstream metabolites can drive a flux, while increasing concentrations of downstream metabolites can reduce a flux. For example, pyruvate accumulation inhibits glycolysis, a process that may involve the inhibition of several different glycolytic enzymes (Williamson and Jones, 1964). When considering the law of mass action, redox pairs such as NAD+ and NADH also play a critical role. Cytosolic NAD+ is needed to support glycolysis flux. A reduction in the cytosolic NAD+/NADH ratio would predictably slow glycolysis flux, while increasing this ratio would predictably accelerate glycolysis flux. A reduction in the mitochondrial NAD+/NADH ratio would predictably slow the Krebs cycle flux while increasing respiratory flux; increasing this ratio would predictably have the opposite effect. NAD+/NADH ratios may also influence pyruvate utilization (Figure 2).

Under conditions of fixed energy expenditure, anaerobic and aerobic fluxes tend to reciprocally relate. The Pasteur effect refers to the observation, initially made in yeast, that enabling respiration reduces fermentation and by extension glycolysis (Krebs, 1972). The Crabtree effect refers to the observation that enabling glycolysis reduces respiration (Crabtree, 1928). More recently, an effect in which reduced glycolysis flux associates with increased respiratory flux was characterized (Swerdlow *et al*., 2013). In the tumour cell-observed Warburg effect, relatively high glycolysis and low respiratory flux rates are observed (Warburg, 1956). What driving forces ultimately underlie these effects is unclear. Obviously, reciprocal relationships such as these help facilitate a constant store of energy, or in other words an energy store equilibrium since changes in ATP production in one arm are offset by opposing ATP production changes in the other arm.

Bioenergetics in physiology and health

Bioenergetic parameters change over the course of development. For example, bioenergetic fluxes tend to decline with

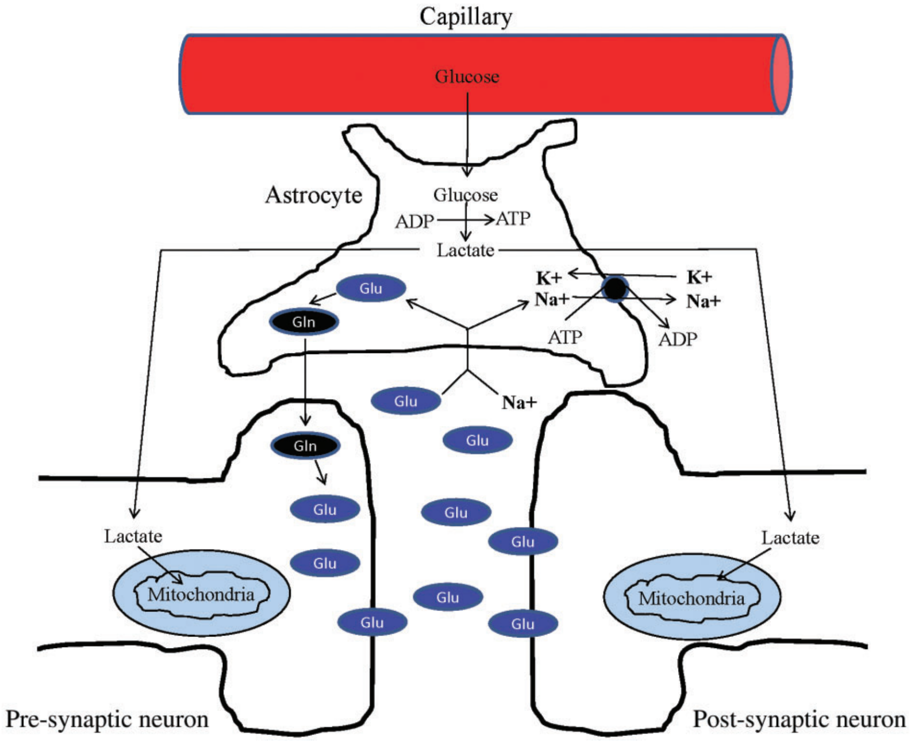

Figure 3

The tripartite synapse. Glutamate released into the synapse facilitates intercellular communication. To terminate this signal, synaptic glutamate is co-imported with sodium into an astrocyte. The glutamate in the astrocyte, following its conversion to glutamine, is returned to the pre-synaptic neuron. The sodium that entered the astrocyte is removed by the sodium-potassium ATPase, which consumes the astrocyte's ATP. The astrocyte replaces its ATP by importing glucose from the blood and increasing its glycolysis flux. This produces lactate in the relatively anaerobic astrocytes, which is exported and taken up by high-affinity MCTs on the neurons. This lactate carbon eventually accesses mitochondria in synaptic boutons, fuels respiration and generates the ATP needed to restore neuron ion gradients.

advancing age (Navarro and Boveris, 2007; Boveris and Navarro, 2008; Bratic and Larsson, 2013). In the brain, this includes decreasing glucose utilization, which suggests reduced glycolysis flux (De Santi *et al.*, 1995; Willis *et al.*, 2002; Kalpouzos *et al.*, 2009; Chetelat *et al.*, 2013; Marano *et al.*, 2013). Mitochondria function less robustly, as illustrated by falling complex I and IV Vmax activities (Navarro and Boveris, 2007). The overall picture is somewhat murky, and some findings may be tissue-specific, but data argue that at least for a period of time during adulthood, some tissues increase their mitochondrial mass (Barrientos *et al.*, 1997a; 1997b; Hirai *et al.*, 2001; Manczak *et al.*, 2005). If this truly happens in the face of declining electron transport chain (ETC) Vmax activities, such changes could represent a compensatory up-regulation (Swerdlow, 2011a).

During this stage, mitochondrial DNA (mtDNA) copy numbers may increase while mtDNA-encoded mRNA transcript levels decrease (Barrientos *et al.*, 1997b). At some point, though, both the drive to maintain mitochondrial mass as well as mitochondrial mass itself falls (Manczak *et al.*, 2005). The fact that some tissues such as brain exhibit concomitant age-related declines in both respiratory capacity and glucose utilization is somewhat paradoxical, since experiments performed with cultured cells typically show inverse anaerobic–aerobic flux relationships (Swerdlow *et al.*, 2013).

The most differentiated tissues, interestingly, are bioenergetically organized in ways that might facilitate such a paradox. For example, in muscle, anaerobic type II fibres produce lactate during glycolysis, and export that lactate. Aerobic type I fibres then import the type II fibre-generated lactate and use it as a respiratory fuel. This may create a situation in which a reduction of the primary flux in one cell type inadvertently reduces the primary flux of the other cell type.

Considerable data argue a similar arrangement exists in brain (Pellerin and Magistretti, 1994; Magistretti and Pellerin, 1999; Pellerin and Magistretti, 2003; Pierre and Pellerin, 2005); this arrangement is shown in Figure 3. In this scheme, relatively anaerobic astrocytes generate lactate via glycolysis and export that lactate to relatively aerobic neurons, whose respiratory chains use it to produce ATP. This bioenergetic relationship likely plays an especially important role during action potential-induced synaptic activity, and defines a 'tripartite synapse' that functionally differs from the traditional bipartite synapse (Pellerin and Magistretti, 2004; Perea *et al.*, 2009; Faissner *et al.*, 2010). Recent studies further report lactate in fact plays a crucial role in memory acquisition (Newman *et al.*, 2011; Suzuki *et al.*, 2011).

Relationships between bioenergetic intermediate import and export also exist between separate organs. In the Cori cycle, lactate produced by exercising white muscle enters the blood and is absorbed by liver hepatocytes. This lactate enters gluconeogenesis, converts to glucose and re-accesses the blood. In this manner, the Cori cycle helps maintain blood glucose levels during exercise. In mice, exercise training optimizes Cori cycle function (E *et al.*, 2013a,b). Hepatocytes increase membrane monocarboxylate transporter (MCT) levels, which facilitates lactate import. Indeed, immediately after an exercise session, serum lactate levels in trained mice fall below their pre-exercise baseline levels, presumably due to more efficient hepatic uptake. Hepatocytes also up-regulate some parts of their mitochondrial mass, but do not increase their mtDNA. This is associated with and likely mediated by peroxisome proliferator-activated receptor γ-complex 1α (PGC1a), a transcription co-activator that facilitates an increase in mitochondrial mass and, concomitantly, mitochondrial uncoupling (Handschin and Spiegelman, 2006; Scarpulla, 2008). The exercise training-associated increase in liver mitochondrial mass, therefore, seems designed not so much to enhance liver respiration, but rather to enhance gluconeogenesis (E *et al.*, 2013a,b).

Bioenergetics in disease

Many disorders feature bioenergetic dysfunction. Bioenergetic lesions can originate in pathways outside of or within mitochondria. Most recognized bioenergetic flux disorders, though, fall into the latter category.

A group of diseases that affect mostly muscle and brain, the mitochondrial encephalomyopathies, occur in conjunction with defined, heritable mtDNA mutations (Betts *et al.*, 2004; Filosto *et al.*, 2007; DiMauro and Schon, 2008; Swerdlow, 2009b). The classic mitochondrial encephalomyopathies were recently reviewed in detail elsewhere (Dimauro, 2013). For most of these diseases, the causal mutation resides within an mtDNA tRNA gene. Protein primary structures are not changed, but nevertheless reduced ETC Vmax activities result. These Vmax reductions presumably reflect diminished ETC protein production, lower the respiratory flux and drive each specific disease-associated phenotype. The clinical syndromes for the different mitochondrial encephalomyopathies show unique features but also clinical and histological overlap. For example, different mtDNA tRNA gene mutation-associated syndromes show subsarcolemmal mitochondrial accumulations, which on Gomori trichrome staining appear as 'ragged red fibres' (Shoffner *et al.*, 1990).

Mutations in mtDNA protein-coding genes also cause disease, presumably by causing changes in respiratory chain enzyme function (Howell, 1998; Rojo *et al.*, 2006; Swerdlow, 2009b). The most common one, Leber's hereditary optic neuropathy, usually associates with mutations in complex I subunit genes. Two other disorders, maternally inherited Leigh's syndrome and the neuropathy, ataxia and retinitis pigmentosum syndrome occur in conjunction with a mutation in a complex V subunit.

Bioenergetic changes may directly affect fluxes. In carnitine palmitoyl transferase deficiency, the abnormal protein resides within mitochondria and directly effects substrate delivery to the fatty acid β-oxidation pathway (Bonnefont *et al.*, 2004). In McArdle's disease, myophosphorylase deficiency prevents glycogenolysis, a cytosolic pathway (Lucia *et al.*, 2008). Upon consuming their available glucose, a situation that occurs during exercise, muscle cells from affected individuals cannot tap glycogen reserves to maintain a glycolysis flux.

Other Mendelian disorders more indirectly affect bioenergetics. In Huntington's disease (HD), the mutant protein, huntingtin, may impact bioenergetics through physical interactions with the external mitochondrial membrane or possibly by affecting transcription of nuclear genes that regulate mitochondrial function (Panov *et al.*, 2002; Cui *et al.*, 2006). In Friedreich's ataxia (FA), recessive mutations in the frataxin gene presumably impair mitochondrial iron handling by the frataxin protein (Pandolfo, 2008). This apparently disrupts formation of iron-sulfur clusters, structures that play critical roles in three ETC enzyme complexes.

Parkinson's disease (PD), a neurodegenerative movement disorder in which patients develop rigidity, tremor and slowness usually presents sporadically, which means recognizable Mendelian inheritance occurs in a minority of cases (Swerdlow, 2012c). PD patients typically show reduced complex I activity. A role for complex I in PD is suggested by several observations. First, exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a toxin that induces a PD-like syndrome, results in complex I inhibition and administering rotenone, a complex I inhibitor, to rats damages dopamine neurons (Langston *et al.*, 1983; Nicklas *et al.*, 1985; Betarbet *et al.*, 2000). Second, PD patients show a potentially systemic change in complex I function, which suggests this defect is not simply a consequence of neurodegeneration (Parker *et al.*, 1989; Parker and Swerdlow, 1998). Third, transferring mitochondria from PD subject platelets to neuroblastoma, teratocarcinoma or lung carcinoma cells that lack endogenous mtDNA and respiratory competence does not restore normal complex I function (Swerdlow *et al.*, 1996; Gu *et al.*, 1998; Esteves *et al.*, 2008). Such cytoplasmic hybrid, or cybrid, cell lines sustain an ETC defect and recapitulate additional biochemical and histologic features seen in PD subject brains (Swerdlow, 2012c). Fourth, particular mtDNA haplogroups reportedly influence PD risk (Swerdlow, 2012c; Hudson *et al.*, 2013). Fifth, in many cases, the mutated proteins that cause Mendelian PD affect mitochondrial physiology (Tan and Skipper, 2007; Cookson, 2012). For example, abnormalities in the α-synuclein, parkin, and PINK1 proteins may each cause PD by ultimately impairing mitochondrial quality control.

Patients with Alzheimer's disease (AD), a disorder of cognitive decline that represents the single most common neurodegenerative disease, also show characteristic bioenergetic pathway-relevant characteristics (Swerdlow, 2012b). Cytochrome oxidase (COX), pyruvate dehydrogenase complex (PDHC) and α-ketoglutarate dehydrogenase complex activities tend to run lower in AD subjects than they do in age-matched control subjects (Parker *et al.*, 1990; Gibson *et al.*, 2010; Swerdlow, 2012b). These activity reductions extend beyond the brain, which makes it difficult to blame these enzyme changes on neurodegeneration or other brain-limited phenomena. Interestingly, while flux into and through the proximal portion of the Krebs cycle should predictably decline, some of the more distal Krebs cycle enzymes may actually demonstrate increased activity (Gibson *et al.*, 2010).

While some of these AD biochemical changes may reflect post-translational modifications or other causes of secondary inhibition (Joffe *et al.*, 1998; Gibson *et al.*, 2010), evidence suggests AD patient COX is genetically altered (Swerdlow, 2012b). One small study showed perturbed COX kinetics, as evidenced by the absence of a specific cytochrome c binding site (Parker and Parks, 1995). Also, AD cybrid cell lines created via the transfer of AD subject platelet mitochondria to neuroblastoma and teratocarcinoma cells previously depleted of endogenous mtDNA show low COX activity, a finding that persists over months of continuous culture (Swerdlow *et al.*, 1997; Cardoso *et al.*, 2004; Swerdlow, 2012b; Silva *et al.*, 2013). Since mtDNA constitutes the only known transferred entity that does not degrade over time or dilute over repeated cycles of cell division, these cybrid experiments suggest AD subject mtDNA differs from control subject mtDNA, and accounts at least in part for the AD COX defect.

Interestingly, glucose utilization is also diminished in AD subject brains. This was first demonstrated several decades ago using a functional neuroimaging technique called 2-fluorodeoxyglucose PET (FDG PET; Foster *et al.*, 1983; Friedland *et al.*, 1983; Silverman *et al.*, 2001; Mosconi *et al.*, 2010). Diminished glucose utilization in AD is sometimes attributed to neurodegeneration or reduced synaptic activity, but the degree to which this phenomenon represents a consequence of AD, a cause of this progressive disorder, or both is unknown. Regardless, diminished glucose utilization implies diminished glycolysis flux, which is perplexing given the fact that both reduced oxygen consumption and oxidative phosphorylation efficiency also reportedly occur in AD (Frackowiak *et al.*, 1981; Sims *et al.*, 1987; Fukuyama *et al.*, 1994). As discussed earlier, aerobic and anaerobic fluxes typically show inverse relationships. Reduced aerobic and anaerobic fluxes in AD brains represent a bioenergetic paradox.

Many neurodegenerative diseases show altered bioenergetics but altered bioenergetics extend beyond this category. The Warburg effect, in which cells boost glycolysis rates and de-emphasize aerobic ATP production, occurs in cancer (Feron, 2009; Vander Heiden *et al.*, 2009). We do not fully understand the Warburg effect's relevance to carcinogenesis, or how it originates, although several potential explanations exist (Ferguson and Rathmell, 2008; Feron, 2009; Vander Heiden *et al.*, 2009; Almeida *et al.*, 2010). Warburg bioenergetics could favour cancer cell propagation and tumour growth for several reasons. It might enhance the survival of cells experiencing poor perfusion, a situation that may apply within solid tumours. Frequent cell divisions could make it difficult to maintain a reasonably constant mitochondrial mass. Perhaps most importantly, increasing glycolysis while reducing respiration should theoretically enhance the flow of carbohydrate carbon to membrane and cholesterol synthesis, processes critical to replicating cells.

Mitochondria appear to play a role in type II diabetes mellitus (DM), although the overall degree to which mitochondria contribute remains controversial (Patti and Corvera, 2010). DM occurs in conjunction with certain mtDNA mutations, which suggests bioenergetic dysfunction can represent a potential primary cause (Maassen *et al.*, 2005; 2007). Mitochondrial function also likely influences insulin resistance, with mitochondrially generated oxidative stress perhaps mediating this phenomenon (Morino *et al.*, 2006; Rains and Jain, 2011). The 'metabolic syndrome', a constellation of findings that feature insulin resistance, oxidative stress and inflammation, is similarly linked to mitochondrial function (Eckel *et al.*, 2005; Ren *et al.*, 2010). Metabolic syndrome prevalence rises with advancing age, and predisposes individuals to DM and other age-related disorders including cardiovascular disease.

This section emphasizes the fact that when it comes to disease, bioenergetic lesions can represent primary or secondary phenomena. Even secondary lesions, though, can have disease-relevant consequences. As will be discussed further, new evidence further suggests primary deficits in one bioenergetic pathway may induce secondary deficits in other pathways. While changes that arise in one flux in response to changes in another flux probably make sense from a strict biochemical perspective, these secondary changes may exacerbate, rather than minimize, dysfunction, pathology and clinical decline (Silva *et al.*, 2013). Recognizing this point can help identify potential treatment strategies.

Mitochondrial medicine

Mitochondria malfunction for many different reasons, and mitochondrial dysfunction takes many different forms. Its consequences are also broad and variable. Taking this into account, the general rationale underlying mitochondrial medicine for the treatment of mitochondrial diseases assumes that if mitochondria function inappropriately, or if inappropriate mitochondrial function harms its host cell, then targeting either the causes or consequences could prove therapeutic (Luft, 1994; Koopman *et al.*, 2012). To date, a number of different mitochondrial medicine strategies have been attempted or proposed (Swerdlow, 2009a; Swerdlow, 2011b; Pfeffer *et al.*, 2013). This section discusses some of these strategies.

Oxidative stress and mitochondrial dysfunction often track together. When both are present, cause and consequence relationships require careful consideration, as oxidative stress impairs respiratory chain function and respiratory chain function increases oxidative stress (Shigenaga *et al.*, 1994; Brown, 1999; Riobo *et al.*, 2001; Swerdlow, 2012a). In either case, oxidative stress could represent a reasonable therapeutic target and several antioxidant strategies exist. Vitamins or other natural compounds, including polyphenols, act as free radical scavengers, but to date clinical trials with human patients show no or at best extremely limited efficacy (Swerdlow, 2011b). Mitochondrially targeted antioxidants created by conjugating scavenger molecules to cationic groups might prove more efficacious (Kelso *et al.*, 2001; Reddy, 2006), but this remains to be shown. Promoting expression of antioxidant enzymes, for example, by stimulating nuclear factor (erythroid-derived 2)-like 2-mediated gene transcription, could provide another approach (Dumont *et al.*, 2010; Greco and Fiskum, 2010). Since respiratory chain uncoupling reduces free radical production, uncoupling agents offer yet another strategy (Korde *et al.*, 2005; Perez-Pinzon *et al.*, 2012).

Minimizing the production or impact of mitochondria-generated free radicals, though, could also theoretically dampen compensatory stress responses, with potentially adverse consequences (Finkel, 2003; Schieke and Finkel, 2006). In support of this, antioxidants appear to minimize exercise-induced mitochondrial biogenesis in human subjects, as well as glycolysis inhibition-induced mitochondrial biogenesis in *Caenorhabditis elegans* (Schulz *et al.*, 2007; Ristow *et al.*, 2009).

A diverse set of other mitochondrial medicine targets have also been the subject of intense recent research (Swerdlow, 2011b). Inhibiting apoptosis, impeding apoptotic signalling, or stabilizing mitochondrial membranes have all been attempted, but such approaches have yet to produce viable therapies (Gordon *et al.*, 2007; Jones, 2010; Cudkowicz *et al.*, 2011; Dorsey *et al.*, 2013). Autophagy, which mammalian target of rapamycin (mTOR) inhibition or other means could potentially enhance, may be leveraged to remove defective mitochondria (Bergamini *et al.*, 2003; Zemke *et al.*, 2007; Harrison *et al.*, 2009; Hepple, 2009; Banerjee *et al.*, 2010; Jung *et al.*, 2010; Kapahi *et al.*, 2010; Rabinowitz and White, 2010; Sudarsanam and Johnson, 2010; Youle and Narendra, 2011). Mitochondrial fission-fusion imbalances, which occur in some neurodegenerative diseases, may be worth addressing (Chan, 2006; Jahani-Asl *et al.*, 2007; Chen and Chan, 2009; Wang *et al.*, 2009; Manczak *et al.*, 2011; Zhu *et al.*, 2013).

As mitochondria do fission and fuse, considering a cell's mitochondrial mass, as opposed to its mitochondrial number, may better quantify its mitochondrial content. Measures of mitochondrial mass include levels of mtDNA, proteins and membrane (Onyango *et al.*, 2010). Increasing mitochondrial mass tends to enhance mitochondrial function in a cell- or tissue-specific fashion. In one recent study, hepatocyte mitochondrial biogenesis induction favoured the production of gluconeogenesis-related infrastructure, while in brain, mitochondrial biogenesis induction favoured the production of respiration-related infrastructure (E *et al.*, 2013b). Also, specific interventions that influence mitochondrial mass may impact different tissues to different extents. For example, caloric restriction most consistently increases liver mitochondrial mass, while exercise most robustly increases muscle mitochondrial mass (Holloszy, 1975; Lambert *et al.*, 2004).

To accomplish mitochondrial biogenesis, cells utilize a specific set of transcription and co-transcription factors. Proteins and pathways that sense and respond to cell energy levels, as well as other parameters such as cell redox states, influence these factors (Onyango *et al.*, 2010). Promoting mitochondrial mass could potentially benefit conditions characterized by declines in mitochondrial mass. Both chemical and molecular-based approaches may accomplish this goal (Canto *et al.*, 2009b; Srivastava *et al.*, 2009; Viollet *et al.*, 2009; Wenz *et al.*, 2010; 2011; Tadaishi *et al.*, 2011).

The proteins and pathways that monitor and react to cell energy and redox states offer additional mitochondrial medicine opportunities. Some of these proteins, such as AMP kinase (AMPK), mTOR, hypoxia induction factor 1α, cAMP response element-binding protein and the sirtuins play roles in human health and disease (Sarbassov *et al.*, 2005; Wu *et al.*, 2006; Guarente, 2007; Canto and Auwerx, 2009a; Semenza, 2012).

The mitochondrial medicine-based treatment of energy metabolism disorders goes back decades (Swerdlow, 2011b). Initial attempts focused more on biochemical than molecular manipulations, and were based on basic knowledge of biochemical fluxes. Various strategies included supplementing vitamins or cofactors utilized in particular bioenergetic pathways, electron acceptors that could potentially facilitate or circumvent ETC defects, or electron donor precursors to ideally promote the flow of respiratory chain reducing equivalents.

Coenzyme Q (CoQ) represents one such example (Mancuso *et al.*, 2010). CoQ embedded within the inner mitochondrial membrane accepts electrons from complexes I and II of the respiratory chain, and delivers them to complex III. This raises the question of whether increasing inner mitochondrial membrane CoQ levels might enhance respiratory fluxes, perhaps through a mass action-related effect. While CoQ supplementation has certainly been attempted in a variety of diseases and conditions (Young *et al.*, 2007; Mancuso *et al.*, 2010; Villalba *et al.*, 2010), from the mitochondrial encephalomyopathies to common neurodegenerative disorders to statin-induced CoQ deficiency, we do not know whether this approach increases amounts of inner mitochondrial membrane CoQ, or if potential physiologic effects might derive from another mechanism, such as a compartmentalization-independent scavenging of oxygen radicals (Mancuso *et al.*, 2010).

We do know CoQ supplementation appears to benefit individuals with inherited disorders of CoQ synthesis (Musumeci *et al.*, 2001; Quinzii *et al.*, 2007). Either CoQ or its water-soluble analogue, idebenone, may to a small extent benefit some aspects of FA (Mariotti *et al.*, 2003; Hart *et al.*, 2005; Cooper and Schapira, 2007; Di Prospero *et al.*, 2007; Meier *et al.*, 2012). Several placebo-controlled trials have argued idebenone may marginally slow cognitive decline in AD subjects, although neither idebenone nor CoQ is currently approved for the treatment of AD (Weyer *et al.*, 1997; Gutzmann and Hadler, 1998; Thal *et al.*, 2003). A phase II placebo-controlled trial of CoQ in PD patients initially suggested those receiving it declined less over time than those receiving placebo (Shults *et al.*, 2002), but this finding remains to be confirmed in a definitive trial (Storch *et al.*, 2007). Small trials of CoQ in patients with other diseases, such as progressive supranuclear palsy, reported a possible positive impact (Stamelou *et al.*, 2008), while small trials of CoQ in other diseases, such as HD, did not (Feigin *et al.*, 1996). In the classic mitochondrial encephalomyopathies, there are anecdotal reports of success (Ihara *et al.*, 1989), but placebo-controlled studies have yet to show clear-cut efficacy (Scaglia and Northrop, 2006).

More detailed discussions of past mitochondrial medicine clinical trials are available (Swerdlow, 2007; Swerdlow, 2011b). In general, although occasional successes were noted, robust responses rarely occurred and clinical trial results were generally disappointing. Still, early bioenergetic flux enhancement interventions represented reasonable efforts with logical rationales. In the sections that follow, this review discusses currently utilized medical treatments that affect bioenergetic fluxes, treatments whose primary targets do not include but may indirectly affect bioenergetic pathways, and new ways to manipulate both intra and extra-mitochondrial bioenergetic fluxes.

Bioenergetic medicine

Bioenergetic medicine involves manipulating a bioenergetic pathway to increase or decrease its associated flux. This can affect cell energy stores as well as fluxes in intersecting pathways. Importantly, flux manipulations alter activities of proteins and pathways that monitor and respond to flux dynamics. Flux changes further modify gene transcription. Because of this, even transient flux manipulations produce durable effects (E *et al*., 2013b).

Bioenergetic medicine includes manipulations of mitochondrial fluxes but is not limited to manipulations of just mitochondrial fluxes. As discussed above, early mitochondrial medicine strategies tried to increase respiratory flux using vitamins, cofactors, electron acceptors and redox molecule precursors. These approaches are essentially bioenergetic medicine approaches. However, bioenergetic medicine interventions may also directly target pathways outside the mitochondria, with the intent of indirectly altering mitochondrial function, indirectly altering other non-mitochondrial parameters, or altering just the targeted pathway itself. Thus, while bioenergetic manipulations will often directly or indirectly affect mitochondria, mitochondrial changes are not obligate and may not be desired. Because cell fluxes span compartments, though, mitochondrial alterations will be difficult to avoid.

Whether one considers bioenergetic medicine a form or subset of mitochondrial medicine, or a unique and separate entity, more fully appreciating flux manipulation and its consequences will hopefully facilitate the design of new, more effective therapies. Using a novel term to define a therapeutic niche will ideally accelerate advances by identifying challenges faced by the field, and by focusing investigators on how to overcome those challenges.

Moving forward, certain principles will play a prominent role. The law of mass action is one such principle. The law of mass action states molecules participating in a chemical reaction reach equilibrium. When equilibrium is reached the reaction stops. Increasing reaction components on the upstream end of a reaction promotes the forward reaction. Increasing reaction components on the downstream end of a reaction reduces the rate of the forward reaction, and may even reverse the direction of the reaction. The law of mass action applies to a series of reactions that, when considered together, constitute a flux. Increasing concentrations of molecules that initiate a bioenergetic pathway will increase that pathway's flux, while increasing concentrations of the flux's end products decrease that pathway's flux.

A recent study of lactate-treated mice illustrates this principle (E *et al*., 2013b). In this study E *et al*. injected lactate ($2\ g{\cdot}kg^{-1}{\cdot}day^{-1}$) or vehicle, for 14 consecutive days, into the i.p. space of 5-month-old C57Bl/6 mice. Blood glucose levels were higher at the end of the treatment period in the lactate-treated mice, but not in the vehicle-treated mice. Since the liver is a gluconeogenic organ, this suggests increasing lactate at the beginning of the gluconeogenesis pathway increased the carbon flux through that pathway.

Plasma lactate levels peaked about 20 min post-injection, fell approximately 50% from its Cmax about 40 min post-injection, and returned to baseline within 3 h of the injection. Because blood glucose measurements were taken after an overnight fast, and not within 3 h of a lactate injection, the blood glucose elevation probably did not reflect an acute effect but rather a more durable change in the liver's bioenergetic infrastructure. Supporting this view, lactate treatment increased liver pyruvate dehydrogenase kinase 4 (PDK4) mRNA expression. PDK4 inhibits PDHC, which could represent an attempt to limit the flow of acetyl groups into the Krebs cycle. PGC1a mRNA levels increased, while PGC1β (PGC1b) and nuclear respiratory factor 1 mRNA levels decreased. PGC1a drives the biogenesis of relatively respiration-uncoupled mitochondria, while PGC1b tends to favour tighter respiratory coupling and more robust respiratory chain subunit expression. MtDNA levels did not change.

Overall, this suggests lactate treatment strategically altered hepatocyte bioenergetic infrastructures. Livers from lactate-treated mice changed in ways that should primarily enhance gluconeogenesis, while minimizing changes to respiration. In further support of this, treadmill exercise sessions, performed over the course of several weeks, increased hepatocyte MCT protein levels and immediately after an exercise session-trained mice actually showed reduced plasma lactate (E *et al*., 2013a). In essence, lactate exposure improved Cori cycle performance.

Boosting substrate levels at the front end of a pathway to increase forward flux, or at the back end to decrease forward flux, is relatively straightforward. Less direct manipulations can produce similar effects. NAD+/NADH ratios affect glycolysis flux rates. Increasing NAD+/NADH ratios promotes glycolysis flux, while decreasing the ratio impedes flux. Administering intermediates that oxidize NADH or reduce NAD+ can accomplish this. For example, adding either pyruvate or oxaloacetate (OAA) to cultured cells increases NAD+/NADH ratios. NADH reduces both intermediates, to lactate in the case of pyruvate and to malate in the case of OAA, yielding NAD+. These interventions, though, have vastly different consequences. Pyruvate sits at the tail end of glycolysis, and reportedly inhibits glycolysis enzyme activities (Williamson and Jones, 1964). In cultured cells, adding pyruvate certainly reduces medium extracellular acidification rates, thereby implying a reduction in the glycolysis flux. OAA, on the other hand, does not sit directly in the glycolysis pathway, and increases medium extracellular acidification rates (Figure 4).

In addition to facilitating or retarding active fluxes, the law of mass action can also be used to target inactive pathways. Under normal-fed conditions, hepatocytes will not convert acetyl units to ketone bodies. Administering medium-chain triglycerides in sufficient amounts, though, will override this and stimulate ketone body production (Reger *et al*., 2004). Two liver-generated ketone bodies, D-β-hydroxybutyrate and acetoacetate, enter the blood and access other organs, such as the brain, that use this carbon to support respiratory flux (Owen *et al*., 1967). Restricted carbohydrate, high fat ketogenic diets that lower insulin levels similarly strengthen ketosis and enhance respiration (Hartman *et al*., 2007; Kossoff *et al*., 2009). Enhancing respiration, in turn, may spare glycolysis.

This approach carries additional flux-related consequences since the conversion of ketone body carbon to acetyl CoA requires the transfer of CoA from succinyl CoA, a Krebs cycle intermediate, to acetoacetate (Figure 5). Loss of the CoA

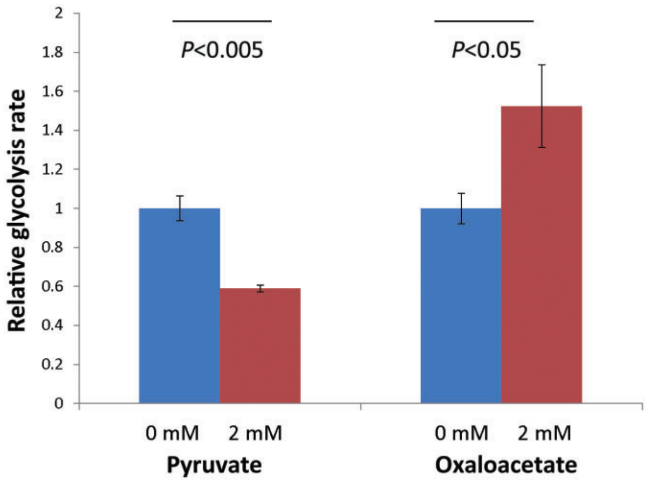

Figure 4

Pyruvate and OAA differently affect cell glycolysis rates. In this experiment, neuroblastoma cells initially maintained in glucose-free medium were acutely exposed to10 mM glucose in the presence or absence of either 2 mM pyruvate or 2 mM OAA. The resulting glycolysis rates were estimated by measuring medium extracellular acidification rates, which largely reflect cell lactate production. Pyruvate diminished the glucose-induced glycolysis rate increase, while OAA potentiated the glucose-induced glycolysis rate increase. These data are previously unpublished.

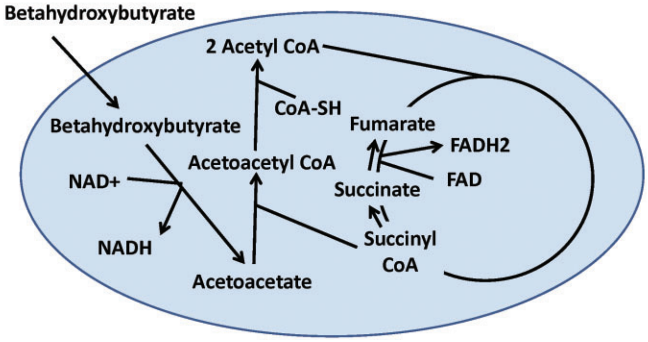

Figure 5

Ketone body utilization may increase a complex II-initiated respiratory flux. Ketone body carbon enters the Krebs cycle as acetyl CoA. To accomplish this, a CoA is transferred from succinyl CoA to acetoacetate by β-ketoacyl CoA transferase. Only tissues capable of metabolizing ketone bodies contain this enzyme; the liver, which produces ketone bodies, does not. β-ketothiolase then adds a second CoA and catalyses the formation of two acetyl CoA molecules. When succinate generated at the β-ketoacyl CoA transferase-mediated step is oxidized to fumarate, FAD is reduced to generate FADH2. FADH2 can contribute electrons to the respiratory chain via complex II.

group from succinyl CoA yields succinate, whose subsequent oxidation to fumarate reduces FAD to FADH2. This should theoretically favour a complex II-initiated respiratory flux, potentially at the expense of the complex I-initiated respiratory flux.

Manipulating ATP production or ATP levels offers another approach. Both glycolysis, an anaerobic pathway, and respiration, an aerobic pathway, synthesize ATP. Limiting ATP production from one flux can induce a presumably compensatory increase in the other flux. Adding 2-deoxyglucose or iodoacetate to cultured cells inhibits glycolysis, and in conjunction with this, mitochondrial oxygen consumption increases (Swerdlow *et al*., 2013).

Conversely, cells maintained in glucose-free medium show relatively high oxygen consumption rates. Upon adding glucose to glucose-free medium, glycolysis flux increases while respiratory flux decreases (Swerdlow *et al*., 2013). Observations such as these demonstrate how knowledge of classic anaerobic–aerobic flux relationships can inform drug development. Indeed, 2-deoxyglucose may prove useful for the treatment of cancers since cancer cell bioenergetic metabolism features increased glycolysis and decreased respiratory fluxes (Yamaguchi *et al*., 2011).

Bioenergetic medicine in neurodegenerative diseases

Multiple neurodegenerative diseases show bioenergetic dysfunction. With some of the most common neurodegenerative diseases, mitochondrial-related bioenergetic dysfunction could represent a relatively upstream or downstream pathology. For example, in AD, other pathologies including synaptic loss, neuron loss or intracellular β-amyloid might drive AD-typical mitochondrial defects (Swerdlow, 2012b). Alternatively, AD-typical mitochondrial defects may actually drive these other pathologies. A ‘mitochondrial cascade hypothesis’ assumes this latter possibility (Swerdlow and Khan, 2004; Swerdlow and Khan, 2009; Swerdlow *et al*., 2010).

Bioenergetic flux manipulation may contribute more to AD management than we currently suspect. AD therapy typically includes AChE inhibitor (AChEI) drugs that increase brain ACh levels. AChEIs typically yield modest but noticeable benefits. While increased cholinergic signalling likely initiates the therapeutic response, secondary changes in glycolysis and respiratory fluxes may also play an important role (Lu *et al*., 2013; Figure 6). Activating cholinergic muscarinic receptors generates inositol triphosphate (IP3), which binds endoplasmic reticulum (ER) receptors and induces ER calcium release. Mitochondria absorb some of this calcium, and the resulting acute depolarization increases mitochondrial oxygen consumption (Cardenas *et al*., 2010). Ultimately, sarcoendoplasmic reticulum calcium ATPase (SERCA) pumps return the calcium to the ER, which consumes ATP and through this effect stimulates glycolysis (Lu *et al*., 2013).

Cholinergic signalling simultaneously activates both anaerobic and aerobic fluxes, which shows it is possible to overcome the inverse relationship these fluxes typically demonstrate (Lu *et al*., 2013). In this specific case, increased cytosolic ATP consumption either counteracts or overrides the temporally concomitant increase in mitochondrial ATP production. Also, alterations in proteins that sense and respond to cell energy levels change (Lu *et al*., 2013). In particular, AMPK phosphorylation, which associates with AMPK activation, increases. AMPK promotes mitochondrial biogenesis (Hardie, 2007).

Increased glycolysis, respiration and AMPK could account for two other phenomena associated with AChEI treatment.

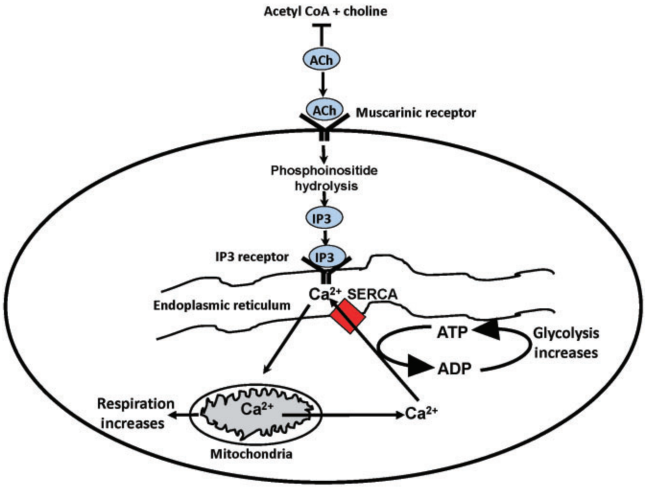

Figure 6

Potential mechanism through which AChEI drugs enhance glycolysis and respiratory fluxes. By preventing ACh hydrolysis, AChEIs increase synapse ACh levels. More ACh is available to bind muscarinic receptors, which in turn enhances phosphoinositide hydrolysis and IP3 synthesis. IP3 translocates to the ER, binds IP3 receptors and induces ER calcium release. Some of this calcium enters mitochondria, depolarizes the matrix and increases respiration. Calcium is returned to the ER via SERCA pumps, which consume ATP. Glycolysis flux increases, presumably to replace the ATP that is used by the SERCA.

First, FDG PET studies show AChEIs increase brain glucose consumption (Tune *et al.*, 2003; Asai *et al.*, 2009; Keller *et al.*, 2011). Enhanced glycolysis flux may wholly or partly mediate this. Second, magnetic resonance spectroscopy studies report AChEI treatment increases neuron n-acetyl aspartate (NAA) levels (Krishnan *et al.*, 2003; Jessen *et al.*, 2006; Modrego, 2006; Henigsberg *et al.*, 2011). NAA locates primarily to the mitochondrial compartment, and its levels may reflect either mitochondrial activation or increased mitochondrial mass (Patel and Clark, 1979; Bates *et al.*, 1996; Clark, 1998; Pfeuffer *et al.*, 1999). Enhanced respiratory flux, AMPK activation or both may wholly or partly drive this NAA increase.

Some AD patients currently use ketone body-based therapies. This idea, first proposed in 1989 (Swerdlow *et al.*, 1989), receives support from three small clinical studies. In two of these studies, administering caprylic triglyceride to AD subjects possibly improved cognitive test performance in at least a subset of subjects (Reger *et al.*, 2004; Henderson *et al.*, 2009). Boosting liver caprylic acid levels induces D-β-hydroxybutyrate and acetoacetate production, even in the presence of insulin, and these ketone bodies presumably account for the reported clinical response. The third study tested the effects of a low-carbohydrate diet on subjects with mild cognitive impairment (MCI; Krikorian *et al.*, 2012), a clinical syndrome that frequently progresses to AD and in many cases represents the earliest observable manifestation of AD (Morris *et al.*, 2001; Albert *et al.*, 2011). This study randomized 12 MCI subjects to a diet that limited daily carbohydrate consumption to 5–10% of total caloric intake. Urine ketones rose from 0 mg·dL^{-1} to 5.4 mg·dL^{-1}. After 6 weeks, performance on a test of memory, the paired associate learning test, significantly improved over baseline. A positive correlation between urine ketone levels and memory test improvement was observed. Eleven subjects concomitantly maintained on a high-carbohydrate diet showed no change in urine ketones and no memory test improvement.

A single uncontrolled study piloted ketone bodies for the treatment of PD (Vanitallie *et al.*, 2005). In this trial, 5 of 7 subjects adhered to a ketonemia-inducing very high-fat, very low-carbohydrate diet for 28 days. Each subject showed symptom improvement over the course of the study, but due to the possibility of placebo effects, an uncontrolled study design and trial size limitations efficacy was not meaningfully addressed. The authors noted the potential for a ketone body-based carbon flux to support a complex II-based, complex I-sparing respiratory flux and concluded further studies were warranted.

Other proposed bioenergetic flux-based therapy approaches include combining malate, glucose and thiamine for the treatment of AD (Blass and Gibson, 2006). Also, trials testing OAA's effects on PD and AD patients are underway. The rationale is that conversion of OAA to malate by malate dehydrogenase will increase cytosolic NAD+/NADH ratios, which could increase glycolysis, and that the resulting malate will enter mitochondria and ultimately support respiratory flux.

Lifestyle interventions such as exercise are also being evaluated for the treatment and prevention of AD. Rodent studies indicate that in addition to promoting hippocampal neurogenesis and reducing markers of brain inflammation (van Praag *et al.*, 2005; E *et al.*, 2013a,b), exercise increases brain PGC1-family coactivator levels, mtDNA, ETC subunits, brain-derived neurotrophic factor and VEGF (Cotman and Berchtold, 2002; Navarro *et al.*, 2004; Steiner *et al.*, 2011; E *et al.*, 2013b). Interestingly, a recent study also found increasing plasma lactate levels through i.p. lactate injection also increased brain PGC1-related coactivator and VEGF mRNA expression (E *et al.*, 2013b). This suggests exercise-generated lactate may drive some exercise-associated brain changes. Such effects could potentially be mediated by lactate-induced bioenergetic flux changes.

Implications and future directions

Should we consider bioenergetic medicine simply another mitochondrial medicine approach, or does the idea of bioenergetic medicine transcend the mitochondrial medicine field? On one hand, most bioenergetic fluxes reside completely or partly within mitochondria, or interconnect with those fluxes. Most flux manipulations, therefore, directly or indirectly affect mitochondria. Addressing the presence or consequences of defective mitochondria is often a goal. Many diseases wherein bioenergetic medicine is or will be used in have either primary or secondary mitochondrial defects. Framed this way, bioenergetic medicine is really just another mitochondrial medicine strategy.

On the other hand, flux manipulations may target non-mitochondrial processes in order to achieve non-mitochondrial outcomes. Further, while mitochondria are central to cell bioenergetics, bioenergetic pathways and infrastructures extend beyond the mitochondria. Although improving the function of poorly functioning mitochondria is certainly a welcome result, this may not be an intervention's main intended goal. Finally, for some diseases in which bioenergetic medicine may apply, mitochondria themselves will be normal, or any observed changes in mitochondrial function may simply reflect normal adaptations to an abnormal cell environment. Framed this way, bioenergetic medicine warrants an independent designation.

This review's intent is not to conclude this debate, but to open it. Either way, bringing attention to the idea will help identify relevant complexities and challenges. For example, brain and muscle, two tissues sensitive to bioenergetic failure, are not bioenergetically homogeneous. Some cells favour anaerobic bioenergetics, some favour aerobic bioenergetics and each population's bioenergetic integrity depends on the integrity of the other. Given such relationships, an intervention designed to boost one cell population's principal flux may not work if it disrupts the other cell type's principal flux.

Another challenge arises from the fact that while we tend to think of bioenergetic pathways as distinct entities, in some ways, these pathways constitute one all-encompassing holonetwork. Pathways directly branch off from each other, and shuttles and shunts abound. Successfully manipulating one part of the overall cell bioenergetic network may adversely perturb other parts of the network.

Lastly, it is important to note that non-primary bioenergetic flux and infrastructure changes caused by other upstream pathologies are compensatory changes (Silva *et al.*, 2013). These compensations can be maladaptive, and further harm the host cell. Or, they can be adaptive, and benefit the cell. Reversing adaptive compensations may prove ineffective and ultimately cause more harm than good.

In closing, manipulating cell bioenergetic fluxes affects the infrastructures that support those fluxes, energy levels, concentrations of organic intermediates, redox states and pathways that both sense and respond to these parameters. Bioenergetic flux manipulations can affect human health. The extent to which bioenergetic medicine approaches can benefit individuals with relevant diseases remains to be seen, but developing this emerging field clearly seems worth pursuing.

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Conflict of interest

The author has no conflict of interest.

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