Comparative Biochemistry and Physiology, Part B xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Comparative Biochemistry and Physiology, Part B

journal homepage: www.elsevier.com/locate/cbpb

Review

"Alternative" fuels contributing to mitochondrial electron transport: Importance of non-classical pathways in the diversity of animal metabolism

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ARTICLE INFO

Keywords:
Proline
Proline dehydrogenase
Insects
Energetics
Mitochondria
Electron transport system
Glycerol-3-phosphate dehydrogenase

ABSTRACT

The study of glycolysis, the TCA cycle, and oxidative phosphorylation in animals has yielded a wealth of information about bioenergetics. Less is known about how animals use fuels other than glucose and less characterized enzymes that are also used to provide electrons to the electron transport system. It has become clear that bioenergetic flexibility is employed by a wide variety of animals in order to successfully grow, maintain cells, and reproduce, and has contributed to the exploitation of new environments and ecological niches through evolution. In most cases, the discovery of these "alternative" fuels and non-classical pathways is relatively recent, but is starting to call into question long believed paradigms about the diversity of animal bioenergetics. We present several specific examples of these "alternatives" and the animals that use them and present some implications for animal mitochondrial physiology research.

1. Introduction

It is highly likely that life arose on Earth under anoxic conditions (Lyons et al., 2014). Initially, only two potential energy sources were available to early life on Earth; solar radiation and molecules produced via geochemical processes (Judson, 2017). Existing processes that are able to transduce these energy sources into usable chemical energy to do work (ATP) involve reduction-oxidation reactions (Judson, 2017). When it comes to the use of solar radiation as an energy source, various lines of evidence indicate that anoxygenic photosynthesis utilizing sulfur and iron containing substrates developed first (Allen and Williams, 2011; Judson, 2017). However, it was the appearance of oxygenic photosynthesis in cyanobacteria that changed the face of the planet to an oxygen containing atmosphere over billions of years (Lyons et al., 2014). Initially this oxygen would have been toxic to most organisms, due to the reactivity of oxygen and its propensity for attacking other molecules (e.g. DNA, membrane lipids, proteins), and species which survived this insult possessed metabolisms capable of scavenging oxygen (Gomes et al., 2001). Over evolutionary time, prokaryotes began to use oxygen in redox reactions involved in energy metabolism due to the amounts of energy that can be generated by using it as a final electron acceptor (Judson, 2017).

The presence of appreciable amounts of oxygen in the atmosphere likely precipitated the most significant evolutionary innovations that have occurred on our planet to date; namely the endosymbiotic events that led to the generation of the mitochondrion and the chloroplast (Judson, 2017). The event that gave rise to the mitochondrion likely occurred first and is proposed to be the union of an archaea and a proteobacterium (Gray et al., 1999). The proteobacterial partner was likely energetically complex and capable of both anaerobic and aerobic respiration given the array of different mitochondria and organelles of mitochondrial origin present on the planet today (Martin and Muller, 1998). The second primary endosymbiotic event occurred between a cyanobacterium and a eukaryotic cell and resulted in the chloroplast (McFadden, 2001). Based on these timelines, it is likely that oxidative phosphorylation (OXPHOS) originated in prokaryotes prior to the development of the eukaryotic cell (Pfeiffer et al., 2001), conferring the ability to transduce large amounts of ATP from various nutrients which in turn contributed to the capacity of animals to increase their sensory abilities, move at increasing speeds using new methods of locomotion, and to prey on non-microbial organisms for the first time (Smith and Harper, 2013; Sperling et al., 2013).

OXPHOS yields much more energy per substrate molecule than any known anaerobic process (Pfeiffer et al., 2001), and can therefore be considered as more energetically efficient. However, it is worth thinking about whether real life trade-offs are made by animals between the competing strategies of energetic efficiency vs. energetic flexibility. For example, animals that are sessile (i.e. do not move or do

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https://doi.org/10.1016/j.cbpb.2017.11.006
Received 23 August 2017; Received in revised form 8 November 2017; Accepted 10 November 2017

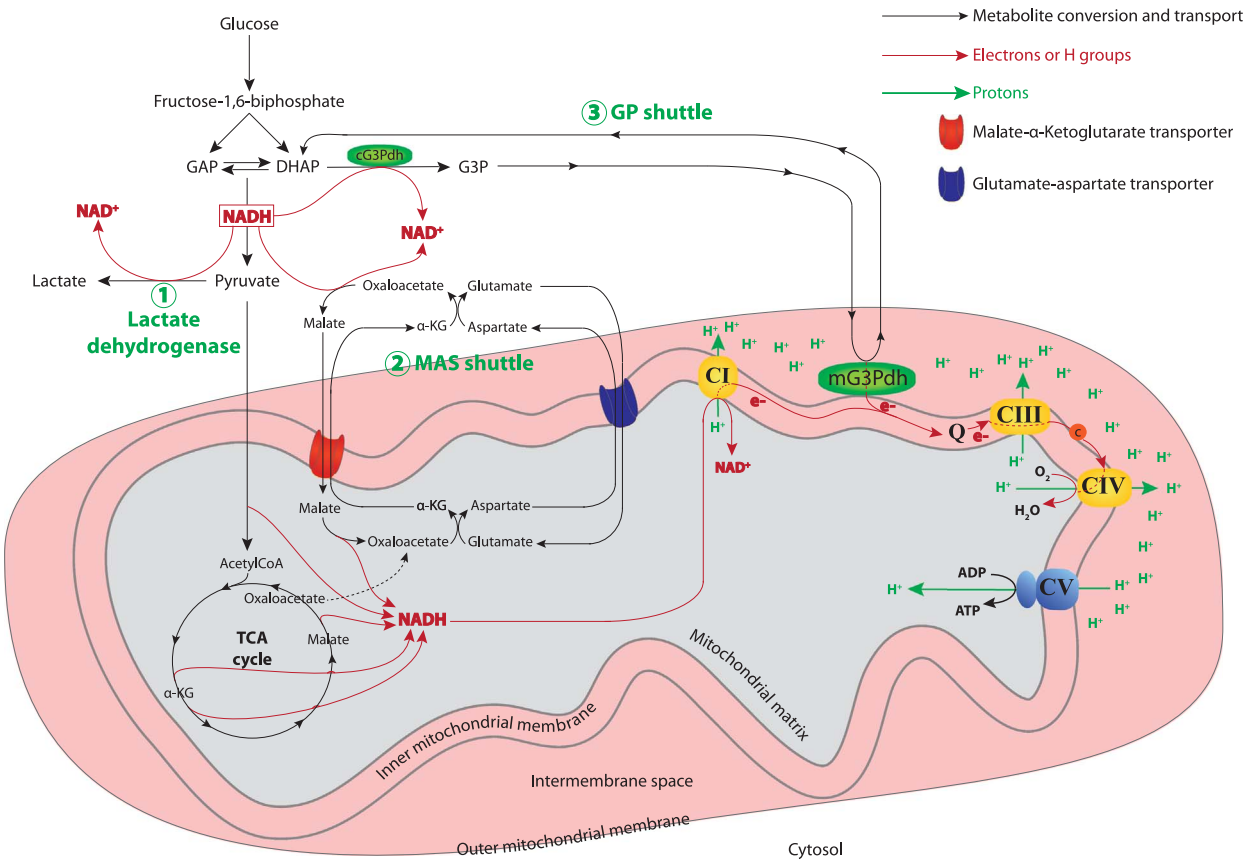

Fig. 1. The cytosolic NADH recycling systems. During glycolysis, glucose is converted to pyruvate through different steps, producing cytosolic NADH at the level of the glyceraldehyde-3-phosphate dehydrogenase. The NADH has to be recycled to NAD^+ mainly to not limit glycolysis, via different systems: 1) the lactate dehydrogenase which converts pyruvate to lactate; 2) the MAS shuttle which is comprised of cytosolic and mitochondrial malate dehydrogenases and aspartate aminotransferases, as well as of malate-α-ketoglutarate and glutamate-aspartate transporters. The cytosolic NADH is oxidized to NAD^+ by the cytosolic malate dehydrogenase which converts cytosolic oxaloacetate to malate. After being transported inside the mitochondrion, the malate is converted back to oxaloacetate, allowing the regeneration of NADH. This NADH can then be used by complex I to generate an electron flux and participate to mitochondrial respiration; 3) the GP shuttle is composed of the cG3Pdh and the mG3Pdh. The dihydroxyacetone phosphate generated by glycolysis can be converted to G3P by the cG3Pdh with concomitant oxidation of the cytosolic NADH. G3P is then transported to the mG3Pdh associated to the inner mitochondrial membrane, where it is converted back to dihydroxyacetone phosphate. This conversion allows the transfer of electrons inside the inner mitochondrial membrane to the ubiquinone pool, which increases the electron flux and participates in the mitochondrial respiration. α-KG: α-ketoglutarate; AcetylCoA: acetylcoenzyme A; c: cytochrome c; CI: complex I; CIII: complex III; CIV: complex IV; CV: complex V-ATPsynthase; cG3Pdh: cytosolic glycerol-3-phosphate dehydrogenase; DHAP: dihydroxyacetone phosphate; e^-: electrons; GP shuttle: glycerophosphate shuttle; GAP: glyceraldehyde-3-phosphate; G3P: glycerol-3-phosphate; H^+: protons; MAS shuttle: malate-aspartate shuttle; Q: ubiquinone pool; TCA: tricarboxylic acid.

so at slow speeds) may have different energetic demands for ATP than highly mobile animals. Different organisms may exhibit different rates of ATP production in addition to the differences in ATP yield that can occur (Pfeiffer et al., 2001). For example, in very active muscle cells, high rates of ATP are required, and metabolism shifts to fermentation from OXPHOS (Pfeiffer et al., 2001). Similarly, during mitotic events which require large amounts of ATP and/or the production of metabolic intermediates, fermentation may be preferred (e.g. during pollen development) (Tadege and Kuhlemeier, 1997). Moreover, recent modelling indicates that organisms that need to maintain a higher metabolic rate may be forced to switch from OXPHOS to a mixture of OXPHOS and fermentation due to macromolecular density constraints (i.e. the proteins in OXPHOS take up more physical space than those used in fermentation) (Vazquez and Oltvai, 2016).

This switching flexibility between OXPHOS and fermentation reflects that the life history and selective pressures experienced by each animal species must be considered. One bioenergetic strategy is not inherently better than another as long as the animal can successfully grow, perform cellular maintenance, and reproduce by matching ATP supply to ATP demand. The focus of this review is the capacity of different organisms to use alternate fuels via several enzymatic pathways leading to the transduction of energy in the form of ATP. While the demands for and consumption of ATP are equally important, we will not be addressing them here.

As noted above, the transduction of energy into ATP requires a fuel source. Unlike microbes and plants, no animals are truly autotrophic throughout their entire lifecycle, although several are autotrophic during some stages due to kleptoplasty (Rumpho et al., 2000). Animals have many different fuel sources available, but they must ingest other organisms or macronutrients in order to obtain them. In many animals, the fuels are processed through some form of digestion and often involve symbiotic microbes (Michl et al., 2017). The collection and conversion of fuels can therefore be considered the first step of energy metabolism. The fuel (and resulting forms obtained via digestion) must then circulate or be directed to the locations in the animal's body where it is needed (Yan, 2017). Some tissues or organs in the animal's' body will require higher amounts of fuel in order to support a higher rate of ATP biosynthesis which in turn will enable energetically expensive activities to take place (Broxterman et al., 2017). Transportation of substrates derived from fuels could therefore serve as a bottleneck in energy metabolism in animals. The transduction of substrate molecules into usable ATP is the last step of energy metabolism in animals that we will consider in this review. This is the step where most of our focus as animal biologists has resided. Unfortunately, we are often fixated on classical mitochondrial metabolism (i.e. the use of glucose as fuel, and the biosynthesis of ATP using glycolysis and oxidative phosphorylation)