Should nutritional therapy be modified to account for mitochondrial dysfunction in critical illness?

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Abstract

Metabolic dysfunction, and its associated muscle atrophy, remains the most common complication of critical care. At the centre of this is mitochondrial dysfunction, secondary to hypoxia and systemic inflammation. This leads to a bioenergetic crisis, with decreased intramuscular adenosine tri-phosphate content and a reduction in the highly energy dependent process of protein synthesis.

Numerous methods have been studied to try and reduce these effects, with only limited success. Trials investigating the use of increased calorie and protein administration have instead found a decrease in relative lean body mass, and a potential increase in morbidity and mortality.

Ketone bodies have been proposed as alternative substrates for metabolism in critical illness, with promising results seen in animal models. They are currently being investigated in critical care patients in the Alternative Substrates in the Critically Ill Subjects trial.

The evidence to date suggests that individualised feeding regimens may be key in the nutritional approach to critical illness. Consideration of individual patient factors will need to be combined with personalised protein content, total energy load received, and the timings of such feeds.

This review covers mitochondrial dysfunction in critical illness, and how it contributes to muscle wasting and the resultant morbidity and mortality and the scientific basis of why current nutritional approaches to date have not been successful in negating this effect.

These two factors underpin the need for consideration of alternative nutritional strategies in the critically ill patient.

Introduction

Metabolic dysfunction, and its resultant muscle atrophy, remains one of the most common complications of critical illness.[1,2] The combination of systemic inflammation and hypoxia leads to disrupted mitochondrial function, reduced ATP function, and an anti-anabolic state.[2,3]

Feeding regimens in the critically ill remain a point of contention. Whilst several nutritional approaches have been attempted, none have been shown to improve metabolic function or reduce intensive care associated muscle wasting.[4] Some of these approaches may in fact have detrimental effects on patient outcome.[5]

In this review we will describe aspects of mitochondrial function that are altered in critical illness, and are of interest to us as potential targets for intervention. Other aspects of mitochondrial biology that are relevant to critical illness in general, but not actively being investigated by ourselves are not addressed.

Normal mitochondrial function

Adenosine Tri-Phosphate production

In normal health mitochondria are the predominant source of cellular energy through the production of adenosine triphosphate (ATP).[6–8] These organelles have retained their own genome which reveals their evolutionary origin as a bacterium that developed a symbiotic relationship with eukaryotic cells.[8]

Mitochondria enable production of ATP from carbohydrates, lipids, and proteins through the Krebs cycle and its substrates.[6–8] They are each metabolised to Acetyl CoA (alongside other intermediates) which can then enter the Krebs cycle.[6–8] The result is the production of ATP through the formation of nicotinamide adenine dinucleotide (NADH), flavin adenine dinucleotide ($FADH_2$), and guanosine-5'-triphosphate (GTP) (See figure 1).[7–9]

The Krebs cycle occurs within the mitochondrial matrix and acts as a common pathway for the metabolism of fats, proteins, and carbohydrates. Its intermediates provide substrates for ketogenesis, gluconeogenesis, and other metabolic pathways.[7,10–12]

The three NADH and one $FADH_2$ produced by the Krebs cycle can be utilised to produce ATP via the electron transport chain within the inner mitochondrial membrane. In health, the electron transport chain is the site of oxidative phosphorylation, the most efficient means of energy production.[7,10] It consists of five protein complexes in the inner membrane of the mitochondria. NADH and $FADH_2$ donate their electrons to the first two of these complexes, these electrons are then passed down the electron chain generating energy that pumps H+ ions out of the mitochondrial cytoplasm. The resultant electrochemical gradient allows transmembrane H+ influx via the ATP synthase complex (V) and thus the phosphorylation of ADP to ATP.[7] NADH results in the formation of three ATP molecules, and $FADH_2$ in the production of two, so each acetyl-CoA produces 11 ATP from one Krebs cycle (See figure 2).[7,8,10]

Amino acid catabolism

Ammonia is produced as a toxic waste product of amino acid catabolism and nitrogenous bases. Its elimination is controlled through the urea cycle, the Cori cycle, and transport intermediates such as glutamine.[13] The Krebs cycle intermediate α-ketoglutarate can be

used to produce glutamate, which is then combined with ammonia to form glutamine and phosphate, however this process depletes the Krebs cycle of its metabolites (cataplerosis).[11,12,14] Glutamine is then transported to the liver where it is converted back to glutamate by glutaminase, releasing ammonia to enter the urea cycle.[15] The mitochondrial enzyme carbamoyl phosphate synthetase I acts to catalyse the reaction between ammonia and carbon dioxide and produce carbamoyl phosphate, which can then enter the urea cycle and be excreted via the kidneys as urea.[16,17]

Effect of critical illness on mitochondrial function

Critical illness has a number of deleterious effects on metabolism and mitochondrial function.[3,18–21] This is likely the result of several physiological insults, most notably systemic inflammation, and tissue hypoxia.[3]

Glucose is a major fuel source, and in the fed state glucose is virtually the sole energy provider for the brain. In health, the Pasteur effect results in the inhibition of anaerobic metabolism, ensuring efficient glucose metabolism via the citric acid cycle.[22] Inflammation and hypoxia disrupt the Pasteur effect, inhibiting pyruvate dehydrogenase.[3,22] As a result, the cell is unable to convert pyruvate to acetyl-CoA, instead converting it into ethanol, carbon dioxide, and lactic acid.[2,19,23,24] This disrupted system results in the net production of only two ATP molecules (in contrast to the 38 produced through aerobic respiration), and the accumulation of harmful waste products.[2,23,24]

In health fats are metabolised via beta-oxidation, generating acetyl-CoA which enters the Krebs cycle.[14] Each oxidation cycle results in the production of approximately 14 ATP, with the oxidation of long chain fatty acids therefore able to generate more than 100 ATP.[25] Early critical illness is associated with impaired beta-oxidation and reduced enzyme

concentrations and thus an inability to effectively utilise fat.[3,19] This is associated with decreased mitochondrial biogenesis and a compromised bioenergetic status.[19,26]

The combination of the mitochondrial dysfunction mentioned above may result in a bioenergetics crisis (noted by an increase in tissue pAMPK concentrations), with decreased intramuscular ATP content and a reduction in the highly energy dependent process of protein synthesis.[3] This could then contribute to critical illness associated muscle wasting, with an associated increase in morbidity and mortality.

Does increased calorie delivery help?

Numerous methods have been theorised and trialled in attempts to counteract the mitochondrial dysfunction and energy deficient state that accompanies critical illness. One such approach is increased calorie delivery in the form of excess dietary carbohydrates and lipids.

The underlying theory is that the administration of more substrate will help overcome to relative energy deficient state. Arguably the biggest flaw in such an approach is that simply increasing the delivery of fuel does not necessarily increase its availability. Further, substrate delivery and utilisation are not always linked, as described above. An increased calorie intake does not address the underlying components driving the mitochondrial dysfunction and will therefore be unable to restore normal metabolic function. [2,5,29,30]

The initiation of early, high calorie feeds in critical illness has shown no effect on reducing muscle wasting in early critical illness.[31] This approach instead resulted in an increase in adipose tissue within muscle compartments, a relative decrease in lean muscle mass, no improvement in outcomes and a potential increase in mortality.[32,33] Increased calorie intake

has also shown to have no effect on patient function, length of hospital admission, or quality of life at six months.[34]

Does increased protein delivery help?

A further hypothesis being tested is that the provision of excess amino acids may result in improved metabolic function and muscle protein synthesis. Spikes in amino acid concentration, specifically leucine, have been identified as an anabolic stimulus in normal health and possibly in critical illness.[30,35,36] However, this does not appear to be effective for several reasons.

The "muscle full effect" describes the phenomena whereby protein delivery beyond a set threshold does not result in increased muscle protein synthesis (MPS).[37] Thus, the simple administration of excess amino acids will not reduce muscle wasting. Energy is also required for protein turnover and MPS, the provision of which is insufficient due to mitochondrial dysfunction.[3,38–40]

Excess protein administration may have detrimental effects. Amino acids are metabolised to ammonia, which is then converted to urea via the urea cycle.[16,17] Raised ammonia concentrations are toxic to mitochondrial function, protein synthesis and muscle function.[36,41,42]

Hyperammonaemia is associated with a reduction in muscle function and quality of muscle architecture, both of which have been observed in critical illness.[41,43,44] Previous work has demonstrated that supplementary glutamine administration in critical illness is associated with increased inpatient and six-month mortality. [45]

Hyperammonaemia also depletes critical Kreb cycle intermediates and thus significantly effects mitochondrial function.[43,46] This is associated with reduced skeletal muscle aerobic respiration, electron transport chain complex dysfunction, and a lower NAD+/NADH ratio and ATP content.[46] It also causes increased muscle autophagy with resultant sarcopenia.[47]

Urea is a by-product of amino acid metabolism. Recent work looking into urea as a catabolic marker in critical illness (in the form of the urea-to-creatinine ratio [UCR]) has demonstrated a significant association between a raised UCR and persistent critical illness. Patients with the highest UCR required the longest intensive care admissions and had an increased mortality.[17,48,49]

Thus, given the first principal of the Hippocratic Oath is to "do no harm", consideration should be given not only to the potential lack of benefit in excess protein feeds, but also the potential harm it may cause our patients. Calorie and protein restricted diets to have a potentially protective effect on mitochondrial function, improving the disrupted autophagy seen in critical illness.[50]

What are the alternatives?

Ketone bodies have been suggested as alternative substrates for metabolism in critically ill patients as they are known to provide a significant proportion of energy in fasted states.[12] The ketone bodies acetoacetate and beta-hydroxybutyrate are produced from acetyl-CoA in hepatic mitochondria for use in brain and skeletal muscle.[11,12,51] Metabolism of beta-hydroxybutyrate reduces one NAD to NADH to produce acetoacetate, which itself can be metabolised to two acetyl-CoA.[11,12] This returns acetyl-CoA to the Krebs cycle bypassing metabolic bottlenecks such as pyruvate dehydrogenase, which may be restricted in critical

illness. [52] The clinical benefits of this may however be limited by altered citric acid cycle and oxidative phosphorylation function in the critically ill.[27]

In animal models ketogenic diets are associated with improved blood glucose control and reduced markers of inflammation when compared to carbohydrate rich diets.[53,54] Ketogenic feeds are currently being investigated in critical care patients as an alternative regimen in the Alternative Substrates in the Critically Ill Subjects trial (ASICS [NCT04101071]).

The importance of individualised feeding regimens

Given the evidence to date, it seems that individualised feeding regimens may be key in the nutritional approach to critical illness, although this is yet to be supported by randomised control trials. Consideration of individual patient factors will enable us to intelligently guide patient feeding in terms of protein content, total energy load received, and the timings of such feeds.

With regards to protein volume required, important factors to consider should include patient age, their exercise capacity, and markers of metabolism such as UCR. When considering overall energy requirements, the use of indirect calorimetry may be aligned with exercise capacity and the patient's physical characteristics to help guide intake. An ideal intervention would be guided by individual patient's ability to metabolise different substrates at different time points. Unfortunately, this is current impossible to do in vivo at the patient's bedside.

The precise timing of feeds remains up for debate. Whilst historically nasogastric feeding regimens on intensive care have been given continuously, recent work has questioned whether this is the best approach.[49,55] In normal health food is consumed intermittently in

the form of separate meals, this leads to anabolic spikes in amino acid concentration and the stimulation of MPS. A recent phase II trial of intermittent feeding did not find it to be associated with an attenuation of muscle wasting (as measure by rectus femoris ultrasound).[55] However, intermittent feeding has been shown to significantly improve the ability to reach nutritional goals and significantly effect metabolic signals such as UCR.[55]

Conclusion

Effective mitochondrial function is vital to metabolism in normal health. Early critical illness is associated with mitochondrial dysfunction, with multiple detrimental effects. Several strategies have been trialled to mitigate the metabolic effects of critical illness, with limited success. Rather than a generic, non-personalised, approach to nutrition in critical illness, the future may instead lie in the utilisation of alternative metabolic substrates and individualised feeding regimens.

Figure legends:

Figure 1: Tricarboxylic Acid Cycle

Figure 2: Biochemical pathways of normal mitochondrial function

ATP – Adenosine Tri-Phosphate; $FADH_2$ - reduced flavin adenine dinucleotide; NADH – reduced nicotinamide adenine dinucleotide; FFA – free fatty acids

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