OLYMPIC LABORATORY

11

NUMBER
YEAR 2

TECHNICAL SCIENTIFIC BULLETIN OF THE BRAZILIAN OLYMPIC COMMITTEE

JUN/JUL 2009

EXERCISE BIOCHEMISTRY AND HEALTH SCIENCES: A JOINT VENTURE

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The energy puzzle

Energy transduction is required in different body compartments to perform required work. To maintain certain levels of work, the organism must make adaptations to meet the energy demand. Exercise is a challenge to the body, inducing both metabolic and mechanical stress[1]. Understanding the metabolism of athletes can provide important information about body behavior during stress situations[2]. Athletes engage in an enormous amount of work and require high levels of energy to maintain potency during training and exercise[2]. In our lab, we use exercise as a way to understand human metabolism. We are interested in how exercise protects the human central nervous system (CNS) against toxic metabolites.

Chemical energy is converted into work during both rest and exercise. The energy is supplied by ATP and is transduced to mechanical energy (sarcomere shortening in muscle tissue), and ion gradient maintenance (Na^+K^+ ATPase and $Ca^{2+}Mg^{2+}$ ATPase)[3]. A decrease in the ATP/ADP ratio activates oxidation systems to promote ATP synthesis (glycolysis, Krebs cycle and oxidative phosphorylation), as well as the use of phosphocreatine to resynthesize ATP. At low ATP levels, an important reaction is catalyzed by myokinase to maintain ATP concentrations inside the cell. This enzyme catalyzes the addition of phosphate to a molecule of ADP, using another ADP molecule as a phosphate donor, thus producing ATP and AMP as products. The increase in AMP concentrations inside the cell activates its deamination to IMP (AMP deaminase), and an amino group is released. Due to its association with the requirement and production of ATP, blood ammonia levels (we will use 'ammonia' to refer to both NH_3 and its conjugate acid form NH_4^+) have been used as an indicator of metabolic activity during exercise[4] (Fig 1).

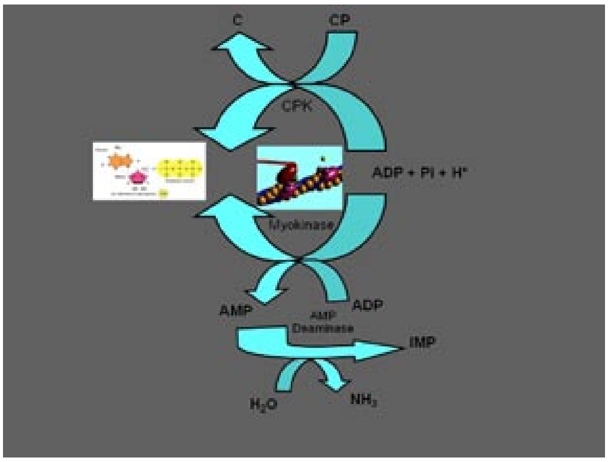

Figure 1. Non oxidative ATP production

Ammonia and exercise

Several studies have shown that both intensity and prolonged exercises are correlated with the appearance of ammonia in blood. During exercise, ammonia can be produced by either an increased breakdown of adenine nucleotides to IMP, which are converted later to urate (Figs 2 and 3), or by deamination of amino acids (Fig 4). Furthermore, it has been suggested that high ammonia levels can be toxic to both muscles and the CNS, and it has been speculated that the accumulation of ammonia could induce central and/or peripheral nervous system fatigue[5].

In humans, glutamine (Gln) is the most abundant circulating amino acid. It is synthesized in large amounts by the muscle, works as a gluconeogenic substrate, and is a non-toxic carrier for ammonia. In order to decrease the toxic effects caused by increased levels of ammonia, the CNS enhances glutamine (Gln) synthesis to buffer free ammonia. The concentrations of plasma Gln decrease as a function of exercise intensity because of the increase in gluconeogenesis and urea synthesis. It has been widely demonstrated that oral supplementation of Gln increases its plasma concentration and increases the efficiency of Gln as an energy substrate during rest or metabolic stress[5, 6].

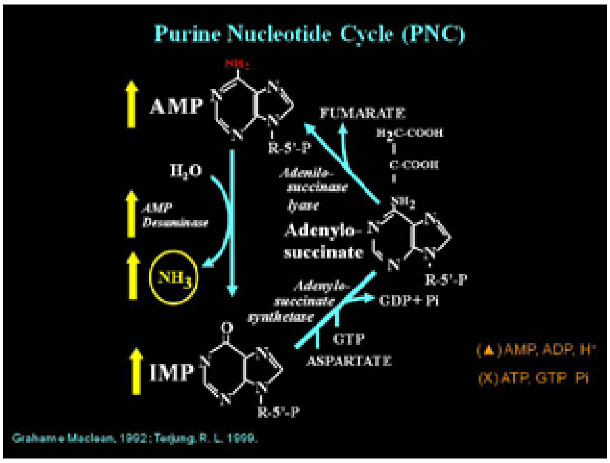

Figure 2. The purine nucleotide cycle.

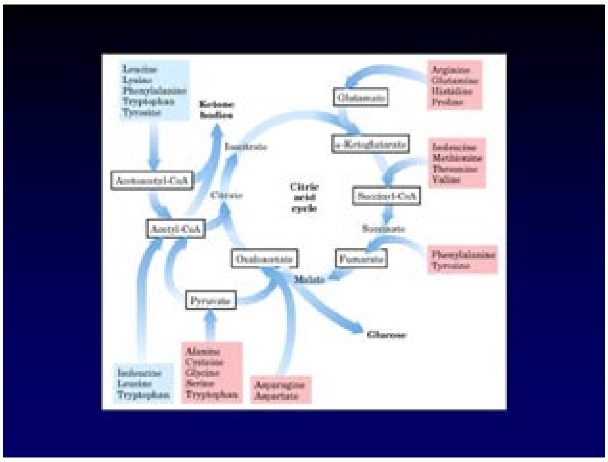

Figure 4. Entry of amino acids as Krebs cycle intermediates after deamination.

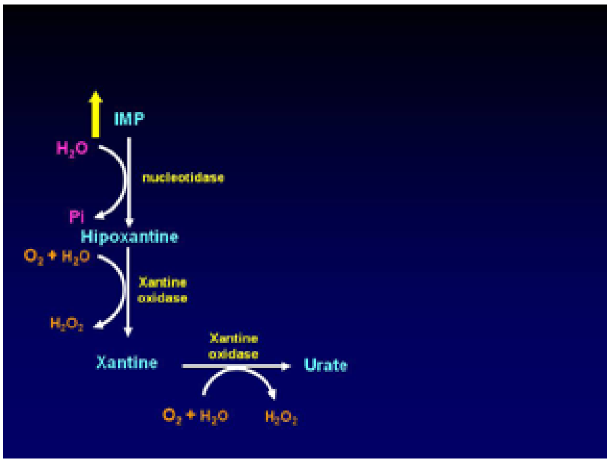

Figure 3. The urate synthesis.

Increases in blood ammonia levels depend on several factors, including glycogen stocks, amino acid deamination and glucose availability. The use of amino acids as energy substrates may increase the pool of ammonia from amino acid deamination. The intramuscular concentration of alanine (Ala) is decreased during exercise because this amino acid effluxes from the muscle and is used as gluconeogenic substrate. The supplementation of Ala alone or in combination with creatine was recently proposed to delay fatigue and potentially enhance endurance. Although Ala is a gluconeogenic substrate, it is not commonly studied as an ergogenic supplement during exercise[7].

Given the above observations, we have been studying various molecules (amino acids, ketoacids, lactate, caffeine and others)[8] that affect ammonia production and metabolism. Studies in our lab have shown that different effects of Gln or Ala supplementation are dependent upon on both exercise cycle and intensity. In addition, we developed methods to control ammonia production during exercise.

Joining exercise, health and disease

Hepatocytes efficiently convert ammonia to urea and help to maintain ammonia levels in the 20–100 μM range. In general, hyperammonemia occurs due to urea cycle enzyme diseases or liver failure. Ammonia can cross the blood–brain barrier, and its concentration can reach levels greater than 800 μM inside the CNS, leading to decreases in cerebral function, neuropsychiatric disorders, and death[9-11]. Ammonia-mediated excitotoxicity was proposed as a mechanism by which damage can spread in the CNS. Excitotoxicity is a Ca^{2+} – dependent signaling process[12, 13]. Here, exercise science joins with health science: data obtained from exercise studies have been used to help to explain the effects of hyperammonemia, as several studies have demonstrated that a rise in ammonemia occurs after different types of exercise[14].

It has been shown that, during exercise, ammonia can reach concentrations near 300 μM. In one of our studies, using diet and exercise as a way to study metabolism, we observed athletes with ammonia blood concentrations higher than 600 μM, demonstrating that exercise is a useful tool to study ammonia production and metabolism[11-15]. A general question to be answered is how exercise protects against the effects of ammonia during and after training. In addition, it is critical to understand that the study of exercise metabolism can be useful not only for enhancing the performance of athletes but also for advancing the fundamental understanding of many physiological and pathological pathways.

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Olympic Laboratory is a publication of the Brazilian Olympic Committee (BOC)