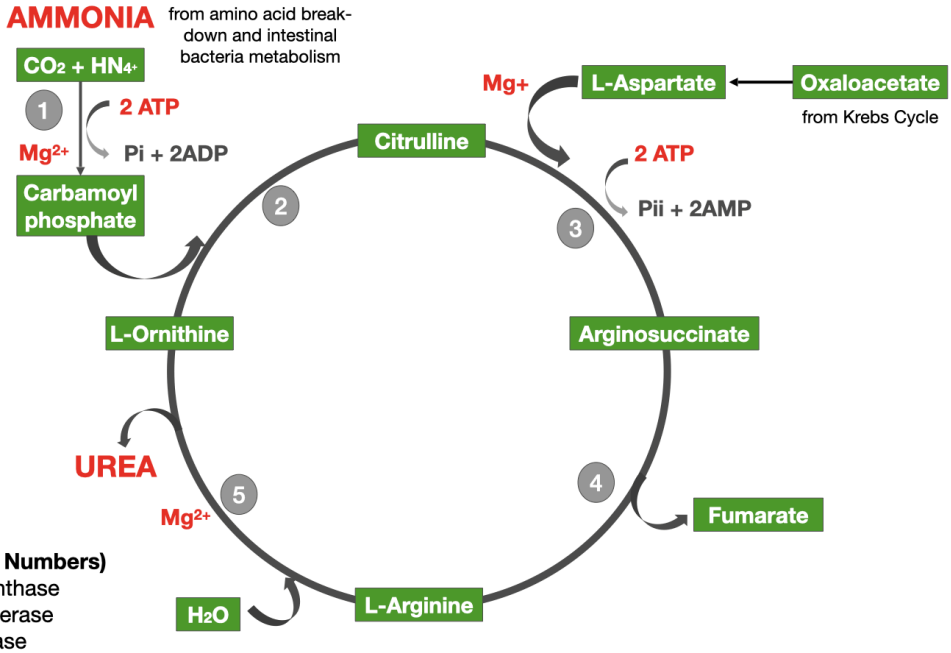
The Urea Cycle

- **supplemental material to the *Textbook of Integrative Sport and Exercise Nutrition***

The urea cycle deserves important detoxification consideration within a sport and exercise context. As described in Chapter 11 of the textbook, when glucose levels are low and/or dietary protein consumption is high, amino acids can be metabolised into glucose, fatty acids or ketones for the provision of energy (Häussinger and Gerok, 1986). However, the by-product of amino acid metabolism is ammonia, which can become toxic to the body in excessive quantities. The urea cycle is required to clear this nitrogenous waste from the body, which is produced from amino acid catabolism and the metabolism of amino acids by intestinal bacteria (Lord and Bralley, 2008).

As shown in Figure 4.5, ammonium ions are converted to urea via the ATP-dependent five-enzymatic steps of the urea cycle, which can be eliminated from the body via urine after it has been filtered by the kidneys (Lord and Bralley, 2008; Trefts et al., 2015). Interestingly, in bodybuilders and strength/power athletes, elevated urea levels are often seen in blood and urine tests, which may be indicative of excessive protein intake, and burdening of this system (Kim et al., 2011). More concerning, however, is that deficits in the urea cycle, or an excessive load on it, can cause hyperammonemic conditions and 'organic acidemia', which obviously disrupts normal amino acid metabolism, and impacts whole body health. With hepatic dysfunction, exercise-induce hyperammonemia may present as central fatigue, with symptoms such as lethargy, incoherence, and loss of coordination (Banister and Cameron, 1990).

Generally, symptoms of an overloaded urea cycle may include: chronic fatigue, headaches, irritability, gastrointestinal disturbances, poor concentration, and intolerance to certain foods (Lord and Bralley, 2008).



KEY TO ENZYMES (Circled Numbers)
1. Carbamyol-phosphate synthase
2. Ornithine carbamoyltransferase
3. Argininoosuccinate synthase
4. Argininosuccinate lyase
5. Arginase

Figure 4.5 - The urea cycle, demonstrating the conversion of ammonia to urea, which is then eliminated through the kidneys and excreted via urine.

It has been shown that moderate to intense exercise can increase muscle ammonia levels to the point that it enters the circulatory system, possibly due to adenosine mono-phosphate (AMP) deamination and skeletal muscle protein breakdown (Trefts et al., 2015). At a certain intensity, ammonia clearance becomes saturated and blood ammonia levels exponentially increase in a similar way to the dynamics of lactate during anaerobic exercise. Ammonia can cross the blood-brain barrier and may be linked to central fatigue and lack of coordination, so high levels of it can also be a causative factor for exercise fatigue (Banister and Cameron, 1990).

To bring these threads together, you might have noted that the urea cycle is an energy (ATP) dependent process, meaning that even if it is managing to keep up with the demands of excessive protein intake from the diet, it is using up valuable energy and nutrients (including arginine, which otherwise has anabolic potential), to break down and clear this excess. What's more, if the urea cycle is depleted, the athlete's body will probably end up in a toxic and acidic state with excessive levels of ammonia in circulation. Apart from obvious health detriments, the athlete will likely experience a lowered buffering capacity for exercise-induced acidemia.

Citrulline (Urea cycle support)

As shown in Figure 4.5, the urea cycle, which is responsible for the removal of excess ammonia from the system, requires various nutrients, including magnesium, citrulline, l-ornithine, and l-arginine (Morris, 2002).

As noted previously, the concentration of ammonia is increased during high intensity exercise (Takeda et al., 2011). Ammonia is known to activate phosphofructokinase, the rate-limiting enzyme in glycolysis (Sugden and Newsholme, 1975), but it inhibits the conversion of pyruvate to acetyl CoA. In other words, ammonia stimulates the anaerobic production of ATP via glycolysis, but limits substrates for the Krebs cycle, which before long will lead to exhaustion. If, however, we can increase the clearance of ammonia via the urea cycle, this impending state of exhaustion could be delayed. As such, Takeda et al. (2011) tested mice in a swim-to-exhaustion trial, with and without citrulline supplementation. What they found was that the citrulline supplementation "repressed exercise-induced blood ammonia and lactate elevation, and time to exhaustion was significantly increased." In humans, Gonzalez and Trexler (2020) have reviewed several studies that reported how citrulline supplementation may enhance exercise performance and recovery. They hypothesised that the benefits may be associated with increases in nitrate concentration and blood flow dynamics. However, consideration of ammonia and the urea cycle in future research studies may elicit further understanding of this important pathway.

References

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