Phase III Detoxification - The Antiporter System

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

The antiporter system is commonly also referred to as phase III detoxification. Logic would suggest that phase III detoxification would directly follow phase I and II, but the antiporter system is actually an upfront gatekeeping system against the over-absorption of toxins and toxicants from the gut and other organs, plus it should prevent the reabsorption of conjugated substances that are being eliminated in bile via the gastrointestinal (GI) tract (Dietrich et al., 2003). Unlike phase I and II activities, it does not biochemically convert xenobiotics into different substances. The antiporter transporters are found predominantly in the intestinal villi, but also in the cell membranes of the liver, kidneys, brain and other tissues (Muller and Yeoh, 2010), and is an important factor in the first-pass metabolism of pharmaceutical drugs and other xenobiotics (Liska et al., 2005), as well as the formation of bile by the liver (Dietrich et al., 2003).

As illustrated in Figure 4.4, various substances are absorbed from the gut lumen into enterocytes via the villi. These include amino acids, ions, lipids, xenobiotics, medications, and already conjugated chemicals (Muller and Yeoh, 2010). The transporters work closely alongside the brush border phase I enzymes, in particular CYP3A4. If an absorbed toxin/ toxicant is not activated by a cytochrome P450 enzyme, the antiporter transporters, which act as ATP-dependent efflux pumps, can push the toxin back out into the gut lumen for another round of detoxification (Dietrich et al., 2003).

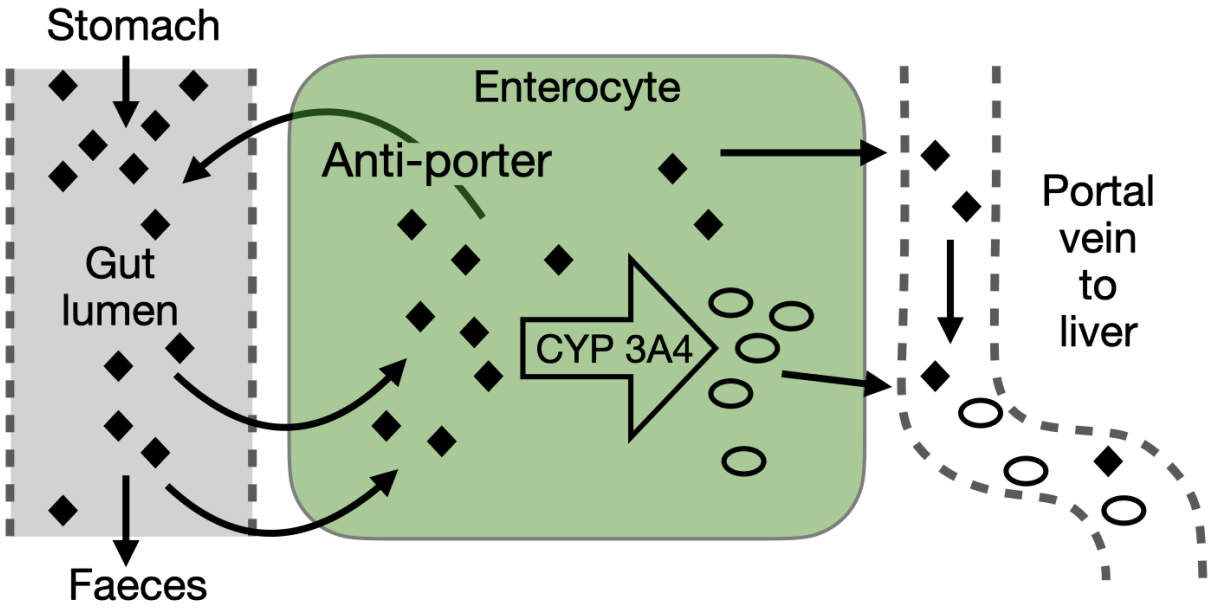

Figure 4.4 - Schematic presentation of the antiporter system, Phase III detoxification (redrawn from Liska et al., 2005, with permission).

The GI tract is a major route for excreting and eliminating conjugated toxins that originate from the liver. Therefore compromised intestinal integrity and dysbiosis, combined with insufficient dietary fibre, and compounded by the state of constipation, may lead to the reabsorption of toxic metabolites. This is known as enterohepatic recirculation (Liska et al., 2005). An imbalance in certain gut microflora can actually produce brush border beta-glucuronidase, which can deconjugate some of the detoxified substances. This will result in these substances being returned to their original toxic state, re-loading the liver all over again. Additionally, local gut mucosal inflammation can result in glutathione depletion, which may in turn compromise the antiporter and Phase II detoxification processes. In other words, optimal GI health is absolutely crucial for the support of effective detoxification activities.

Some specific areas of consideration here for athletes are the use of non-steroidal anti-inflammatory drugs (NSAIDs), the impact of endurance exercise, and disruption of heat promoting endotoxins knowns as lipopolysaccharides (LPS). NSAIDs are well evidenced to disrupt gut integrity and the gut microbiome, potentially having much wider and longer implications beyond race day (Maseda and Ricciotti, 2020). Indeed, NSAID use is banned now in some races, such as the UTMB World Series of ultra endurance trail marathons (UTMB). GI ischaemia during exercise has been associated with increased gut permeability and systemic circulation of LPS, and it has been suggested that repeated exposure to low-grade LPS can promote a mild chronic inflammatory state (Roberts et al., 2016), which could set in a motion a chain of related chronic health conditions, as well as impaired performance.

For further information, you are referred to the comprehensive description of the antiporter system by Liska et al. (2005) and Muller and Yeoh (2010).

References

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