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IMPACT OF NUTRITION ON METABOLIC AND IMMUNE SYSTEM RECOVERY FROM HEAVY EXERCITION: VALUE OF MULTI-OMICS APPROACHES

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KEY WORDS: Immunometabolism, metabolomics, polyphenols, carbohydrate, immunonutrition support, inflammation

IMMUNE RESPONSE TO INTENSIVE EXERCISE, OVERREACHING, AND OVERTRAINING

Athletes participating in one bout of prolonged and intensive exercise such as marathon and ultramarathon race events experience acute physiological stress reflected by muscle microtrauma, oxidative stress, and systemic inflammation. Concomitant with these stressors are widespread perturbations in innate and adaptive immunity including decreases in natural killer (NK) cell cytotoxic activity, granulocyte respiratory burst activity, nasal and salivary IgA (sIgA) secretion, delayed type hypersensitivity, and mitogen-induced lymphocyte proliferation, as well as extensive alterations in circulating immune cell populations. This period of decreased host protection is often followed by elevated rates of upper respiratory tract infections in the athletes 1-2 weeks after competition.

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METABOLOMICS, LIPIDOMICS, PROTEOMICS, AND IMMUNOMETABOLISM RELATIONSHIPS

Heavy exertion has a profound, acute effect on human metabolism, but most studies have focused on a small, targeted number of biochemical outcome measures. The recent development of metabolomics profiling technologies provides a system-wide view of the metabolic response to exercise by simultaneously measuring and identifying a large number of small molecules. Metabolomics, lipidomics, and proteomics data from sports nutrition

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based studies have the potential to shape a new generation of integrative studies using metabolite measurements with immunology, molecular epidemiology, genomics, transcriptomics, and proteomics.

Seminal papers using the latest multi-omics technology indicate that heavy exertion has wide ranging, substantial, and prolonged influences on lipid and protein metabolism, marked by increases in metabolites related to carnitine metabolism and long chain, dicarboxylate, and essential fatty acid metabolism, and proteins related to immune function (half of the proteins expressed after heavy exertion are immune-related). Perturbations in many of these metabolites and proteins are still apparent in endurance athletes after 14 h of recovery. Carbohydrate intake strongly attenuates the magnitude of increase in exercise-induced metabolites from the lipid super pathway, and the rate of recovery to pre-exercise levels is quicker.

IMMUNONUTRITION STRATEGIES

The unexpected discovery during the 1990s that carbohydrate ingestion influenced the acute immune response to prolonged and intense exercise inspired a new line of research in the area of nutrition-exercise immunology. Nutritional components and products of every conceivable category have been tested for their capacity to attenuate post-exercise inflammation and immune changes, with a focus on the nonspecific, innate arm of the immune system. The primary hypothesis is that the risk of immunosuppression and respiratory illness is more effectively countered if the nutritional agent augments post-exercise natural killer cell, macrophage, and granulocyte function in comparison to the slower moving adaptive immune system.

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Unfortunately, except for carbohydrate, results have been disappointing, although some would argue that much remains to be studied and discovered (in particular, the myriad polyphenols) in the fledgling field of nutrition-exercise immunology. At this time, data from exercise-immune studies are non-supportive, mixed, or of limited clinical, countermeasure significance for use of various products including antioxidants, N-acetylcysteine, vitamins and minerals, glutamine and other amino acids, protein, beta-glucans, fish oil, alpha-linoleic acid, probiotics, bovine colostrums, ginseng, Echinacea, and other nutritional components. The proposed benefits of antioxidant supplementation in attenuating oxidative stress and immune dysfunction during exercise remain unsubstantiated, and may work contrary to expectations, as highlighted by the finding that large dose vitamin E supplementation amplified post-race inflammation and oxidative stress in Kona Ironman athletes. Glutamine is essential for optimal immune function, and a popular rationale for glutamine (and many other nutrients) is that higher than normal intake is needed to counter exertion-related demands from the immune system. However, glutamine supplements are not recommended

because the best studies show no benefits when compared to placebo, perhaps due to abundant storage pools within the body that cannot be sufficiently depleted by exercise.

CARBOHYDRATE

A series of studies dating back to the mid-1990s showed that ingestion of carbohydrate supplements (30-60 g/h) during prolonged, intensive exercise attenuated increases in blood neutrophil and monocyte counts, granulocyte phagocytosis, stress hormones, and anti-inflammatory cytokines such as IL-6, IL-10, and IL-1ra. At the same time, however, null effects of carbohydrate ingestion were measured for exercise-induced decrements in naturally killer cell lytic activity, salivary IgA output, and T lymphocyte proliferative capacity. Thus, carbohydrate ingestion emerged as an effective but partial countermeasure to immune dysfunction during recovery from heavy exertion.

Carbohydrate may exert these impressive countermeasure effects through multiple mechanisms including an elevation in blood glucose and tissue glucose uptake leading to diminished central nervous system activation and stress hormone output, decreased cytokine mRNA expression, lower beta-oxidation of lipid fuels, reduced pro-inflammatory signals, and attenuated IL-6 release from the working muscle tissue. Exercising with higher blood glucose levels decreases hypothalamic-pituitary-adrenal activation, leading to moderated release of adrenocorticotrophic hormone and cortisol, growth hormone, and epinephrine. Stress hormones have an intimate link with genes that control cytokine production, and the function of multiple cell types of the immune system. Exercise-carbohydrate interactions, especially during exercise and the early post-exercise recovery period, may modulate signal transduction cascades that influence protein regulatory systems. Thus there is a strong rationale for providing carbohydrate as a countermeasure to exercise-induced inflammation when body carbohydrate stores are challenged. Perhaps just as importantly, studies consistently show a 2 to 6% improvement in performance by athletes ingesting carbohydrate compared to water during intensive exercise bouts lasting longer than two hours.

The value of using carbohydrate and other types of immunonutrition support for athletes has been questioned because blocking transient post-exercise elevations in inflammation, oxidative stress, and stress hormones may interfere with important signaling mechanisms for training adaptations. The literature is limited and not consistent in this area, however, especially in regards to combining carbohydrate intake with heavy training. Training with limited carbohydrate availability may lead to some improved metabolic adaptations, but studies have been unable to link this with performance improvements. Part of the problem is that training with limited carbohydrate is difficult, leading to decreased intensity and duration. One argument is that carbohydrate ingestion only partially lowers

post-exercise inflammation and stress hormones, analogous to the beneficial use of ice packs to “take the edge off” swelling following mild injuries. In the end, the value of carbohydrate and other forms of immunonutrition support for athletes during periods of heavy exertion and competitive races should be evaluated by whether or not the athlete has improved recovery, lowered illness rates, reduced muscle damage and soreness, and enhanced overall athletic performance.

POLYPHENOLS

Due to their pleiotropic properties and structural diversity, polyphenols have created much interest as potential countermeasures to exercise-induced physiological stress. The 8,000 phenolic compounds are divided into four main classes, including the six sub-classes of flavonoids that comprise nearly 50% of all polyphenols. Improved assessment techniques have led to many recent publications that support a strong and impressive linkage between high versus low dietary polyphenol intake and reduced risk for overall mortality, a wide spectrum of chronic health conditions, systemic inflammation, and acute respiratory illness. Flavonoids exert anti-viral effects, modulate natural killer (NK) cell activities and regulatory T (Treg) cell properties, and influence macrophage inflammatory responses.

Most polyphenols, however, are poorly absorbed in the human small intestine and undergo extensive biotransformation after ingestion. A large proportion of ingested plant polyphenols reaches the colon, and microbial degradation produces gut-derived phenolics that can be reabsorbed into the systemic circulation, exert a variety of bioactive effects, and then finally be excreted in the urine. Thus most studies incorporate a 1-6 week loading period prior to an exercise stress intervention to allow sufficient time for body tissues to adapt to the higher phenolic flux level. Although there are indications that the biotransformed, gut-derived phenolics exert anti-inflammatory and anti-viral effects, these bioactive influences are subtle and become clinically important over long time periods. Dosing strategies (duration, frequency, amount, timing) are still being explored, and supplements vary from single and combined purified polyphenols (e.g., resveratrol, quercetin), to plant extracts (e.g., black currant, bilberry, green tea) and increased fruit and vegetable food or juice intake (e.g., bananas, tart cherry juice, fresh blueberries). A common finding thus far is that polyphenol-rich plant extracts or supplements have small but significant effects in increasing anti-oxidant capacity, with inconsistent, short-term effects on exercise-induced oxidative stress, inflammation, and immune dysfunction. High blueberry and green tea flavonoid versus placebo intake for 17 days was linked to reduced ex vivo viral replication in blood samples collected from athletes after a 3-day overreaching, running protocol. Long-term studies are needed to better understand the potential benefits of increased polyphenol intake for athletes during periods of intense training. Polyphenols may serve as a useful sub-

stitute for ibuprofen, a drug which blunts early translational signaling responses in human skeletal muscle and amplifies post-exercise inflammation.

CONCLUSIONS

In general, exercise activates multiple molecular pathways, many involving the immune system, and these are sensitive to nutritional influences (e.g., the inverse relationship between carbohydrate supplementation and post-exercise plasma IL-6 levels). Multi-omics-based approaches are particularly useful in interpreting human responses to nutritional manipulation within the exercise context, and improves the capacity to capture complex and subtle influences on whole body metabolism and physiology. Future studies using multi-omics approaches will help determine if increased long-term intake of high carbohydrate-polyphenol food sources is an effective immunonutrition support strategy for athletes.