ANNUAL REVIEWS

Annual Review of Food Science and Technology

Immunometabolism: A Multi-Omics Approach to Interpreting the Influence of Exercise and Diet on the Immune System

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Annu. Rev. Food Sci. Technol. 2019. 10:341–63

First published as a Review in Advance on January 11, 2019

The *Annual Review of Food Science and Technology* is online at food.annualreviews.org

https://doi.org/10.1146/annurev-food-032818-121316

Keywords

exercise, diet, immune function, metabolomics, lipidomics, proteomics

Abstract

Immunometabolism is an evolving field of scientific endeavor that merges immunology and metabolism and has provided valuable context when evaluating the influence of dietary interventions on exercise-induced immune dysfunction. Metabolomics, lipidomics, and proteomics provide a system-wide view of the metabolic response to exercise by simultaneously measuring and identifying a large number of small-molecule metabolites, lipids, and proteins. Many of these are involved with immune function and regulation and are sensitive to dietary influences, especially acute carbohydrate ingestion from either sugar beverages or fruits such as bananas. Emerging evidence using large multi-omics data sets supports the combined intake of fruit sugars and phytochemicals by athletes during heavy exertion as an effective strategy to improve metabolic recovery, augment viral defense, and

counter postexercise inflammation and immune dysfunction at the cell level. Multi-omics methodologies have given investigators new outcome targets to assess the efficacy of various dietary interventions for physiologically stressed athletes.

INTRODUCTION TO IMMUNOMETABOLISM

Immunometabolism, a term first used in 2011, is a new field of research endeavor that seeks to improve our understanding of the multifaceted interchanges between the metabolic and immune systems (Mathis & Shoelson 2011). Improvements in mass spectrometry technology and bioinformatics support have enhanced the capacity to utilize a systems biology approach when measuring these complex interactions within the human body. Global and targeted metabolomics-, proteomics-, and lipidomics-based investigations have revealed that metabolism and immunity are inextricably interwoven (Hotamisligil 2017, Van den Bossche et al. 2017). Metabolic processes such as glycolysis, the Krebs cycle, and fatty acid metabolism have highly specific effects on immune cell function and are now regarded as key immunoregulatory factors governing the immune response in health and disease (O'Neill & Pearce 2016).

The link that exists between the metabolic state of immune cells and the nature of the stimulated immune response has revolutionized the field of immunology. This new focus has shown that in response to an acute immunological challenge, including exercise stress and infection, or chronic conditions such as obesity and diabetes, cells of the immune system engage in growth and proliferation to generate effector cells that produce molecules such as cytokines and cytotoxic granules. This immune activation is associated with energy and biosynthetic demands, and immune cells must engage in metabolic reprogramming to generate sufficient energy to fuel these demands (Shehata et al. 2017). This linkage between metabolic and immune systems is particularly apparent during recovery from physiologically demanding bouts of intensive exercise. This review provides emerging data showing that carbohydrate from both sugar beverages and fruits such as bananas, and the polyphenols from foods such as blueberries and green tea, provide special advantages for the athlete's immune system during recovery from demanding exercise workloads.

THE IMMUNE RESPONSE TO EXERCISE STRESS

This review focuses on diet-based countermeasure strategies to exercise-induced immune deficiency and the value of using mass spectrometry–based methods to detect the potential significance of specific interventions. This section summarizes how the immune system responds to intense exercise workloads and how multi-omics methodologies are being utilized to better characterize this interaction, providing new biomarker targets for diet interventions.

Transient Immune Dysfunction and Elevated Infection Risk

The influence of exercise on the immune system is a relatively new area of scientific endeavor, with approximately 90% of research data published since 1990 (van Dijk & Matson 2016). The immune response to exercise depends on the accumulated metabolic stress from the frequency, intensity, and duration of effort (Nieman 2000). Regular moderate exercise such as 30- to 60-minute brisk walking bouts improves the recirculation and function of several types of immune cells, especially those of the innate immune system including natural killer cells, neutrophils, and macrophages

(Adams et al. 2011, Bigley et al. 2014, Nieman et al. 2005). This circulation surge of immune cells is transient but when repeated on a regular basis improves overall immunosurveillance against pathogens, leading to a 40–50% decrease in the number of illness days with common upper respiratory tract infections (URTIs) (Nieman et al. 2011). Another long-term immune-related benefit of regular exercise and physical fitness, especially when combined with maintenance of a healthy body weight, is reduced systemic inflammation, a condition that undergirds most of the common chronic diseases (Shanely et al. 2013, Wedell-Neergaard et al. 2018). Mounting evidence supports the role of habitual exercise in favorably regulating the immune system and delaying the onset of immunosenescence and tumorigenesis (Hojman 2017, Koelwyn et al. 2015, Müller & Pawelec 2014, Simpson et al. 2012, Turner 2016).

In contrast, high exercise workloads and the associated physiological and metabolic stress is linked to transient immune impairment, inflammation, oxidative stress, muscle damage, and an elevated URTI risk (Nieman et al. 1990, 2014a, 2015b, 2016, 2017b; Peake et al. 2017; Santos et al. 2016; Siedlik et al. 2016; Walsh et al. 2011). Until recently, these effects were measured using a few targeted outcomes, but increasingly the focus has shifted to multi-omics approaches.

Multi-Omics Data

Metabolomics, lipidomics, and proteomics provide a system-wide view of the metabolic response to exercise and nutritional interventions by simultaneously measuring and identifying a large number of small-molecule metabolites, lipids, and proteins.

Metabolomics. Metabolomics is the study of small molecular weight molecules (metabolites) present in a biological system and is positioned as a key tool for dietary and exercise biomarker discovery, and in the evaluation of treatment efficacy (O'Gorman & Brennan 2017). The metabolome refers to the complete set of small-molecule metabolites found within a biological organism. Metabolomics measurements with gas chromatography–mass spectrometry (GC-MS) began in the 1970s but was still considered an emerging field as late as 2010 (Tolstikov 2016). The human metabolome includes more than 114,000 small molecules (identified and expected), including peptides, lipids, amino acids, nucleic acids, carbohydrates, organic acids, biogenic amines, vitamins, minerals, food additives, drugs, cosmetics, contaminants, pollutants, and other chemicals that humans come into contact with (Wishart et al. 2018). Metabolomics requires sophisticated mass spectrometry platforms, exact quality control procedures, a large reference library of chemical standards, and precise biochemical identification protocols (Lu et al. 2017). Metabolomics-based approaches in exercise, diet, and lifestyle interventions improve the interpretation of the metabolic response by simultaneously measuring and identifying shifts in hundreds of metabolites from diverse pathways (Nieman et al. 2015a, 2017a; Rangel-Huerta et al. 2017).

In a typical randomized clinical trial with human athletes exercising intensely for more than two hours, significant increases in at least 300 identified metabolites can be measured, with more than 100 increasing twofold or greater (Nieman et al. 2013a,b, 2014b,c, 2015a, 2018a). Intensive and prolonged whole-body exercise such as running and cycling depletes muscle and liver glycogen stores causing an extensive and prolonged shift in numerous and varied lipid superpathway metabolites with a pronounced fatty acid oxidation signature (Chorell et al. 2009; Lehmann et al. 2010; Lewis et al. 2010; Nieman et al. 2014c, 2015b, 2016, 2017b, 2018a). Postexercise increases can be measured for plasma medium- and long-chain fatty acids, fatty acid oxidation products (dicarboxylate and monohydroxy fatty acids, acylcarnitines), ketone bodies, and sulfated bile acids with decreases in plasma triacylglycerol esters, primary and secondary bile acids, and minor phospholipids such as lysophosphatidylcholines and lysophosphatidylethanolamines. Postexercise

Table 1 Immunometabolism-based evidence of the physiological stress and immune dysfunction associated with intense and prolonged exercise[a]

Biomarker group	Specific outcome measures
Metabolomics	↑ metabolites (primarily lipid superpathway): palmitoleic acid, glycerol, total FFAs, linoleic acid, α-linolenic acid, palmitic acid, acetylcarnitine, heptadecanoic acid, oleoyl ethanolamide, linoleoyl ethanolamide, oleoylcarnitine, 3-hydroxylaurate, 3-hydroxyoctanoate, tryptophan, oleic acid, hexanoylcarnitine, xanthine, *cis*-4-decenoylcarnitine, 9-hydroxystearate, myristic acid, myristoylcarnitine, octanoylcarnitine, 5-bromotryptophan, decanoylcarnitine, laurylcarnitine, linoleoylcarnitine, 9+13-HODE, 3-hydroxymyristate, caprate, 16-hydroxypalmitate
Lipidomics	↑ linoleic acid pathway– and DHA-EPA-derived lipid mediators: 9+13-HODEs, 9+13-oxo-ODE, 9,10-DiHOME, 12,13-DiHOME, 8+15-HETrE, 9+13-HOTrE, 8+10+11+13+14+16+20-HDoHE, 5+12+15+18-HEPE, 5,15-DiHEPE, 8,15-DiHEPE, (5- to 20-)HETEs, 5,15-DiHETE, 8,15-DiHETE, 5,6-DiHETrE, 8,9-DiHETrE, 11,12-DiHETrE, 14,15-DiHETrE, LxA_4, LTB_4, PGE_2, $PGF_{2\alpha}$, 15-keto-$PGF_{2\alpha}$, 6-keto-$PGF_{1\alpha}$
Proteomics	Proteins with ↑ plasma levels related to immune function: lysozyme C, neutrophil elastase, neutrophil defensin 1, protein S100-A12, protein S100-A8, cathelicidin antimicrobial peptide, alpha-actinin-1, actin cytoplasmic 1, profiling-1, platelet factor 4, histone H2A types, serum amyloid A-4 protein, myeloperoxidase, complement component C8 gamma chain, complement C4B, protease C1 inhibitor, interalpha-trypsin inhibitor heavy chain H4, alpha-1-acid glycoprotein 2, complement component C7, alpha-2-HS-glycoprotein

[a]Many of these biomarkers are involved with immune function and are potentially sensitive to diet-based interventions.
Abbreviations: ↑, increased; DHA, docosahexaenoic acid; DiHEPE, dihydroxy-eicosapentaenoic acid; DiHETE, dihydroxy-eicosatetraenoic acid; DiHETrE, dihydroxy-eicosatrienoic acid; DiHOME, dihydroxy-9Z-octadecenoic acid; EPA, eicosapentaenoic acid; FFAs, free fatty acids; HDoHE, hydroxy-docosahexaenoic acid; HEPE, hydroxy-eicosapentaenoic acid; HETE, hydroxy-eicosatetraenoic acid; HODE, hydroxy-octadecadienoic acid; HOTrE, hydroxy-octadecatrienoic acid; LT, leukotriene; Lx, lipoxin; oxo-ODE, oxo-octadecadienoic acid; PG, prostaglandin.

increases also occur for energy tricarboxylic acid cycle components including malate, aconitate, citrate, fumarate, succinate, and α-ketoglutarate (Nieman et al. 2018a), with shifts in tryptophan- and other amino acid–related metabolites (see **Table 1** and **Figure 1**). Most of the postexercise shifts in plasma metabolites reach their nadir within a few hours and then return to near-pre-exercise levels by the next day as depicted in **Figure 2**.

This profound, exercise-induced perturbation in metabolites has a direct influence on immune function. As summarized in **Figure 3**, human peripheral blood THP-1 monocytes incubated for six hours in postexercise plasma samples obtained from overnight fasted cyclists drinking water without carbohydrates had a markedly reduced oxygen consumption rate (OCR) in response to lipopolysaccharide (LPS) stimulation (Nieman et al. 2018a). This contrasted with a substantially higher OCR when monocytes were incubated in postexercise plasma samples following trials in which cyclists were fed carbohydrates (0.8 g/kg body weight per hour) through banana fruit or a 6% carbohydrate beverage.

Inflammatory LPS activation of monocytes stimulates a rapid nonmitochondrial consumption of oxygen by NADPH oxidase-2 (NOX-2). This is defined as the proinflammatory oxidative burst (Kramer et al. 2014). ATP production in monocytes is based both on mitochondrial OCR and glycolysis in the cytosol (measured as lactate production or the extracellular acidification rate) (Chacko et al. 2013). Following LPS stimulation, monocytes have the capacity to increase ATP production by increasing mitochondrial respiration or switching to glycolysis. Spare respiratory capacity [(maximal respiration)/(basal respiration) × 100] was 37.9% in the water-only trial and significantly lower when compared to 97.5% and 90.5% in the Cavendish banana and sugar beverage trials, respectively (Nieman et al. 2018a). These data indicate an abnormally low spare

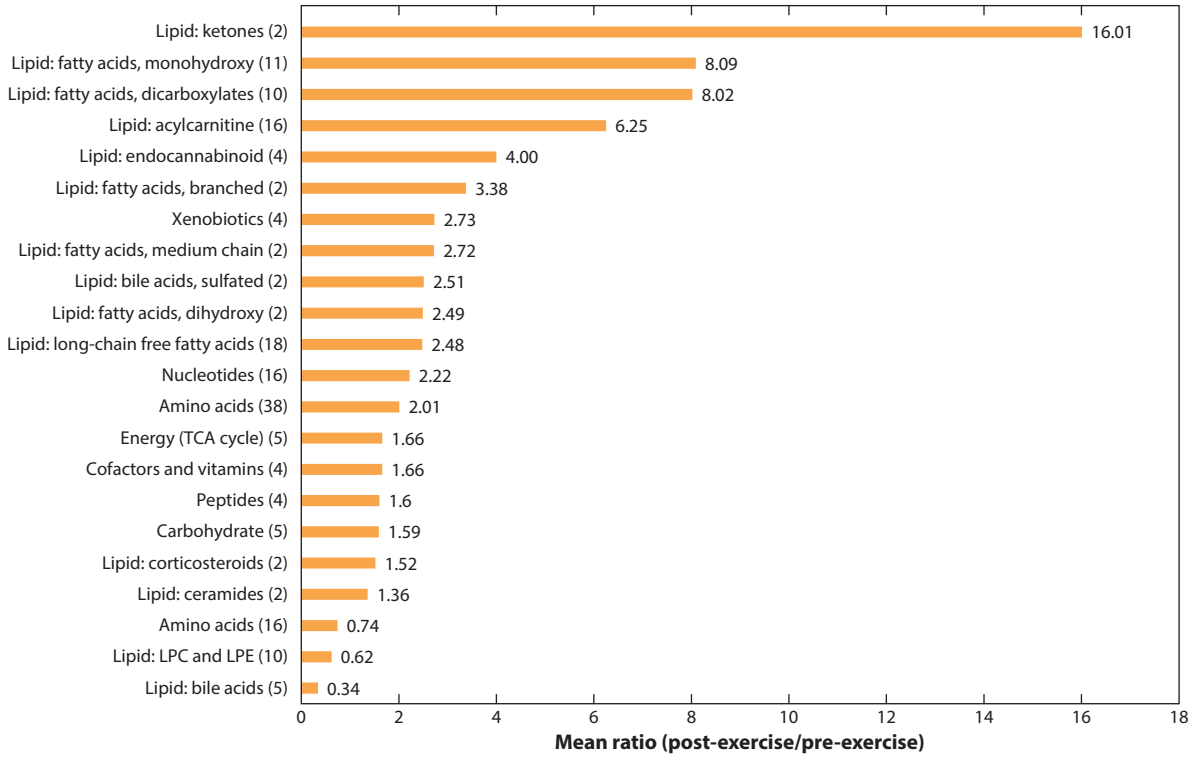

Figure 1

Mean postexercise to pre-exercise ratios for shifts in metabolites (grouped according to subpathways) during the first 1.5 hours of recovery from 75-km cycling. Numbers in parentheses represent the number of metabolites in each subpathway. All metabolites ($N = 207$) in this analysis had variable importance in projection (VIP) score above 1.5 [OPLS-DA (orthogonal partial least squares–discriminant analysis)]. Abbreviations: LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; TCA, tricarboxylic acid cycle. Data from Nieman et al. (2018a).

respiratory capacity of LPS-stimulated monocytes that lacked the metabolic power to launch a proinflammatory oxidative burst response when cultured in plasma samples obtained from overnight fasted, exercise-exhausted athletes drinking water. As depicted in **Figure 3**, this effect was countered by carbohydrate ingestion and is discussed further, along with other related immune benefits, in the carbohydrate section of this review.

Oxylipins as lipid mediators. Linoleic acid (18:2n-6) is a common polyunsaturated fatty acid (PUFA) in human diets and adipose tissue (Ramsden et al. 2012). Ingested linoleic acid is converted to longer and more unsaturated fatty acids through enzymatic desaturation and elongation in the endoplasmic reticulum of cells, as summarized in **Figure 4**. Eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3) are available from fish but can also be synthesized by humans from α-linolenic acid (ALA; 18:3n-3), as shown in **Figure 5**. Conversion of dietary ALA into EPA and DHA is limited in humans and is, in part, dependent on the amounts of ALA and linoleic acid in the diet (Goyens et al. 2006).

Oxylipins are bioactive lipids that are produced via the oxygenation of PUFAs (Caligiuri et al. 2017). Most oxylipins are oxidation products from n-6 and n-3 PUFAs in the linoleic acid and α-linolenic desaturation pathways (Gabbs et al. 2015). A significant proportion of the

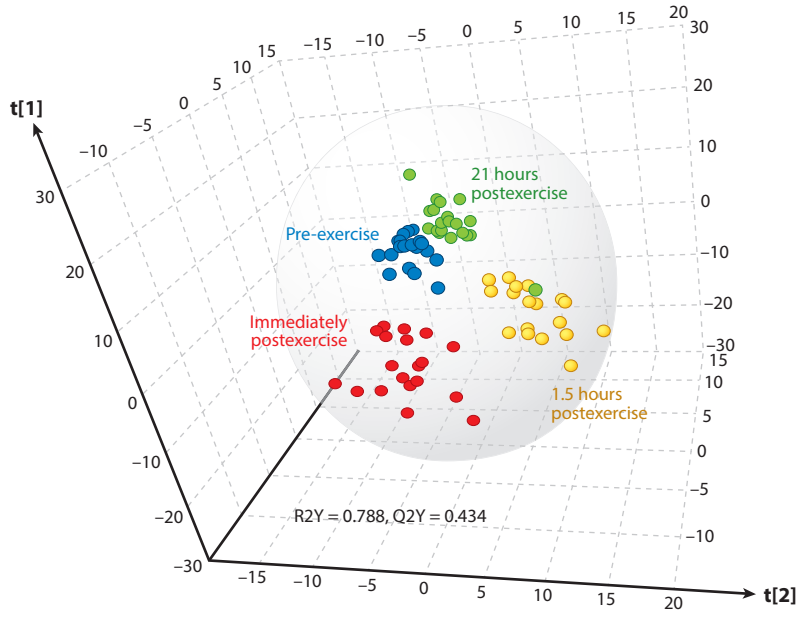

Figure 2

PLS-DA (partial least squares–discriminant analysis) shows the extent, duration, and separation in total metabolite shifts from pre-exercise (*blue*), immediately postexercise (*red*), 1.5 h postexercise (*yellow*), and 21 h postexercise (*green*). Data are from $N = 20$ male athletes who cycled for 75 km at 68% VO_{2max} while consuming water only in an overnight fasted state. A total of 107 metabolites increased more than twofold immediately after exercise. Data from Nieman et al. (2018a).

physiological and immune system effects from n-6 and n-3 PUFAs are mediated through these oxidative metabolites, which are thus called lipid mediators (Kasuga et al. 2015). Oxylipin formation begins with cell activation from injury or inflammatory stimuli resulting in precursor PUFAs in membrane phospholipids being released by phospholipase A_2. The released PUFAs are then metabolized into oxylipins by three enzyme pathways: cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) (**Figures 4** and **5**). Oxylipins such as isoprostanes can also be derived nonenzymatically and can be used as biomarkers for oxidative stress (Caligiuri et al. 2017). Once formed, oxylipins act as autocrine and paracrine lipid mediators by binding to G-protein-coupled receptors or to multiple intracellular effectors such as peroxisome proliferator-activated receptor-γ (PPAR-γ).

Lipidomics is a branch of metabolomics first introduced in 2003, with a focus on the analysis of lipid components, including fatty acids, glycerolipids, glycerophospholipids, sphingolipids, prenol lipids, saccharolipids, and polyketides (Zhao et al. 2015). Global metabolomics and complex lipid panels are not sensitive enough to detect oxylipins except for direct linoleic acid oxidized derivatives, including 9+13-hydroxy-octadecadienoic acid (9+13-HODEs), (Z)-9,10-dihydroxyoctadec-12-enoic acid (9,10-DiHOME), and (Z)-12,13-dihydroxyoctadec-9-enoic acid (12,13-DiHOME). Recent advances in mass spectrometry techniques have revealed large numbers of oxylipins and increased awareness of their vital regulatory roles in innate immune function, inflammation, cardiac function, vascular tone, blood coagulation, and many other physiological processes (Caligiuri et al. 2017, Gabbs et al. 2015). Lipidomics measurements using sensitive mass spectrometry platforms allow the simultaneous measurement of large numbers of these lipid

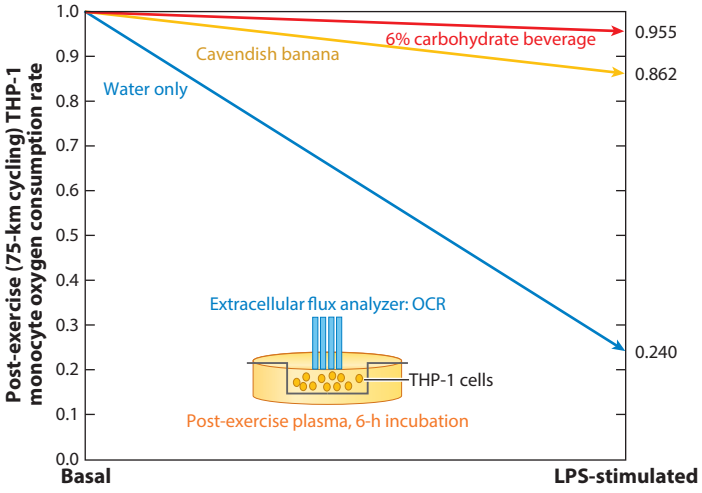

Figure 3

Monocyte oxygen consumption rate (OCR) is influenced by serum metabolic factors following heavy exertion. Human peripheral blood THP-1 monocytes were incubated for 6 hours in plasma samples obtained from cyclists immediately post-75-km cycling, with OCR measured under basal and lipopolysaccharide (LPS)-stimulated conditions using the XF 24 Extracellular Flux Analyzer (Seahorse Biosciences; North Billerica, MA) (Nieman et al. 2018a). The data indicate that carbohydrate ingestion (0.8 g/kg per hour) from either Cavendish bananas or a 6% sugar beverage was associated with higher OCR compared to water only. Data were measured in pmol/min and normalized to 1.

mediators, facilitating the systematic investigation of their roles in immune regulation and inflammation and resolution and the influence of various exercise workloads and diet interventions.

The role of lipid mediators in the pathogenesis of disease, particularly inflammation, is a new and active area of research endeavor (Xu et al. 2016). Oxylipin and immune responses are highly integrated, and although these lipids are involved in important and beneficial physiological roles, including the resolution of inflammation, certain environmental, metabolic, and lifestyle stresses can turn these lipids into mediators of systemic inflammation, immune dysfunction, and other detrimental responses (Ackermann et al. 2017, Ertunc & Hotamisligil 2016). As summarized in **Figure 6**, plasma levels of many oxylipins are substantially higher in obese individuals compared to lean athletes when in an overnight, fasted, resting state (Nieman & Mitmesser 2017). This elevation in harmful plasma oxylipins is termed lipotoxicity and may undergird many of the health problems associated with obesity (Mika & Sledzinski 2017). Whether or not omega-3 supplementation has an influence on lipotoxicity is an active area of research, but no clear consensus has emerged because of strong interindividual variances (Gabbs et al. 2015, Ostermann & Schebb 2017).

Exercise-induced muscle tissue injury and inflammation invoke a strong innate immune response involving granulocytes, monocytes, and macrophages, and recent evidence indicates that oxylipins are involved in initiating, mediating, and resolving this process (Markworth et al. 2013, 2016b). Of the 12 n-3 PUFAs and n-6 PUFAs in the ALA and linoleic acid pathways (**Figures 4** and **5**), each is mobilized strongly from adipose tissue stores during intensive exercise, with increases in postexercise plasma samples ranging from two- to sixfold over pre-exercise levels (Nieman et al. 2014b, 2015a, 2018a). At the same time, a large number of exercise-related oxylipins are produced, and although some have a short half-life, act locally, and do not accumulate in human

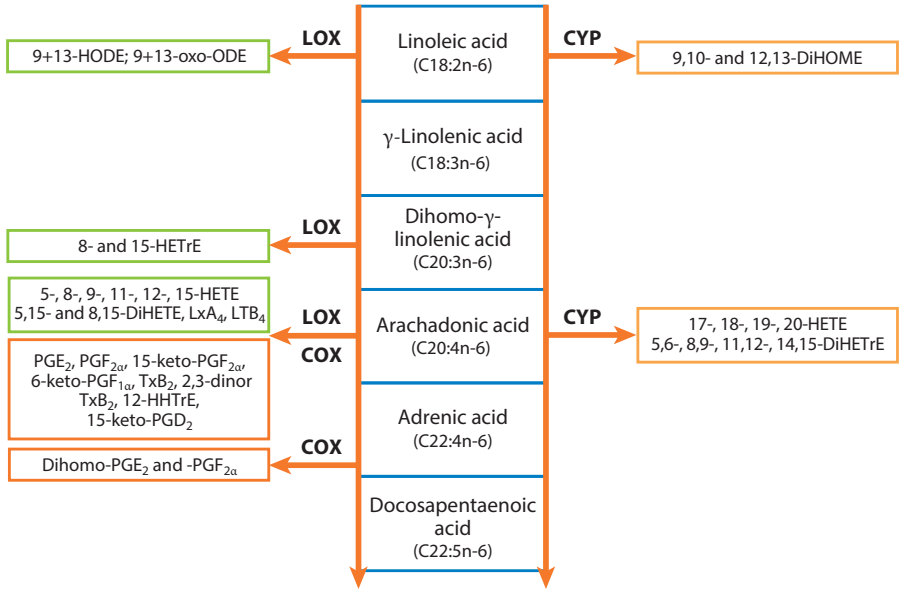

Figure 4

Oxylipins increasing postexercise from n-6 PUFAs via cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) pathways. Abbreviations: DiHETE, dihydroxy-eicosatetraenoic acid; DiHETrE, dihydroxy-eicosatrienoic acid; DiHOME, dihydroxy-9Z-octadecenoic acid; HETE, hydroxy-eicosatetraenoic acid; HETrE, hydroxy-eicosatrienoic acid; HHTrE, hydroxy-heptadecatrienoic acid; HODE, hydroxy-octadecadienoic acid; LT, leukotriene; Lx, lipoxin; oxo-ODE, oxo-octadecadienoic acid; PG, prostaglandin; Tx, thromboxane. Data from Markworth et al. (2014, 2016b) and Nieman & Mitmesser (2017).

plasma, many are stable enough to be measured for several hours of recovery, as summarized in **Table 1** and **Figures 4** and **5**.

Linoleic acid is a direct precursor to 9- and 13-hydroxy-octadecadienoic acids (9+13-HODEs), which are stable and abundant oxidation products in human plasma. 9+13-HODEs have emerged as important indicators of oxidative stress and inflammation following stressful exercise and in a wide variety of pathological conditions (Nieman et al. 2014c, 2016; Vangaveti et al. 2016). The largest number of oxylipins produced by activated cells during intensive exercise come from the n-6 PUFA substrate arachidonic acid and include prostanoids from COX enzymes and eicosanoids, including at least 16 varieties of hydroxy-eicosatetraenoic acids (HETEs) and dihydroxy-eicosatetraenoic acids (DiHETEs, DiHETrEs) from LOX and CYP enzymes (Markworth et al. 2013, 2016a,b; Nieman & Mitmesser 2017). The HETEs, DiHETEs, and DiHETrEs have multiple roles including the regulation of leukocyte migration and chemotaxis, PPAR activation, vascular tone, and platelet regulation (Caligiuri et al. 2017, Powell & Rokach 2015). Exercise-induced increases in prostanoids such as PGE_2, $PGF_{2\alpha}$, and 6-keto-$PGF_{1\alpha}$ (a product of prostacyclin or $PG1_2$) exert proinflammatory effects, may function as acute signaling molecules for postexercise muscle adaptation, and help regulate blood flow (Boushel et al. 2002; Heinonen et al. 2017; Markworth et al. 2014, 2016a,b). However, chronic ingestion of COX-inhibiting drugs such as ibuprofen does not interfere with muscle adaptations to exercise training; to the contrary, it may promote muscle mass and strength gains by upregulating the $PGF_{2\alpha}$ receptor (Trappe & Liu 2013, Trappe et al. 2013).

The postexercise, acute inflammatory response supported by prostaglandins and leukotrienes plays an important role in training adaptations but must be resolved in a timely manner to avoid

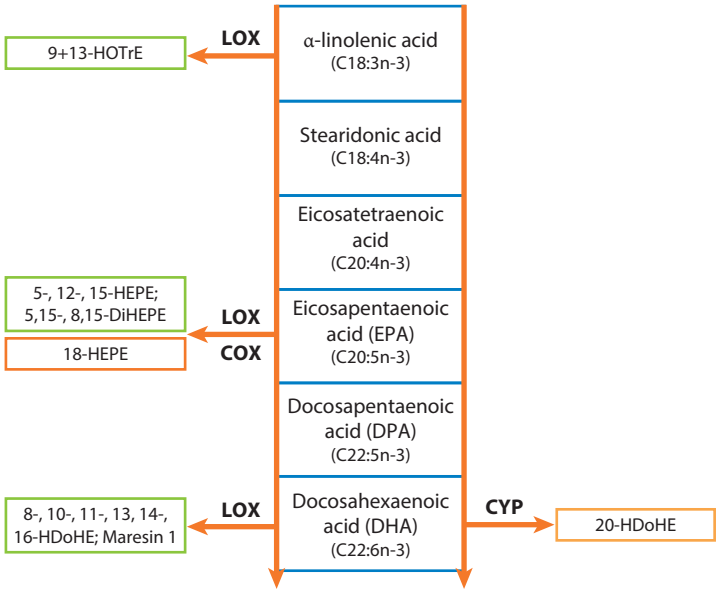

Figure 5

Oxylipins increasing postexercise from n-3 polyunsaturated fatty acids via cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) pathways. Abbreviations: DiHEPE, dihydroxy-eicosapentaenoic acid; HDoHE, hydroxy-docosahexaenoic acid; HEPE, hydroxy-eicosapentaenoic acid; HOTrE, hydroxy-octadecatrienoic acid. Data from Markworth et al. (2014, 2016b) and Nieman & Mitmesser (2017).

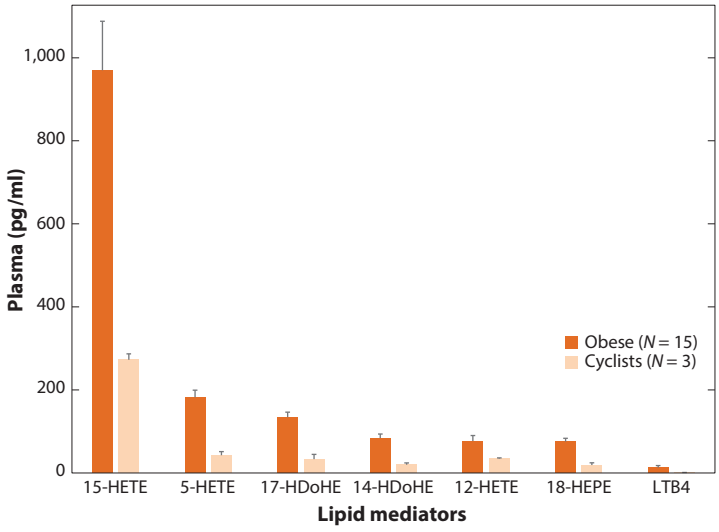

Figure 6

Differences in selected lipid mediators between obese individuals and trained cyclists. All group differences, $P < 0.05$. Subjects included 15 overweight/obese females [mean ± SE: age, 49.9 ± 1.8 years; BMI, 32.9 ± 1.9 kg/m^2; C-reactive protein (CRP), 4.19 ± 0.8 mg/L] and 3 competitive male cyclists (age, 38.7 ± 5.5 years; BMI, 28.0 ± 1.9 kg/m^2; CRP, 0.57 ± 0.15 mg/L). Abbreviations: HDoHE, hydroxy-docosahexaenoic acid; HEPE, hydroxy-eicosapentaenoic acid; HETE, hydroxy-eicosatetraenoic acid; LTB4, leukotriene B4. Data from Nieman & Mitmesser (2017).

undue tissue damage (Serhan 2014, 2017; Serhan et al. 2012, 2015). Neutrophils are the first immune cells to migrate to the site of exercise-induced muscle tissue damage and inflammation, but excessive accumulation and activity can be injurious. Specialized proresolving mediators (SPMs) from n-3 PUFAs include resolvins, protectins, and maresins, which resolve the inflammatory response, stop the recruitment of neutrophils, promote macrophage clearance of debris, and help repair and return the tissue back to homeostasis. Lipoxins from arachidonic acid are also potent anti-inflammatory and proresolving lipid mediators (Serhan et al. 2015).

As with n-6 PUFAs in the linoleic acid pathway, prolonged and intensive exercise is associated with increased plasma levels for each of the n-3 PUFAs in the ALA pathway (**Figure 5**). The mobilized n-3 PUFAs can be oxidized during exercise, and some of these are stable enough in plasma to be measured during exercise recovery. The roles for these exercise-induced n-3 PUFA oxylipins are still being explored, but most appear to exert anti-inflammatory effects. ALA-derived 9- and 13-(*S*)-hydroxy-octadecatrienoic acid (9,13-HOTrE) increase strongly postexercise via LOX and appear to mediate anti-inflammatory effects through several pathways including PPAR-γ (Kumar et al. 2016). Of all SPMs, maresin 1 (MAR1) is the most responsive to exercise, even though levels are very low in athletes compared to obese individuals (Nieman & Mitmesser 2017). MAR1 has several important tasks during exercise recovery and functions as an anti-inflammatory, proresolving mediator that prevents polymorphonuclear neutrophil (PMN) infiltration, stimulates macrophage phagocytosis, promotes tissue regeneration, and regulates inflammation and pain resolution (Serhan et al. 2012, Serhan 2017). Exercise increases plasma levels of multiple hydroxy-docosahexaenoic acids (HDoHE), and these autoxidation products of DHA may serve as indicators of oxidative stress (**Figure 5**). Several EPA-derived hydroxy-eicosapentaenoic acids (HEPEs) are produced during exercise, and these appear to mediate anti-inflammatory effects. Exercise increases 18-HEPE, the resolvin E1 precursor. Although resolvin E1 does not appear to accumulate in human blood postexercise, this SPM dampens inflammation and pain (Serhan 2017).

Proteomics. Proteomics (first coined in 1997) is the large-scale study of proteins and the proteome. The proteome is the entire set of proteins, produced or modified by an organism or system and varying over time and in response to a wide variety of stresses (Blackstock & Weir 1999). The utilization of global proteomics procedures in human exercise-based studies is an emerging science. Proteins are the main components of the metabolic pathways of cells and are secreted discretely or within extracellular vesicles (EVs) by skeletal muscle and other tissues into circulation during exercise (Whitham et al. 2018). Mass spectrometry procedures are rapidly improving, increasing the number of proteins that can be simultaneously measured in body matrixes. The concentrations of hundreds of proteins are increased in human plasma during intensive exercise and are involved in a broad array of biological processes across body tissues, including cell communication and signaling, the regulation of immune responses, and metabolic processes such as glycolysis (Balfoussia et al. 2014, Nieman et al. 2018b, Whitham et al. 2018). Within the muscle tissue, proteomics-based studies indicate that the primary chronic exercise training response is a greater concentration of proteins from the mitochondrial electron transport chain, tricarboxylic acid cycle, and mitochondrial respiratory chain complex I assembly (Srisawat et al. 2017).

Stressful exercise workloads are associated with the release of proteins into the circulation, especially those related to immune function (**Table 1**) (Balfoussia et al. 2014, Nieman et al. 2018b). **Figure 7** depicts Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) protein–protein interactions for 15 proteins expressed acutely and most consistently following intense and prolonged exercise (Nieman et al. 2018b). Most of these immune-related proteins are involved

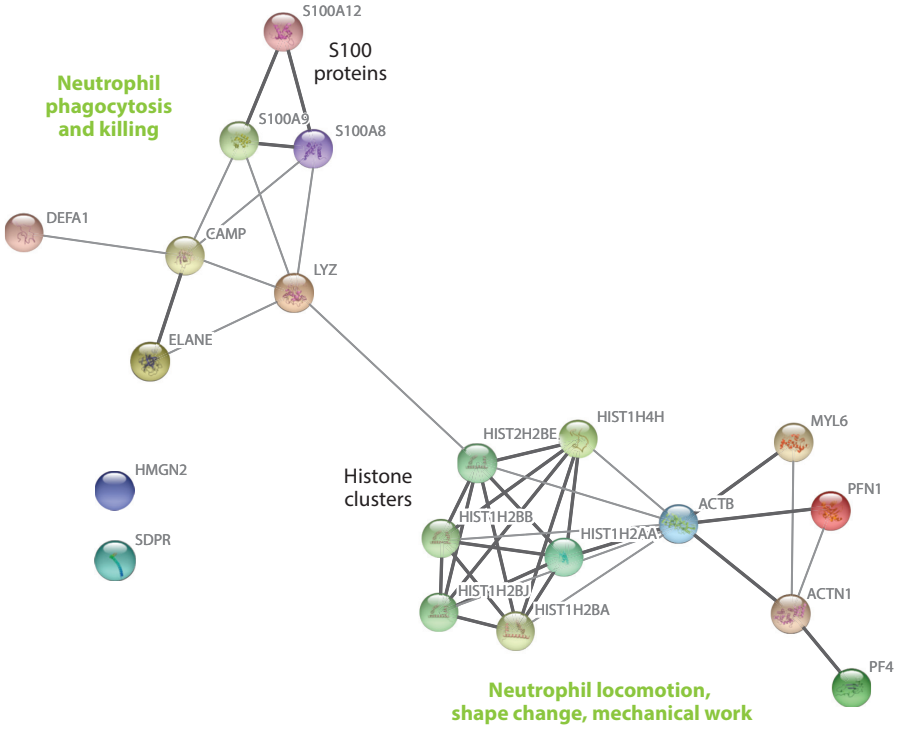

Figure 7

STRING protein–protein interaction graph using immune-related proteins that are consistently expressed following 2.5 h running or cycling. The thickness of the network lines indicates the strength of data support (**https://string-db.org**). Abbreviations: ACTB, actin, beta; ACTN1, actinin, alpha 1; CAMP, cathelicidin antimicrobial peptide; DEFA1, defensin, alpha 1; ELANE, elastase; HIST1H4H, histone cluster, H4 family; HIST1H2AA, BA, BB, BJ, histone clusters, H2A family; HIST2H2BE, histone clusters, H2B family; HMGN2, high mobility group nucleosomal binding domain 2; LYZ, lysozyme; MYL6, myosin, light chain 6; PF4, platelet factor 4; PFN1, profilin 1; S100A8, A9, A12, S100 calcium binding proteins; SDPR, serum deprivation response. Data from Nieman et al. (2018b).

with pathogen defense and immune cell chemotaxis and locomotion. As emphasized earlier in this review, neutrophils are among the first cells translocated to inflammatory sites following heavy exertion, and multiple proteins, including elastase, S100-A8, and S100-S12, reflect their heightened state of activity (Mortensen et al. 2008, Nieman et al. 2018b, Pyne et al. 2000). Postexercise increases in profilin-1 and actin (cytoplasmic 1) support neutrophil actin filament polymerization, which facilitates migration to involved tissues (Nieman et al. 2018b, Whitham et al. 2018).

Some proteins are not elevated acutely in the circulation during exercise but increase chronically for a few days during recovery from stressful training bouts (Nieman et al. 2018b). Most of these proteins are involved in immune defense and acute phase responses, complement activation, and humoral responses mediated by circulating immunoglobulins. The acute phase response is a systemic reaction to environmental insults including trauma, infection, and muscle-damaging exercise, and involves the production of many proteins including serum amyloid A, complement proteins, C-reactive protein, complement proteins, transport proteins, antiproteases, and coagulation and fibrinolytic proteins (Gabay & Kushner 1999, Ye & Sun 2015).

FOOD AND DIET-BASED COUNTERMEASURES TO EXERCISE-INDUCED IMMUNE DYSFUNCTION

Overview

Immunonutrition support is the use of diet-based intervention strategies to counter immune dysfunction linked to disease, traumatic injuries, surgeries, burn injuries, and physiologically stressful conditions (Chow & Barbul 2014, Patel et al. 2017). Athletes experience regular cycles of physiological stress, inflammation, oxidative stress, and transient immune dysfunction, and various immunonutrition strategies are being explored using multi-omics approaches (Bermon et al. 2017, Nieman 2008, Nieman & Mitmesser 2017). This section focuses on the benefits of increased intake of carbohydrates and polyphenols for athletes during periods of high exercise workloads. Other nutrition support recommendations for athletes have failed to provide consistent and clinically meaningful advantages, including those for antioxidant vitamins, vitamin D, minerals, glutamine and other amino acids, herbs such as Echinacea and ginseng, bovine colostrums, probiotics/prebiotics, and β-glucan (Nieman & Mitmesser 2017). More information is needed regarding the potential value of n-3 PUFAs for athletes. There is a growing awareness that n-3 PUFA supplementation alters cell membrane phospholipid fatty acid composition and subsequent SPM release, an effect missed in previous studies using standard outcome measurements and now detected using multi-omics strategies (Calder 2017, Nieman et al. 2009, Ostermann & Schebb 2017).

Carbohydrates

Carbohydrate supplementation during prolonged and extensive exercise has multiple benefits for the athlete, including improved performance and reduced postexercise inflammation and metabolic perturbation.

Exercise performance and dosing regimen. Carbohydrates are the body's preferred fuel during prolonged, high-intensity exercise, and analysis of the optimal dosing regimen has dominated sports nutrition research for decades. In general, the data support that endurance athletes participating in one to three hours of exercise experience 2–6% performance improvements when ingesting 20 to 80 g per hour of a sugar mixture, including fructose, glucose, and sucrose (Baker & Jeukendrup 2014, Cermak & van Loon 2013, Vandenbogaerde & Hopkins 2011). Studies indicate that sugar intake during exercise can come from a variety of products that are equally efficacious, including 6–8% sugar-based beverages, solid gels, and fruits such as bananas, pears, grapes and grape juice, raisins, and watermelon (Rietschier et al. 2011, Shanely et al. 2016, Toscano et al. 2015). Fruits contain a wide variety of biologically active phytochemicals, and increasing attention is being devoted to exploring potential added advantages for the athlete during demanding training regimens (see section titled Polyphenols below).

Anti-inflammatory influence. An unexpected finding during the 1990s was that acute carbohydrate ingestion during exercise was associated with lower postexercise plasma stress hormone levels and inflammation (MacLaren et al. 1994; Mitchell et al. 1998; Nehlsen-Cannarella et al. 1997; Nieman 1998; Nieman et al. 1997, 1998). As summarized in **Figure 8**, a consistent finding is that carbohydrate intake during prolonged and intense exercise, whether from a 6% sugar beverage or bananas (with water), is associated with higher plasma glucose levels, diminished epinephrine and cortisol, and reduced inflammation as measured by a variety of biomarkers, including blood neutrophil and monocyte cell counts, cytokines such as IL-6, IL-1ra, and IL-10, and granulocyte

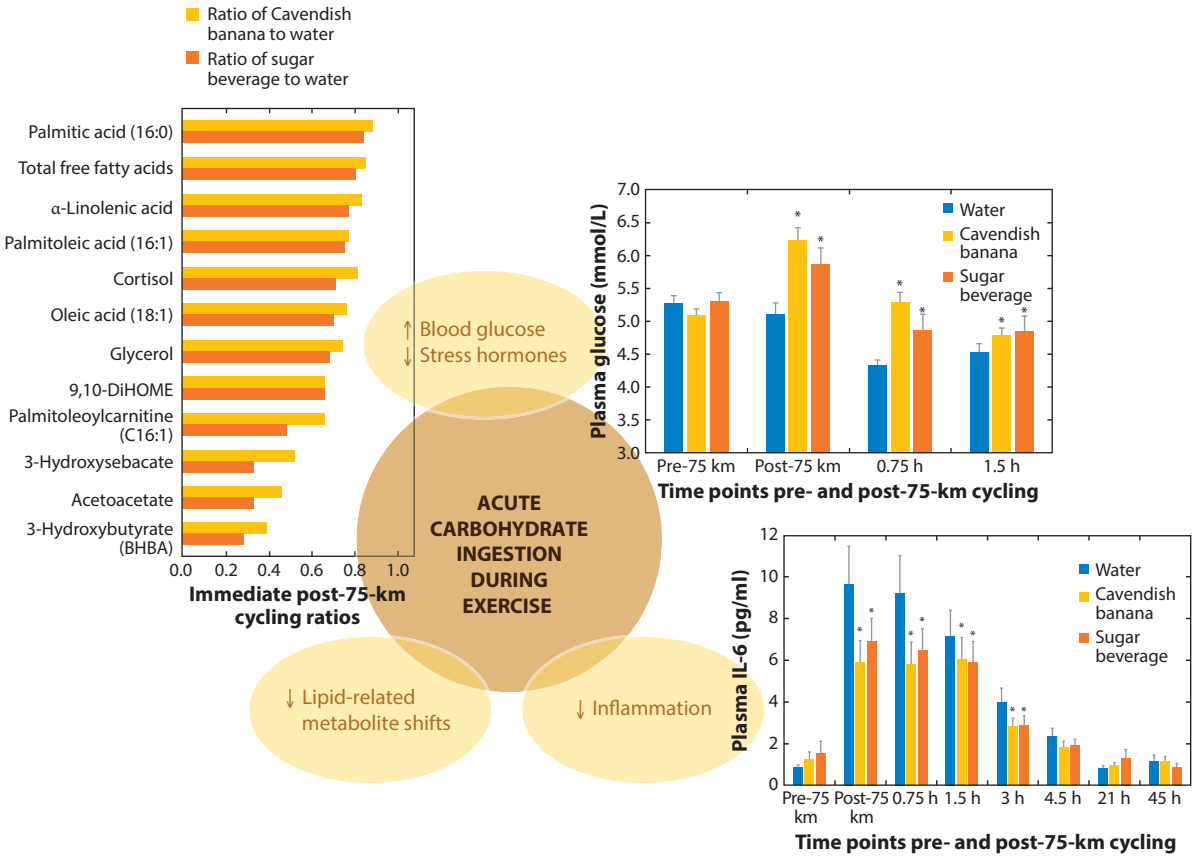

Figure 8

Acute carbohydrate (either a 6% sugar beverage or banana fruit) compared to water ingestion during prolonged and intensive exercise is associated with elevated blood glucose levels, decreased plasma cortisol and epinephrine, decreased levels of multiple inflammation biomarkers, and a 25% to 75% reduction in postexercise plasma levels of lipid-related metabolites. Abbreviation: DiHOME, dihydroxy-9Z-octadecenoic acid. Data in graphs from Nieman et al. (2018a).

phagocytosis (Davison et al. 2016; Nieman et al. 2003, 2015a, 2018a). Stressful exercise causes a transient decrease in lymphocyte proliferative responses, natural killer cell lytic activity, neutrophil oxidative burst activity, and other immune cell function outcomes, but acute carbohydrate intake does not appear to act as an effective countermeasure for these biomarkers (Davison et al. 2016, Mitchell et al. 1998, Nieman et al. 1997).

Multiple potential mechanisms underlie the significant carbohydrate anti-inflammatory influences during heavy exertion (Nieman & Mitmesser 2017). Acute carbohydrate intake during glycogen-depleting exercise results in higher blood glucose levels; decreased hypothalamic-pituitary-adrenal activation; reduced release of adrenocorticotrophic hormone, cortisol, epinephrine, and growth hormone; reduced cytokine mRNA expression and cytokine release from the working muscle tissue; and markedly lower blood concentrations of phagocytic cells, including neutrophils and monocytes (Hennigar et al. 2017; Nieman 1998; Nieman et al. 1997, 1998, 2003, 2006, 2015a,b).

The first metabolomics-based study to measure the potential influence of carbohydrate ingestion on exercise-induced shifts in metabolites was published by Chorell et al. (2009). Although the

number of metabolites identified was low compared to more recent investigations, the data showed that carbohydrate ingestion was linked to reduced levels of fatty acids and increased sugars, amino acids, and insulin in 24 males exercising intensely for 90 minutes. As depicted in **Figure 8**, more recent studies using sensitive mass spectrometry platforms show that acute carbohydrate intake from sugar beverages or bananas compared to water intake results in an extensive reduction in postexercise shifts in numerous lipid superpathway metabolites, including ketones, glycerol, long-chain fatty acids, and oxidized linoleic acid derivatives such as 9,10-DiHOME and 9+13-HODE (Nieman et al. 2015a, 2018a).

Additional studies are being conducted to determine whether carbohydrate intake during exercise counters other n-6 and n-3 PUFA oxylipins, a likely finding given their important immune and inflammation regulatory roles. One potential mechanism for the influence of carbohydrate intake on lipid-related metabolites during exercise is the associated increase in insulin that inhibits tissue triacylglycerol lipase, hormone sensitive lipase, and phospholipase A_2, thus reducing triacylglycerol breakdown and the release of free fatty acids into circulation (Lin et al. 2016, Spriet 2014). Prolonged exercise increases phospholipase A_2 activity in muscle tissue, and the potential countermeasure influence of acute carbohydrate ingestion through related increases in insulin should result in a reduced release of n-6 PUFA inflammatory lipid mediators. Accordingly, studies are ongoing in our laboratories to determine whether carbohydrate intake during exercise attenuates the increase of inflammation-related proteins, a likely outcome because of the well-established lowering effect on inflammatory cytokines (**Figure 8**) (Nieman & Mitmesser 2017).

Immunonutrition support and training adaptation signaling. Carbohydrate intake before, during, and after exercise has multiple benefits for the athlete, including enhanced performance, improved mood state, moderated inflammation, reduced lipid metabolite perturbation, and improved postexercise glycogen repletion (Cermak & van Loon 2013; McCartney et al. 2018; Nieman et al. 2015a, 2018a; Welsh et al. 2002). Concerns, however, have been expressed that acute carbohydrate intake during intensive and prolonged exercise may interfere with signaling pathways for training adaptations (Akerstrom et al. 2009, Bartlett et al. 2015, Hawley & Morton 2014, Impey et al. 2018). Exercising with reduced carbohydrate availability is physiologically stressful and associated with widespread gene expression, cell signaling, inflammation, immune system activation, and elevated oxylipin production. Although this has been hypothesized to be conducive to improved training adaptations, most studies have not been able to link the strategy of "training carbohydrate low" to improved exercise performance (Impey et al. 2018). Counterarguments include the importance of training specificity (train with high carbohydrate to simulate competition) and that sufficient signaling for muscle adaptations still takes place (carbohydrate does not completely counter physiological stress, just attenuates the magnitude) (Nieman & Mitmesser 2017).

Polyphenols

Phytochemicals, including phenolics (polyphenols), alkaloids, nitrogen-containing compounds, organosulfur compounds, phytosterols, and carotenoids, are non-nutritional bioactive compounds found in fruits, vegetables, nuts, grains, and seeds and can be classified according to their chemical structure (Zhang et al. 2015). Nearly half of the polyphenols are flavonoids, and these are further divided into flavan-3-ols, flavanones, flavones, isoflavones, flavonols, anthocyanins, and proanthocyanidins (Balentine et al. 2015).

Polyphenols have attracted much attention due to their bioactivity and related health benefits, and comprehensive databases are now available through the USDA (Bhagwat et al. 2014) and Phenol-Explorer (Rothwell et al. 2013). Phenol-Explorer contains values for 500 different

polyphenols in more than 400 foods, includes comprehensive data on polyphenol metabolism, and provides data on the effects of food processing and cooking (**www.phenol-explorer.eu**). Studies using these databases support a robust relationship between high dietary polyphenol intake and reduced risks for overall mortality and several chronic diseases, acute respiratory illness, inflammation, and oxidative stress (Cassidy et al. 2015; Cialdella-Kam et al. 2016, 2017; Ivey et al. 2015; Somerville et al. 2016; Wang et al. 2014).

These findings have led to a surge of research activity evaluating polyphenols as potential countermeasures to the physiological stress induced by heavy exertion (for reviews, see Bermon et al. 2017, Myburgh 2014, Nieman & Mitmesser 2017). Many of the earlier studies reported few discernable benefits of increased polyphenol intake for athletes, but research design deficiencies portrayed a misunderstanding of polyphenol bioavailability and metabolism, the appropriate outcome measures, and the most effective dosing protocols with a misplaced emphasis on a "pharma" approach and the use of large doses of flavonoid aglycones (Konrad et al. 2011). More recent exercise-based studies are focused on increased intake of plant extracts and fruit, with the complex and pleiotropic physiological outcomes captured using multi-omics approaches and ex vivo cell cultures with postsupplementation blood samples (Ahmed et al. 2014; Nieman et al. 2015a, 2018a).

Polyphenol bioavailability and immune bioactivity. Polyphenol absorption, disposition, metabolism, and excretion (ADME) are complex and require both untargeted and targeted metabolomics procedures to measure small-molecule shifts in humans following increased intake (Czank et al. 2013, Kay 2015, Kay et al. 2017, Lila et al. 2016, Nieman et al. 2017a). Nearly all ingested polyphenols pass through the small intestine unabsorbed and reach the colon where bacterial degradation produces smaller phenolics that can be reabsorbed into circulation after undergoing phase 2 conjugation in the liver. The gut-derived phenolics circulate throughout the body, exerting a variety of bioactive effects that are best captured using ex vivo cell cultures with human serum samples that contain the biotransformed phenolics (Kay et al. 2017). These types of studies support a variety of biological activities important to athletes including anti-inflammatory, antiviral, antioxidative, and immune cell signaling effects (Ahmed et al. 2014, Amin et al. 2015, di Gesso et al. 2015, Edwards et al. 2015, Kay 2015, Warner et al. 2017). As summarized in **Figure 9**, one study showed that ingestion of a high polyphenol supplement from blueberries and green tea compared to placebo during a three-day period of intense exercise training was associated with increased postexercise translocation of gut-derived phenolics (e.g., hippurate, 2-, 3-, and 4-hydroxyhippurate) into the circulatory system, an adaptive mechanism that may support other endogenous anti-inflammatory, antioxidative, and immune defense systems in the athlete during the recovery process (Nieman et al. 2013a). In this same study, the serum of runners who ingested the high polyphenol supplement significantly attenuated the postexercise increase in virus replication, supporting the role of gut-derived phenolics derived from blueberries and green tea in protecting athletes from virus infections when they are most susceptible (**Figure 9**) (Ahmed et al. 2014).

Several studies comparing acute ingestion of bananas (Cavendish or mini-yellow) with intake of a 6% sugar beverage or water during prolonged and intensive cycling have shown large increases in at least 18 banana-related metabolites (Nieman et al. 2012, 2015a, 2018a). As emphasized earlier in this review, carbohydrate intake in these studies, whether from the bananas or a 6% sugar beverage, strongly attenuated increases in multiple measures of postexercise inflammation, reduced increases in cortisol and most lipid-related metabolites, and countered impairment in monocyte function (**Figures 3** and **8**). In the most recent study of this series (Nieman et al. 2018a), an important objective was to determine whether increases in plasma levels of banana-related

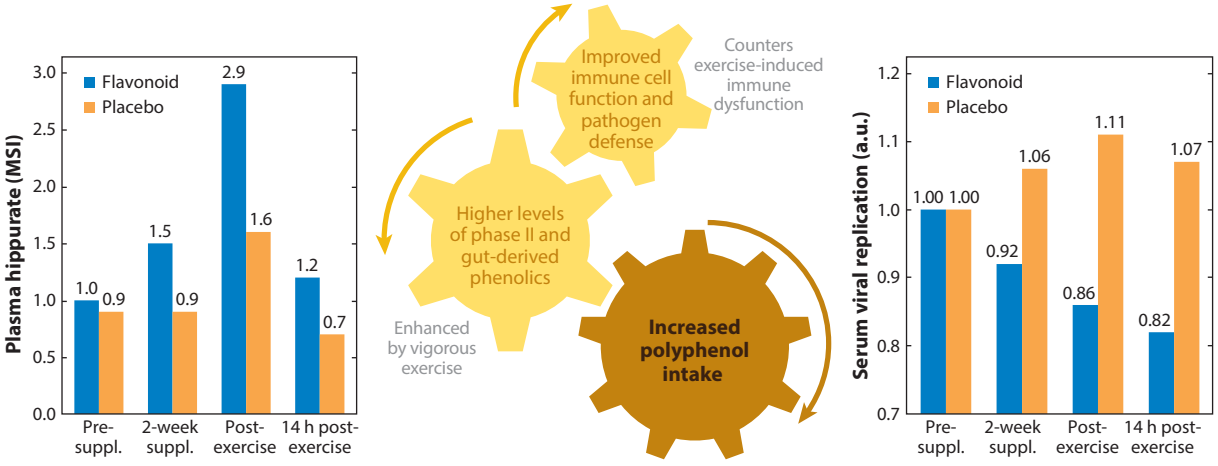

Figure 9

Increased polyphenol intake leads to higher levels of circulating phase II and gut-derived phenolics (a translocation augmented by vigorous exercise) and improved immune cell function and pathogen defense. Although data are limited, the net effect is a better buffer against exercise-induced immune dysfunction following heavy training. Data from Nieman et al. (2013a) and Ahmed et al. (2014).

metabolites following banana ingestion conferred any metabolic advantage during two days of recovery after cycling 75 km beyond those linked to carbohydrate intake.

Banana flesh contains many unique molecules, including serotonin and dopamine, and soon after ingestion, plasma levels of many related metabolites increase, including sulfated dopamines and related tyrosine metabolites, serotonin breakdown products, and related tryptophan metabolites, xenobiotics (e.g., 2-isopropylmalate), sulfated phenolics, and urea cycle metabolites (**Table 2**). Increases in these metabolites had a significant effect on the metabolome of the cyclists, and OPLS-DA (orthogonal partial least squares–discriminant analysis) of immediate postexercise metabolite shifts showed a significant separation of Cavendish and mini-yellow banana trials from both the water-only and sugar-beverage trials (Nieman et al. 2018a). COX-2 mRNA expression increased strongly following the intensive exercise bout as shown by others (Trappe & Liu 2013) and helps convert arachidonic acid to prostaglandins that exert proinflammatory effects. Using an ex vivo assay, COX-2 mRNA expression in THP-1 monocytes was lower when cultured in plasma samples collected 21 h postexercise from both banana trials compared to the water-only or the sugar-beverage trials (Nieman et al. 2018a). These data suggest that banana flesh metabolites that increase in human circulation following ingestion may confer anti-inflammatory effects within monocyte cells, as evidenced by reduced COX-2 mRNA expression the morning following heavy exertion. Thus, within an exercise context, banana metabolites may function similar to aspirin or ibuprofen, which inhibits COX-2 activity.

SUMMARY

The role of food and diet-based support in improving the rate of immune and metabolic recovery from intensive and prolonged exercise is receiving much attention from investigators. The primary and most effective diet-based strategy to attenuate exercise-induced metabolic perturbation and inflammation is acute carbohydrate ingestion from either sugar beverages or fruits such as bananas. Fruit ingestion provides more than sugars, however, and recent evidence using multi-omics and ex vivo cell culture approaches support that fruit metabolites and gut-derived phenolics

Table 2 Pre- to postexercise (75-km cycling) increases in plasma metabolites related to Cavendish and mini-yellow banana compared to 6% carbohydrate ingestion (0.8 g/kg each hour of exercise)

Plasma metabolite related to acute banana ingestion during 75-km cycling[a]	Cavendish banana, fold increase	Mini-yellow banana, fold increase
2-Isopropylmalate	166.25	39.55
Dopamine 4-sulfate	38.76	39.75
2,3-Dihydroxyisovalerate	36.65	3.44
S-Methylmethionine	35.81	5.46
Eugenol sulfate	26.60	8.01
Dopamine 3-*O*-sulfate	19.95	23.14
5-Hydroxyindoleacetate	17.47	64.32
Ferulic acid 4-sulfate	13.45	15.45
2-Oxoarginine	7.78	10.12
Tyramine *O*-sulfate	7.41	13.34
Hydantoin-5-propionic acid	6.14	5.09
Vanillic alcohol sulfate	5.58	10.40
4-Imidazoleacetate	5.31	1.79
4-Acetylphenol sulfate	4.49	29.54
3-Methoxytyramine sulfate	3.60	3.35
Caffeic acid sulfate	2.93	6.58
Pyridoxate	2.79	1.92
Trigonelline (*N*′-methylnicotinate)	2.75	2.78

[a]Data from Nieman et al. (2018a).

exert anti-inflammatory and antiviral effects. At the same time, fruit ingestion by athletes is recommended for the promotion of long-term health benefits such as lowered odds of URTI and incidence of chronic disease. Taken together, emerging evidence supports the combined intake of sugars and phytochemicals from fruits such as bananas and blueberries by athletes during heavy exertion as an efficacious strategy to improve metabolic recovery and counter postexercise inflammation and immune dysfunction at the cell level. Whole-system, metabolomics, lipidomics, and proteomics methodologies have given investigators new outcome targets to assess the efficacy of various dietary interventions (Cassidy & Minihane 2017), and in the near future should reveal optimal dosing regimens for physiologically stressed athletes.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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