Is the GI System Built For Exercise?

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The gut usually meets the fluid, electrolyte, and nutrient requirements of mild to heavy exercise. Gastric emptying and intestinal absorption rates of beverages ingested during exercise equal sweat rates. However, strenuous or prolonged exercise under dehydrated conditions can produce gastrointestinal distress and tissue damage.

Prolonged exercise, especially when performed in the heat, can result in hypovolemia, hyperthermia, hyponatremia, hypotension, and thermal injury. Only recently has the importance of the gastrointestinal (GI) system been revealed in attenuating these responses by meeting the demands of fluid, electrolyte, and nutrient provision during exercise. On the other hand, the GI system has been shown to precipitate circulatory impairment and the circumstances leading to GI and thermal injuries secondary to splanchnic ischemia and gut-barrier dysfunction. A further complication of prolonged exercise is the use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) to relieve pain. These drugs are associated with colonic bleeding, gastritis, ulcers, and diarrhea.

In 1959, Stickney and Van Liere (15) concluded from their review of the literature that mild to moderate exercise does not alter normal digestive function. On the other hand, in 1993, Brouns and Beckers (1) concluded from their review of the literature that the gut was not an "athletic organ" on the basis of the large number of competitors suffering from GI symptoms and the death of one athlete from GI complications. This review provides evidence to support both viewpoints. The gut can meet the demands of prolonged severe exercise and can even show signs of adaptation to exercise training but can also signal conditions of impending injury.

During severe exercise, splanchnic blood flow is markedly reduced and intestinal permeability can increase. When severe exercise is performed in the heat, splanchnic blood flow may further decline, gastric emptying and intestinal absorption reportedly decrease, cutaneous blood flow is reduced, and sweating rate decreases. When exercise in the heat is accompanied by dehydration (>3.0% body weight), circulatory and thermal functions are further impaired and the gut may be subjected to the combined effects of ischemia, hypoxia, and hyperthermia. Under these conditions, gut-barrier function may be compromised, leading to tissue necrosis, endotoxemia, and circulatory impairment. What is the evidence that the gut is built for exercise?

Gastroesophageal function

Soffer et al. (14) studied esophageal motility and gastroesophageal reflux in eight trained cyclists exercising at 60%, 75%, and 90% of their maximum aerobic capacity (V_{O_2} max)

for 60, 45, and 10 min, respectively. Duration, amplitude, and frequency of esophageal contractions decreased with increasing exercise intensity ($P < 0.05$) for all three variables at 90% V_{O_2} max. The number of gastroesophageal reflux episodes and the duration of esophageal acid exposure (pH < 4) significantly increased at 90% V_{O_2} max. However, there were no GI symptoms during any of the exercise sessions. The lack of GI symptoms in these athletes may be attributed to their training status and to the mode of exercise. Running produces more reflux and belching than other modes of exercise. The observation that there were no significant alterations in esophageal motility and gastroesophageal reflux during 45 min of exercise at 75% V_{O_2} max and no GI symptoms, even at 90% V_{O_2} max, when reflux and acidity were present indicated that the upper digestive tract functions normally during most frequently encountered exercise intensities.

To meet the fluid and nutrient needs of exercise, orally ingested beverages must first be emptied from the stomach. Gastric emptying follows an exponential time course that shows marked interindividual differences. The primary determinants of gastric emptying are gastric volume and the caloric content of the fluid ingested. The larger the volume of fluid ingested, the greater the gastric emptying rate. The higher the glucose content, the slower the emptying rate. When subjects initially ingest a relatively large volume of fluid (~500 ml), gastric volume declines rapidly. Repeat drinking of ~200 ml of fluid every 10–15 min helps to maintain a high gastric volume and therefore a high gastric emptying rate; however, the addition of glucose to the solution significantly reduces gastric emptying.

Can the stomach empty a sufficient amount of fluid and carbohydrate (CHO) to match sweat rate and to achieve the maximal exogenous CHO oxidation rate, respectively? Mean sweat rate of endurance athletes ranges from 1.5 to 2.0 l/h, although the sweat rate of some athletes can exceed 4.0 l/h. The maximum oxidation rate of exogenous CHO is 1.0 g/min. Figure 1A shows that the mean gastric emptying rate from repeat drinking of water and 6% and 10% glucose solutions was 2.4, 1.8, and 1.5 l/h, respectively. On the basis of these emptying rates, CHO delivery from just the 6% glucose solution was 108 g/h (1.8 g/min), which far exceeds the maximum oxidation rate of exogenous CHO. Thus gastric emptying should not be considered a limiting factor in maintaining hydration during exercise or providing adequate delivery of CHO. However, because the rates of sweating and gastric emptying are highly variable between individuals, some athletes will be unable to achieve euhydration during exercise.

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Mild to moderate exercise (25–75% V_{O_2} max) either enhances or does not affect gastric emptying. Only when exercise intensity exceeds 80% V_{O_2} max is gastric emptying delayed. Even fatiguing exercise lasting 2 h or 90 min of exercise superimposed on a state of dehydration by 3% of body weight does not reduce gastric emptying (6). However, exercise in the heat and dehydration ≥4.0% body weight significantly reduce gastric emptying.

Intestinal absorption

Even if the stomach can empty sufficient fluid and nutrient to keep pace with the loss of fluid in sweat and with CHO oxidation, respectively, can the small intestine absorb this fluid and nutrient at the same rate at which they are delivered by the stomach?

In a landmark investigation, Fordtran and Saltin (5) found no consistent effect of exercise at 64–78% V_{O_2} max on glucose, water, electrolyte, or urea transport. They concluded that exercise had no consistent effect on carrier-mediated or passive absorption, nor was intestinal permeability altered based on the diffusion ratio of passively absorbed solutes. This study tested five different solutions but only in one or two subjects; nevertheless, the conclusions regarding intestinal absorption were confirmed by Gisolfi et al. (7). The latter investigators determined the effects of 1-h bouts of cycle ergometer exercise at 30%, 50%, and 70% V_{O_2} max while perfusing the duodenojejunum of six trained cyclists with water. They found no significant difference in fluid absorption during rest, exercise, or recovery periods, and there were no significant differences among absorption rates for the three exercise intensities (Fig. 1B).

The addition of CHO to an electrolyte solution can increase water absorption sixfold. Moreover, when the intestine is perfused with water or a glucose-electrolyte solution at a rate that exceeds the gastric emptying rate by 70–100%, absorption is not reduced. Active absorption has been shown to significantly decline as measured by 3-O-methyl glucose, but these experiments were performed in the heat (38°C) and could be the result of combined exercise and heat stress. Thus it is unlikely that intestinal absorption serves as a limiting factor in fluid or nutrient provision during mild to heavy exercise (30–80% V_{O_2} max) lasting as long as 60–90 min.

Signs of GI adaptation

Hyperphagia in response to increased energy demands causes small bowel adaptations in several animal species. Confronted with the need to process more food quickly, small intestinal transit and absorptive capacity are both increased. Highly trained endurance athletes consume up to four times more calories than their sedentary counterparts, an amount that exceeds most animal models of intestinal adaptation to hyperphagia. Can the human GI system adapt to chronic exercise? Evidence below indicates that endurance training can increase gastric emptying rate and can increase GI transit without a decrement in absorptive capacity. Furthermore, endurance-trained animals provide evidence of improved gut-barrier function.
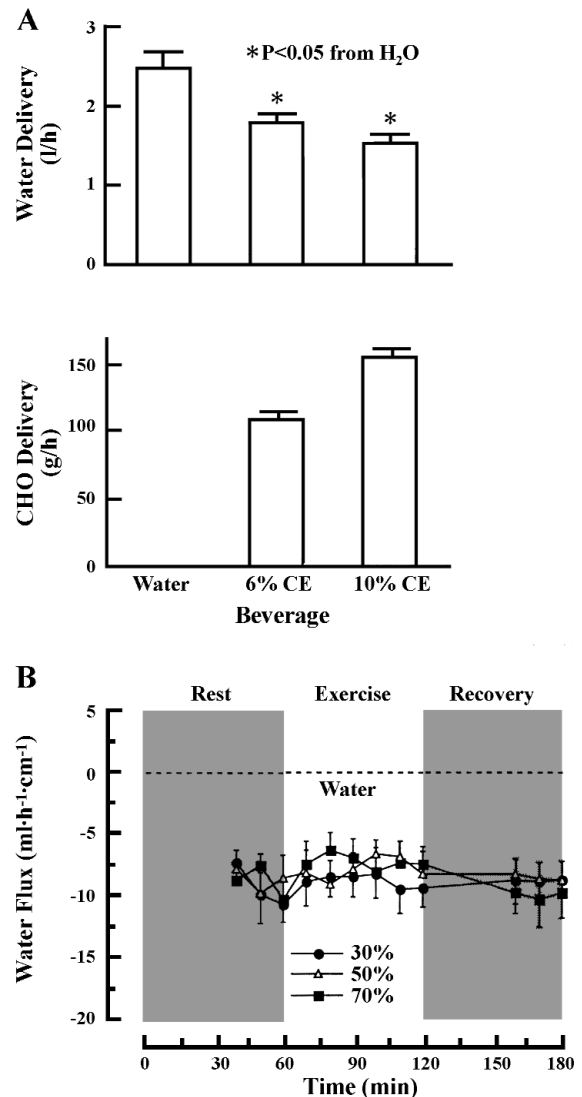

FIGURE 1. A: mean values for gastric emptying and glucose delivery per hour for water and 6% and 10% carbohydrate (CHO)-electrolyte (CE) solutions. Initially, 750 ml of each solution was passed into stomach via nasogastric tube followed by repeat infusions of 180 ml every 7 min for water and every 10 min for CE solutions. CHO in these solutions was glucose. [Data taken from Duchman et al. (3)]. B: net water flux (means ± SE) during duodenojejunal perfusion of water at rest, during 60 min of exercise at 30%, 50%, and 70% V_{O_2} max, and during 60 min of recovery. Infusion began at time 0. Negative values indicate absorption. [Data from Gisolfi et al. (7)].

Endurance runners (2–7 yr of training and 171 ± 12 min marathon time) show a significantly accelerated basal gastric emptying rate using Technetium 99-labeled serum albumin as a test meal (2). The mean percentage of the solid component of the test meal retained in the stomach at rest fits a linear model, with half time for gastric emptying $(t_{1/2})$ = 67.7 ± 5.9 min for runners and 85.3 ± 4.5 min for sedentary controls $(P < 0.001)$, respectively. When the runners exercised (4.0–4.5 min/km for 90 min), the $t_{1/2}$ = 66.8 ± 4.5 min. Thus the runners emptied their stomachs significantly faster than controls both at rest and during exercise (Fig. 2A). These data provide evidence for an adaptive process of gastric motility with exercise training.
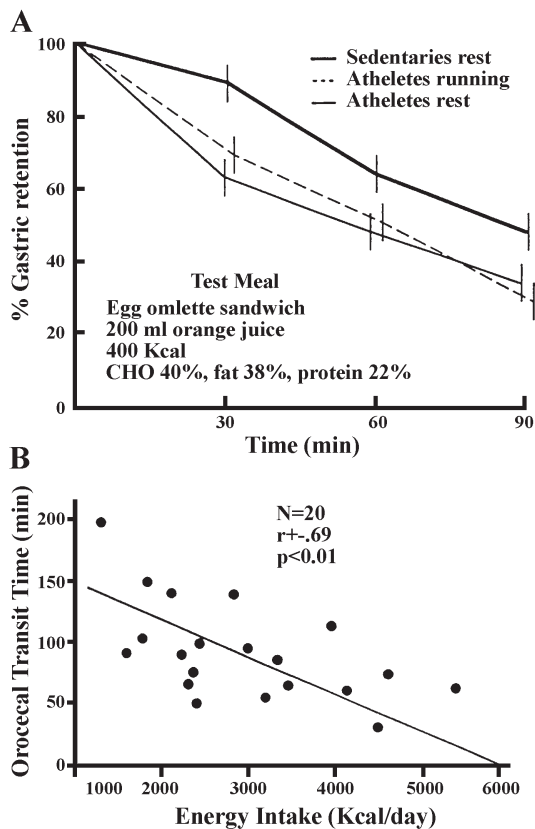
FIGURE 2. *A*: effects of endurance training on gastric emptying rate at rest and during exercise. [Data taken from Carrio et al. (2)]. *B*: orocecal transit time (OCTT) for subjects with markedly different energy intakes. Note that athletes with very high energy intakes had fastest OCTTs. [Data from Harris et al. (9)].

The stimulus for such a response may be enhanced gastric distention associated with the increased food intake that usually accompanies increased energy expenditure. In support of the latter concept is the study by Harris et al. (9). These investigators showed that orocecal transit time (OCTT, mouth-to-colon lactulose transit) was more rapid in athletes with high caloric intakes than sedentary subjects with low energy intakes (Fig. 2*B*). This enhanced OCTT occurred without a decrease in intestinal absorption, indicating that the hyperphagia of chronic exercise was associated with adaptations within the GI system. Although Harris et al. (9) drew their regression line through the *x* axis, it is unlikely that transit time goes to zero when energy intake rises to 6000 kcal/d.

In addition to these changes in gastric emptying and intestinal transit, there is also evidence of improved gut-barrier function with exercise training. It is generally well accepted that physically fit individuals have greater heat tolerance than unfit individuals. The normal circulatory response to exercise in the heat is to increase blood flow to the skin and to reduce flow to vital organs, including the liver and intestine. There is also evidence indicating that reduced mesenteric blood flow reduces intestinal barrier function and promotes endotoxin leak (4). The accumulation of endotoxin in the blood, in turn, reduces heat tolerance. Sakurada and

Hales (12) exposed physically fit and sedentary sheep to a heat stress (42°C and 35°C dry and wet bulb temperatures, respectively) following intravenous infusion of saline and indomethacin. Core temperature rose significantly higher in sedentary sheep than in trained sheep following saline infusion, demonstrating the greater heat tolerance associated with training. However, when both groups of animals were injected with indomethacin, which blocks endotoxin-induced fever, the rise in core temperature was reduced in the sedentary group to the level observed in the fit group. These results provide evidence that the difference in heat tolerance between sedentary and physically fit animals is in part attributable to endotoxin leaving the gut. The mechanism responsible for this observation is the maintenance of a greater GI blood supply during heat stress in trained animals vs. ischemia in the sedentary sheep. Thus the trained sheep maintain a more normal GI barrier to endotoxin translocation from gut lumen to plasma than sedentary sheep. Splanchnic blood flow at any given absolute workload is greater in exercise-trained than in untrained subjects. Moreover, the GI system has remarkable regenerative capacity. Epithelial cells, for example, have a life span of only 4–5 days. Even when GI bleeding occurs, it is often not observed when esophagogastroduodenoscopy and colonoscopy are performed >48 h after a competitive endurance event (13).

Colonic function

There are numerous anecdotal accounts suggesting that mild to moderate exercise benefits constipation, but it is also suggested that runner's diarrhea is of colonic origin. There is increasing evidence that acute and chronic exercise in humans and dogs reduces whole gut transit time and increases colonic motility. In a recent human study that measured colonic motility from six sites during exercise at 25–75% VO_2 max, it was concluded that colonic motility was significantly reduced by graded exercise but increased in recovery. The authors interpreted these findings to support faster colonic transit because the reduction in motility during exercise would reduce resistance to colonic flow, whereas enhanced motility in recovery would increase propulsion. If indeed colonic motility is enhanced as a result of exercise, this would provide rationale, in part, for the lower relative risk of colon cancer among individuals with high-activity occupations. Enhanced colonic transit times are also associated with lower incidences of diverticular disease and hemorrhoids.

The exercise-related diarrhea reported by numerous clinicians and investigators is associated with more prolonged bouts of exercise that frequently result in hyperthermia and dehydration. Diarrhea in runners is due either to increased transit of food through the GI tract or alterations in absorption or secretion. Because the latter are not markedly changed during exercise, Moses (11) suggests that diarrhea, abdominal cramps, gas, and the urge to defecate during or immediately after exercise are due to a direct effect of exercise on colonic function. The decrease in splanchnic blood flow during exercise is well documented, and the colon may be more

sensitive to ischemia than the small intestine because it lacks collateral circulation, especially around the splenic flexure. Loose stools frequently observed early in a training program are transformed to normal bowel movements with continued training. This point requires investigation, but indicates together with the other evidence above that the gut may adapt to the effects of chronic exercise.

GI function under conditions of severe stress

Although the GI system handles the majority of exercise well, conditions that promote ischemia, hypoxia, and hyperthermia can be detrimental. Such conditions prevail when exercise is prolonged, performed in the heat, and/or combined with dehydration. Under such conditions, a variety of GI symptoms appear, including bloating, nausea, vomiting, diarrhea, and intestinal bleeding (1). Although any one of these stresses (exercise, heat, dehydration, NSAIDs), if severe, can produce tissue damage, it is usually the combination of two or more that initially produce GI symptoms and gut-barrier dysfunction. Evidence that exercise can impair gut-barrier function includes studies that show GI bleeding, endoscopic observations of mucosal lesions including hemorrhagic gastritis and ischemic colitis, increased intestinal permeability, and the development of systemic endotoxemia.

An increase in gut permeability may be an important link to gut-barrier impairment (Fig. 3). The hypothesis proposes that exercise stress produces biochemical changes that uncouple oxidative phosphorylation, reducing ATP production and increasing Ca^{2+} efflux from mitochondria and endoplasmic reticulum. These events lead to increased cytosolic Ca^{2+} concentration, the generation of reactive oxygen species, and loss of tight junction control, producing increased intestinal permeability. The increase in intestinal
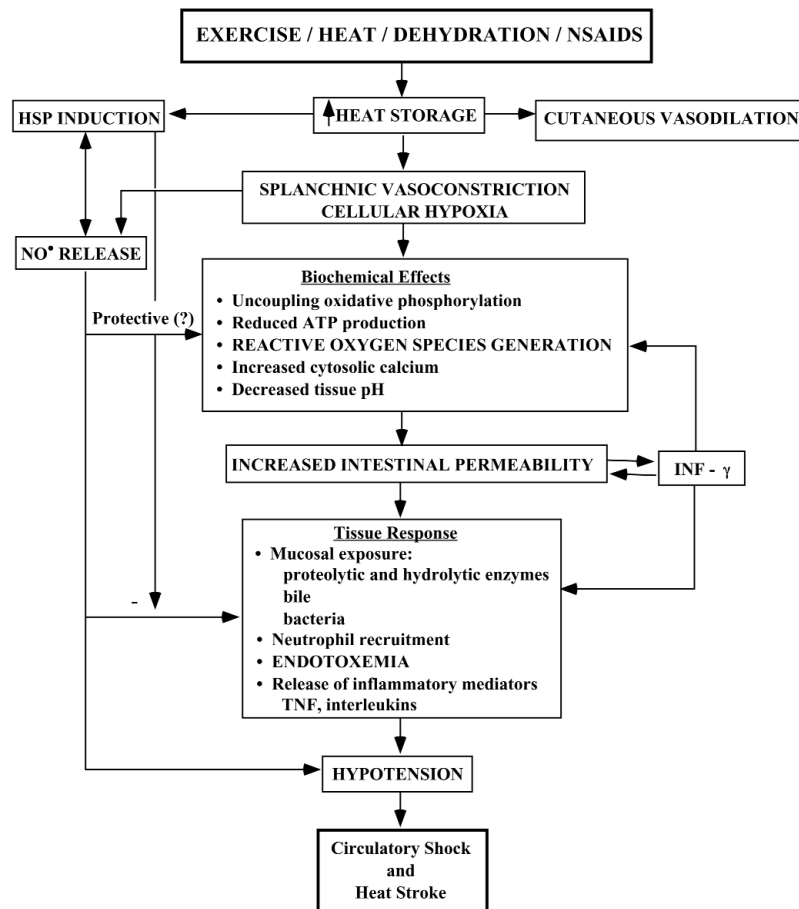

FIGURE 3. Schematic diagram illustrating proposed mechanisms of gut-barrier impairment produced by exercise and related stresses leading to circulatory and thermal injury. Factors for which experimental evidence exists are capitalized. Exercise, especially when performed in heat under dehydrated conditions, increases heat storage and core body temperature. Rise in core body temperature produces cutaneous vasodilation. Splanchnic vasoconstriction occurs, making more blood available to exercising muscle and skin; however, with prolonged exercise in heat, and if coupled with dehydration and perhaps nonsteroidal anti-inflammatory drug (NSAID) use, splanchnic ischemia, cellular hypoxia, and nitric oxide (NO•) induction combine to produce biochemical effects that can lead to increased intestinal permeability. This increased permeability leads to secretion of interferon-γ (INF-γ), which further reduces gut-barrier function and exacerbates biochemical and tissue responses. Constitutive NO• may protect gut-barrier function by inhibiting inflammatory cells or by scavenging cytotoxic superoxide anion. However, when massive amounts of NO• are produced by activation of inducible NO•, gut-barrier function is further compromised, leading to endotoxin leak, production of inflammatory mediators, hypotension, and circulatory shock/heat stroke. Heat shock protein (HSP) production in response to high core body temperature can attenuate effects of NO•. TNF, tumor necrosis factor.
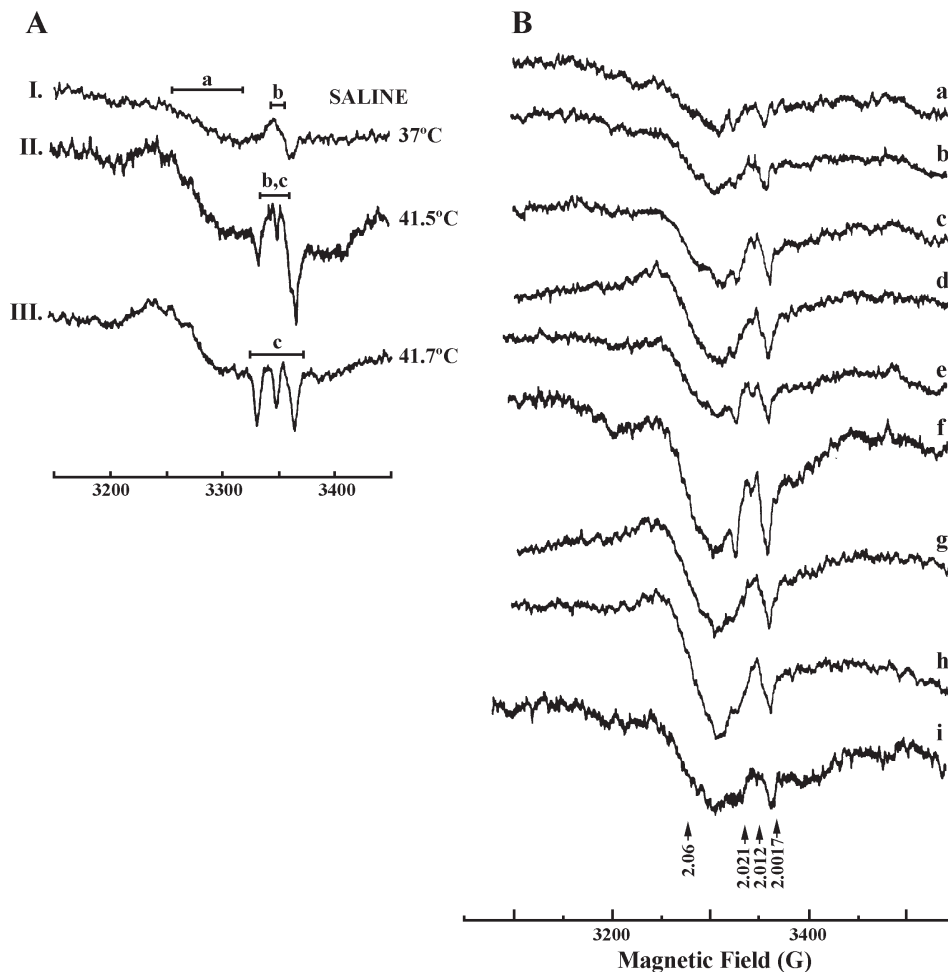
FIGURE 4. *A*: electron paramagnetic resonance (EPR) spectra for saline (I), and portal venous blood samples collected from heat-stressed rats with core temperatures of 41.5°C (II) and 41.7°C (III), respectively. See text for description of ceruloplasmin, semiquinone, and hemoglobin-NO$^\bullet$ (HbNO$^\bullet$) radicals. *B*: EPR spectra recorded from portal venous blood obtained from rats subjected to passive heating. Samples were collected at colonic temperatures of ~37°, 39°, 40°, 41°, and 41.5°C (*a–e*, respectively) or 1, 2, and 24 h after heat exposure (*f–h*, respectively). Trace *i* represents femoral areterial blood collected 1 h after heat stress. EPR conditions were receiver gain 5.00 × 10^5, modulation frequency 100 kHz, modulation amplitude 4.0 G, microwave frequency 9.43 GHz, microwave power 10 mW, and scan rate 6.2 G/s. [Data from Hall et al. (8)].

permeability is proposed as the central mechanism in the transition from the biochemical to the tissue reaction changes shown. When the tight junctions open, their maximal channel size is too small to permit passage of endotoxin but will allow passage of luminal contents that are chemotactic for neutrophils. These agents (dietary antigens, chemotactic oligopeptides) stimulate intraepithelial lymphocytes to secrete interferon-γ. These lymphocytes are wedged between epithelial cells beneath the tight junctions. Interferon-γ opens tight junctions and activates macrophages and neutrophils to release oxygen radicals and immunosuppressive peptides (10). Thus increasing intestinal permeability by opening tight junctions can initiate immunologic and inflammatory events that can alter gut structure and function. With the use of the urinary excretion of CHO probes as a measure of intestinal permeability, prolonged exercise (triathlon competition), exercise at 80% $\dot{V}O_2$ max, and exercise at 60–65% $\dot{V}O_2$ max combined with aspirin ingestion significantly increase intestinal permeability.

The mechanism responsible for GI dysfunction and damage is hypothesized to be the generation of reactive oxygen species (ROS) and the release of nitric oxide (NO$^\bullet$). We have provided evidence that circulatory dysfunction with heat stroke may be triggered by splanchnic vasodilation, which is not the result of a decrease in sympathetic nerve activity, a reduction in circulating catecholamines, or a direct effect on the vascular contractile machinery. These data suggest that this dilation is mediated locally. Evidence that NO$^\bullet$ may participate in splanchnic vasodilation and overall circulatory impairment comes from data in the hyperthermic rat. Figure 4 shows electron paramagnetic resonance tracings of portal venous blood collected from hyperthermic rats as colonic temperature rose from 39°C to 42°C. The tracings show ceruloplasmin, semiquinone radical, and hemoglobin-NO$^\bullet$ (HbNO$^\bullet$), all of which can be stimulated by cellular hypoxia (Fig. 4*A*). Ceruloplasmin is a copper-binding acute-phase protein with potent antioxidant actions. Semiquinone radical is a biomarker of mitochondrial

oxidative stress. Vascular HbNO• is used extensively as an index of altered NO• production. Ceruloplasmin increased 20% in signal intensity at a core temperature of 39°C, then almost doubled 1 h after heat stress and remained elevated at 24 h (Fig. 4B). The semiquinone and HbNO• spectra also increased with increasing core temperature, but these two spectra overlapped, making the semiquinone radical difficult to assess. These data provide evidence that heat stress results in increased concentrations of metal-binding proteins (ceruloplasmin) and semiquinone radicals in the splanchnic circulation. Moreover, hyperthermia markedly increased the concentration of NO• complexed with heme in portal venous blood. Because HbNO• did not appear in arterial blood (Fig. 4B), this suggests that the enhanced release of NO• within the splanchnic circulation preceded splanchnic vasodilation, thus contributing to local vascular dysfunction in the heat-stressed rat.

Summary

In summary, the GI tract readily meets the fluid and nutrient requirements of mild to moderately severe exercise. Gastric emptying rate can keep pace with sweating rate up to 2.0 l/h, and intestinal absorption of CHO-electrolyte beverages, in the concentration range of most sport drinks, can even exceed the rate of gastric emptying. Moreover, the increased energy requirements of chronic exercise training can increase GI functional capacity, providing evidence that this system can adapt. Thus it is concluded that for the vast majority of situations requiring even heavy (70–80% V_{O_2} max) and prolonged (1-2 h) work, the GI system is built for exercise. The capacity to perform this amount of exercise, without detrimental effects, also includes the colon. Chronic exercise is associated with clinical benefits to the colon, which may also show signs of trainability.

On the other hand, when heavy exercise becomes prolonged, performed in the heat, and the overall stress is exacerbated by dehydration, GI symptoms emerge, gut-barrier function can become impaired, and tissue damage, including necrosis, can occur. These conditions produce ischemia, hypoxia, and hyperthermia, which, in turn, can result in the generation of ROS. The consequences of accumulating ROS together with large quantities of NO• are increased GI permeability, endotoxemia, cytokine release, and circulatory impairment.

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