A toast to health and performance! Beetroot juice lowers blood pressure and the O_2 cost of exercise

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Invited Editorial

A toast to health and performance! Beetroot juice lowers blood pressure and the O_2 cost of exercise

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THE PIONEERING WORK OF SCIENTISTS such as A. V. Hill (7) and August Krogh (10), investigating the dynamics of O_2 uptake during exercise, challenged our understanding of bioenergetics and energy homeostasis. Applied physiologists continue to advance our knowledge of altered energy transfer and efficiency during exercise, as exemplified by the work of Lansley and colleagues (11) in this issue of the *Journal of Applied Physiology*.

Lansley and colleagues (11) demonstrate that dietary NO_3^-, administered in the form of beetroot juice (500 ml/day for 6 days), decreases resting systolic blood pressure (SBP) and O_2 consumption during walking and running. This study is part of a series of investigations, led by Prof. Jones, demonstrating the effects of beetroot juice on cardiovascular and metabolic responses to exercise (1, 2, 15). So what is novel? In this double-blind, placebo-controlled study, the authors selectively remove NO_3^- from beetroot juice to produce a NO_3^--free juice as placebo. There was no placebo effect in any of the variables measured. Thus the decrease in O_2 uptake and SBP in their investigations can be assigned to dietary NO_3^-, rather than other compounds present in beetroot juice (e.g., polyphenols and/or quercetin). Moreover, the responses occurred in the absence of changes in phosphocreatine (PCr) recovery kinetics (estimate of mitochondrial oxidative capacity). Lastly, the effects of dietary NO_3^- occurred within 2.5 h and promoted an increase in exercise tolerance (11). Whether dietary inorganic NO_3^- is given as beetroot juice (1, 2, 11) or pharmacologically (12), the responses are seemingly consistent across different exercise modalities, although the precise mechanisms remain unclear.

The effects of dietary NO_3^- are thought to be mediated via reduction to biologically active NO_2^- and nitric oxide (NO) molecules (13). Within the vasculature, NO elicits vasodilation through well-known pathways, including activation of soluble guanylate cyclase and subsequent elevations of cGMP levels. Augmentation of NO bioavailability through paradigms such as dietary NO_3^- (in addition to endogenous NO production) may enhance vasodilation and/or O_2 distribution within the contracting skeletal muscle. Specifically, NO elevates the driving pressure of O_2 in the microcirculation during contractions (5), which facilitates transcapillary O_2 flux, as dictated by Fick's law. Interventions that increase the driving pressure of O_2 in the microcirculation blunt PCr breakdown during exercise and prolong exercise tolerance (6, 16). Thus, NO derived from dietary NO_3^- may improve the matching of O_2 delivery ($\dot{Q}O_2$) to O_2 uptake ($\dot{V}O_2$) in active motor units, resulting in an elevated driving pressure of O_2 in the microcirculation during exercise that contributes to diminished PCr degradation and/or enhanced exercise tolerance. This postulate remains to be explored using techniques to measure the driving pressure of O_2 in the microcirculation and $\dot{V}O_2$-to-$\dot{Q}O_2$ heterogeneity.

In skeletal muscle cells, the potential mechanisms whereby NO-stimulated signaling increases metabolic efficiency are puzzling. Intramyocyte proteins sensitive to NO signaling include those from mitochondria, sarcoplasmic reticulum (SR), and myofibrils. The available evidence briefly discussed below suggests SR Ca^{2+}-ATPase (SERCA) as the plausible site downstream of dietary NO_3^- responsible for reduced ATP cost of force production during exercise.

NO inhibits mitochondrial respiration (3). In the physiological (nanomolar) range, partial inhibition of cytochrome *c* oxidase enhances oxidative phosphorylation efficiency (3). The outcome of this process is a higher ATP-to-O_2 ratio, which could determine the decreased O_2 cost of exercise. However, total ATP turnover estimated by ^{31}P-magnetic resonance spectroscopy was decreased with dietary NO_3^- (1). These results do not rule out mitochondria but suggest that we should start our search for mechanisms elsewhere.

Myofibrillar proteins are subject to modifications triggered directly (oxidation) or indirectly (kinase/phosphatase-mediated) by NO signaling. However, we expect that effects of NO on the contractile apparatus would elicit responses opposite to those described by Lansley et al. (11). Specifically, NO decreases actomyosin ATPase activity of permeabilized single fibers, which is accompanied by decreases in force and shortening velocity (14). NO_2^- or NO donors increase SR Ca^{2+} release without effects on muscle force or power output (14). Sequestration of the additional Ca^{2+} into the SR by SERCA would raise the ATP demand of force/power generation. On the basis of these findings and the cross-bridge theory of muscular contraction (8), it is difficult to envision a mechanism for reduced ATP cost of force generation involving actin-myosin interactions.

SERCA is a potential candidate responsible for the reduced ATP cost of force production elicited by dietary NO_3^-. The stoichiometry of Ca^{2+} transport to ATP hydrolysis by SERCA is 2:1 in isolated preparations (4). However, when conditions mimic the intracellular environment, the stoichiometry ranges from 0.3 to 0.6 (4). This reflects ATP hydrolysis that is uncoupled from translocation of Ca^{2+} into the SR. One possibility is that dietary NO_3^- increases the stoichiometric efficiency of SERCA. NO decreases SERCA activity and Ca^{2+} uptake in isolated SR membrane preparations (9), but it seems that ATPase activity decreases by a greater extent than Ca^{2+} uptake. Hence, NO may increase the energetic efficiency of Ca^{2+} transport by SERCA, a hypothesis that needs to be examined in detail.

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The novel findings of Lansley et al. (11) have several clinical implications (13). A dietary therapy that lowers blood pressure and increases exercise tolerance may obviate the use of expensive drugs with potentially deleterious side effects. However, before beetroot juice can be safely used in the clinical setting, further research is necessary to address questions pertaining to the applied aspects of dietary NO_3^-, including *1*) defining the dose dependence, *2*) determining the impact on human health of prolonged supplementation, and *3*) evaluating the effects of chronic dietary supplementation on adaptations elicited by exercise training. Answers to the following research questions for basic scientists are needed to clarify the mechanisms of action of inorganic NO_3^-. *1*) Are the effects of dietary NO_3^- consistent among striated muscles or exclusive to skeletal muscles? If the myocardium responds in a similar fashion to skeletal muscle, beetroot juice will emerge as a powerful therapy for patients with angina. *2*) Does the cGMP pathway mediate the effects of inorganic NO_3^- on O_2 cost of force production? *3*) What site(s) of action and posttranslational modification(s) of proteins confer the effects of dietary NO_3^- on muscle metabolism?

Investigations such as that performed by Lansley et al. (11) certainly challenge our understanding of integrative physiology. We can be cautiously optimistic that a relatively simple approach for treating cardiovascular perturbations and exercise intolerance is within our sight.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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