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PERSPECTIVE

Chasing the hunger-suppressive signals of human exercise

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The basic principle for the development of obesity is a positive energy balance resulting from an imbalance between energy expenditure and energy intake. However, reaching this state depends, among others, on several physiological factors, such as caloric ingestion, diet composition, macronutrient absorption, hormonal profile and physical activity. Today, the most effective pharmacotherapies for obesity rely on the satiating effects of meal-induced gut hormones such as glucagon-like peptide-1 (GLP-1). Lifestyle therapies (i.e. diet and exercise) are recommended as the first-line treatment for obesity. Although chronic exercise training induces numerous positive metabolic adaptations, it is often followed by a compensatory increase in appetite and therefore is much less effective at lowering body weight and fat mass. Yet, acute exercise suppresses appetite (Hazell et al., 2016), suggesting that novel strategies for the treatment of obesity might be developed by understanding the molecular mechanisms that underlie the transient loss of appetite after exercise.

The complex relationship between physical activity and energy balance was addressed by Frampton et al. (2023) in this issue of *The Journal of Physiology*. The authors conducted a randomized crossover study in which 12 adult men performed 30 min of exercise (ergometer bicycling at 75% $\dot{V}_{O_2max}$), either in a fasted state or after ingesting a bolus of carbohydrate (75 g maltodextrin). Thereafter, participants were offered an *ad libitum* meal where the researchers assessed caloric intake, subjective feelings of appetite and nausea, and blood-borne metabolites and hormones. Using this design, Frampton and colleagues explored the effects of exercise in two different metabolic states and the effect of carbohydrate ingestion on plasma hormone/metabolite profiles and their relationship with appetite. The authors found that both carbohydrates and exercise increased the blood levels of the hunger-reducing hormone, GLP-1, while on the other hand, the circulating level of the hunger-increasing hormone, ghrelin, was diminished by both interventions. However, metabolites appeared to be more responsive to exercise than carbohydrate ingestion, producing an exercise-dependent set of hormones/metabolites with the potential to suppress appetite despite the increase in energy expenditure induced by exercise.

Over the last two decades, research has shown that metabolites not only serve as energy substrates but also actively regulate biological processes through signalling mechanisms (Baker & Rutter, 2023). Exercise leads to profound changes in the blood metabolome of humans (Morville et al., 2020) and once secreted, metabolites can modulate metabolic pathways and regulatory proteins in neighbouring cells and possibly also in distant organs (Baker & Rutter, 2023; Morville et al., 2020). Frampton et al. showed that carbohydrates and exercise suppressed appetite to the same magnitude but with a different metabolite profile. As such, increased blood levels of acetate and lactate but also peptide YY (PYY) were found to be linked with lower appetite during exercise. Although the changes in appetite did not affect energy intake at the subsequent *ad libitum* meal, the authors still found that higher blood levels of GLP-1 and succinate after exercise were linked to a lower energy intake during the post-exercise meal. This suggests that both metabolites and peptide hormones act to control appetite and possibly also eating behaviour acutely after exercise. In addition, Frampton and colleagues show that the elevated energy expenditure induced by one acute exercise bout is not sufficient to elicit compensatory changes in eating behaviour during a subsequent meal. Therefore, it is tempting to speculate that the metabolite milieu induced by exercise may play a more important appetite-regulatory role than calorie combustion at least in the acute time frame tested.

The findings in humans by Frampton and colleagues align with previously reported hypophagic and anorectic effects of lactate (Hazell et al., 2016). Yet, to determine if lactate, succinate, acetate, or other exercise-induced metabolites regulate appetite and food intake, future studies should administer such metabolites to rodents and humans in doses that mimic exercise-induced blood levels and investigate the appetite-regulatory effects. In doing so, such studies should carefully control for treatment tonicity and any co-administered counterions, if exogenous metabolite salts are used (Lund et al., 2023). In the future, it will also be interesting to explore if exercise-induced metabolites exert synergistic and/or antagonistic effects on classical appetite regulatory hormones (i.e. GLP-1, PYY, ghrelin) and how the effects of such potential interactions might differ between individuals with leanness and obesity. Computational prediction analysis associated with hormonal/metabolite profiles in different conditions as used by Frampton et al. (2023) might help to map the ideal endogenous milieu necessary to suppress appetite and provide hints at the regulatory mechanisms involved. Ultimately, such discoveries may help the development of more efficient and safer exercise-based therapeutical approaches to mitigate obesity and its associated cardiometabolic disorders.

References

Baker, S. A., & Rutter, J. (2023). Metabolites as signaling molecules. *Nature Reviews Molecular Cell Biology*, **24**(5), 355–374.

Frampton, J., Serrano-Contreras, J. I., Garcia-Perez, I., Franco-Becker, G., Penhaligan, J., Tan, A. S. Y., de Oliveira, A. C. C., Milner, A. J., Murphy, K. G., Frost, G., & Chambers, E. S. (2023). The metabolic interplay between dietary carbohydrate and exercise and its role in acute appetite-regulation in males: a randomised controlled study. *The Journal of Physiology*, **601**(16), 3461–3480.

DOI: 10.1113/JP285096

Hazell, T. J., Islam, H., Townsend, L. K., Schmale, M. S., & Copeland, J. L. (2016). Effects of exercise intensity on plasma concentrations of appetite-regulating hormones: potential mechanisms. *Appetite*, **98**, 80–88.

Lund, J., Breum, A. W., Gil, C., Falk, S., Sass, F., Isidor, M. S., Dmytriyeva, O., Ranea-Robles, P., Mathiesen, C. V., Basse, A. L., Johansen, O. S., Fadahunsi, N., Lund, C., Nicolaisen, T. S., Klein, A. B., Ma, T., Emanuelli, B., Kleinert, M., Sørensen, C. M., … Clemmensen, C. (2023). The anorectic and thermogenic effects of pharmacological lactate in male mice are confounded by treatment osmolarity and co-administered counterions. *Nature Metabolism*, **5**(4), 677–698.

Morville, T., Sahl, R. E., Moritz, T., Helge, J. W., & Clemmensen, C. (2020). Plasma metabolome profiling of resistance exercise and endurance exercise in humans. *Cell Reports*, **33**(13), 1–12.

Additional information

Competing interests

None.

Author contributions

Both authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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