Response to Wood re: “Oxidative Priority, Meal Frequency, and the Energy Economy of Food and Activity: Implications for Longevity, Obesity, and Cardiometabolic Disease”

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To the Editor:

WE APPRECIATE THE REVIEW of our “metabolic winter hypothesis” and “oxidative priority” manuscripts by Dr. Wood¹ and the opportunity to respond to his comments.

First, one goal of our work has been to better elucidate why the mitochondrial response to dietary restriction and mild cold stress appear to have overlapping responses. Although eating on the left side of the Food Triangle (which would fit a traditional “high-fat diet”) may result in greater weight loss during a caloric deficit under specific conditions as Dr. Wood proposes, such an approach to overall diet does not align with longevity and an increased healthy life span—two other important tenets of our hypothesis. Separate from that is an appreciation of how animals and plants fundamentally concentrate nutrition in different ways—something that may be taken advantage of to implement dietary restriction with a much higher volume of food from less energy dense plant-based sources. Moreover, promoting an ill-defined “high-protein diet” without addressing other aspects of nutrition to individuals to improve their health is an example of how the macronutrient organization of food continues to obfuscate the general population when it comes to healthy eating.

Second, we recognize and have specifically stated several times that our observations do not negate the myriad health benefits of exercise or discourage physical activity as a means to improve and maintain health, and our “metabolic winter hypothesis” does not dismiss exercise as a tool to enhance metabolic adaptation.^{2,3} But, we have also made it a point not to conflate the “metabolic winter hypothesis” with the science of oxidative priority—the notion that each meal should be handled as a discrete event and that nutrient distribution is completed by ~6 hr postprandially. Rather, we suggest that some of the adaptive benefits of exercise

might have arisen as an evolutionary adaptive survival strategy to mild cold stress—utilizing energy-dense fat stores in upregulated mitochondrial nonshivering thermogenesis.

Beyond that, the oxidative priority of ingested fuel sources and the ability to store excess calorie sources are separate issues from the partitioning of fuel during activity. Moreover, our discussion on the limitation of exercise is not directed at elite athletes; rather, we suggest that the somewhat “blanket” application of the benefit of exercise and its implications on weight management to the average population may be contributing to the myriad media and fitness advice misunderstandings. Perhaps, the underlying molecular mechanisms explaining why an athlete does not gain weight are not physiologically identical to those mechanisms that need to be engaged by an overweight person to lose weight.

Our hypothesis offers an alternate explanation that is consistent with both scenarios and further elucidates how the oversimplistic caloric deficit fails to explain a much more complex accumulation and depletion of adipose tissue from mixed diets and fuel partitioning during physical activity. Indeed, the work cited by Hetlelid et al. was centered on elite trained athletes (none of whom were overweight) and adaptations that occurred at a high VO_2 max that was maintained for short periods.⁴ Our example comparison (figure 3A, B)² illustrates an even more favorable fat disposal condition and one that better represents the wider population beyond highly trained athletes. The salient point made is that comparing total integrated fat disposed during limited periods of exercise with how easy it is to nullify the same quantity by diet supports the position that diet may be much more important.

Finally, the discrepancy of the dietary restriction data in free-living primates has been thoroughly discussed^{5–8}; and, although there is currently no direct evidence that caloric

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restriction increases life span in humans, there is no reason not to expect mitigation or delay of certain age-related diseases and an improved healthspan.^{9,10} However, we feel that the use of dietary restriction as a means to improve health and longevity is worth interrogating in as rigorous a manner as possible, and our Food Triangle provides an alternate framework to the traditional macronutrient-centric approach to diet that incorporates the nuanced differences in nutrient-signaling pathways seen in successful dietary restriction interventions.¹¹

It very well may be that we uncover ways to delay the onset of age-related diseases before we fully understand the reasons why; and, as Dr. Wood mentions, we also appreciate the potential role of circadian rhythms and time-restricted feeding in these phenomena.^{12,13} However, the chronic postprandial state, extended periods of artificial light, and a chronically warm environment—all elements we would classify as characteristics of a “metabolic summer”—may act synergistically to contribute to cardiometabolic and other disease states, and this appears to stand in stark contrast of seasonally imposed environmental effects throughout biology.

Disclaimer

The contents of this response represent the authors' views and do not constitute an official position of the National Institutes of Health or the United States Government.

Author Disclosure Statement

No competing financial interests exist.

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