METABOLIC SYNDROME AND RELATED DISORDERS
Volume XX, Number XX, 2017

P. 1
DOI: 10.1089/met.2016.0139

LETTER TO THE EDITOR

If the Metabolic Winter Is Coming, When Will It Be Summer?

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To the Editor,

Cronise et al.[1] recently expanded upon their metabolic winter hypothesis, which is a welcome move away from current reductionist dietary approaches. For instance, although ''low carb'' proponents state that (refined) carbohydrates caused the growing burden of obesity and metabolic disease, Cronise et al. correctly assert that the majority of fat deposited in adipose tissue comes directly from the diet. The idea of oxidative priority explains this well (with insulin as the most obvious hormonal integrator). As the evidence mounts behind the ways in which food processing can negatively alter the gut microbiota and hormonal responses to food, a focus on whole foods rather than specific macronutrients is also increasingly important. However, although the authors provide evidence that alcohol and carbohydrates supersede fat in the oxidative priority, the effect of protein is less clear. Higher protein diets tend to result in greater fat loss, and better maintenance of lean mass, during a caloric deficit. This may be caused by factors other than pure oxidative priority, including increased satiety and the central regulation of protein appetite. Although complex hormonal interactions can detract from the broad utility of a more simplified model, these aspects may need to be taken into consideration.

One potential discrepancy in the current metabolic winter hypothesis is the dismissal of exercise as a tool to enhance metabolic adaptation, with a focus instead on fasting, caloric restriction (CR), and cold thermogenesis. Although respiratory quotient may increase during an intense exercise bout, fat oxidation (and, therefore, the potential for fat loss) is often increased in the 24 hr after exercise. Endurance training also results in upregulation of capacity for fat oxidation in line with VO_2Max,[2] as well as increased defense of glycogen stores. A switch to fat mobilization should, therefore, occur earlier and more easily in those that exercise. Although an acute calorie deficit from exercise can easily be overcome by eating, it is also worth noting that the inclusion of exercise in weight loss trials results in a greater relative loss of fat mass. In addition, the current data suggest that aerobic exercise activates 5′ adenosine monophosphate-activated protein kinase more efficiently than fasting does,[3] and could in many respects be considered ''fasting in fast-forward.''

Finally, although CR may indeed increase longevity, the authors fail to mention the lack of direct evidence for its efficacy outside of the laboratory, including the fact that primates eating a high-quality diet do not experience a longevity benefit from CR. The effects of CR on PGC-1a and its downstream effects (*i.e.,* mitochondrial biogenesis) are also still highly debated.[4] As processes such as mitochondrial biogenesis are anabolic in nature, at least part of this discrepancy may be because of the fact that certain benefits of CR and fasting are only realized with periods of refeeding, especially if appropriately timed with circadian rhythm.[5] Therefore, if we are to promote a population-wide metabolic winter to initiate fat loss and promote long-term health, we must also acknowledge that many of those benefits will be reaped by occasionally basking in the summer sun.

References

1. Cronise RJ, Sinclair DA, Bremer AA. Oxidative Priority, Meal Frequency, the Energy Economy of Food and Activity: Implications for Longevity, Obesity, and Cardiometabolic Disease. *Metab Synd Relat Disord* 2016; [Epub ahead of print]; DOI: 10.1089/met.2016.0108.
2. Hetlelid KJ, Plews DJ, Herold E, et al. Rethinking the role of fat oxidation: Substrate utilisation during high-intensity interval training in well-trained and recreationally trained runners. *BMJ Open Sport Exerc Med* 2015;1:e000047.
3. Moller AB, Vendelbo MH, Christensen B, et al. Physical exercise increases autophagic signaling through ULK1 in human skeletal muscle. *J Appl Physiol (1985)* 2015;118:971–979.
4. Hancock CR, Han DH, Higashida K, et al. Does calorie restriction induce mitochondrial biogenesis? A reevaluation. *FASEB J* 2011;25:785–791.
5. Longo VD, Panda S. Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan. *Cell Metab* 2016;23: 1048–1059.

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