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DOES HEPATIC CARBOHYDRATE AVAILABILITY INFLUENCE POST-EXERCISE COMPENSATION IN ENERGY INTAKE?

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Abbreviations:

FGF21; fibroblast growth factor 21

There has long been interest in how increases in energy expenditure influence the biological and behavioural determinants of energy balance (1). By experimentally manipulating exercise-induced energy expenditure over the short or long term, studies have helped reveal the plasticity in which individual components of the energy balance system respond to energy imbalance (2). In the current issue of the Journal of Nutrition, Edinburgh and colleagues (3) demonstrated that even when coupled with breakfast omission, the energy expended during a single bout of exercise is not fully compensated for with increased post-exercise energy intake. This is consistent with previous findings demonstrating that a single bout of exercise does not stimulate an obligatory rise in post-exercise energy intake to restore energy balance (2). There is increasing recognition that the appetitive responses to exercise are individually subtle, with marked inter-individual variability evident in key appetite-related processes (e.g. hunger, satiety and gut peptides) and *ad libitum* food intake following acute and chronic exercise (4). However, the underpinning mechanisms that determine an individual's susceptibility to such compensation remain to be fully understood.

Significant attention has been given to how transient changes in appetite-related hormones during the post-exercise period influence energy intake (5), but such changes do not appear to fully account for the changes in appetite and energy intake seen after exercise. This reflects a wider focus in the field of appetite on the adipose and gastrointestinal derived peptide hormones that convey information from the periphery concerning nutrient and energy availability to regions of the brain thought to be involved in energy balance regulation (such as the hypothalamus) (6, 7). However, in the 1990s there was strong interest in the role of nutrient storage and oxidation in the control of food intake, and whether perturbations to nutrient availability conferred properties on feeding behaviour. In particular, JP Flatt's glycogenostatic theory (8-10) focused attention on glycogen availability as a negative feedback signal in the control of food intake. Due to its tight regulation, Flatt suggested that carbohydrate stores were strongly defended, and the depletion of endogenous liver and muscle glycogen acted as a stimuli to increase food intake to replete these stores (8-10). This theory was based around a negative relationship between carbohydrate balance and *ad libitum* feeding in mice

(9), but subsequent findings in humans were equivocal (11-13), and the utilization or storage of specific macronutrients is not currently thought to exert powerful negative feedback on day-to-day food intake in humans (11, 14, 15).

As a potent a metabolic stimulus that has the capacity, *inter alia*, to markedly perturb liver and muscle glycogen (16), there has also been interest in whether carbohydrate utilization plays a role in exercise-induced compensatory eating (17). However, such work has until recently been hampered by the lack of non-invasive means of directly measuring tissue-organ carbohydrate utilization or availability. Edinburgh et al. (3) demonstrated using 6, 6-$^{2}H_{2}$ glucose infusion that hepatically derived plasma glucose utilization was associated with post-exercise energy intake compensation, but no such associations were seen for muscle glycogen utilization, whole-body lipid utilization or the exercise-induced energy expenditure. These data are consistent with the glycogenostatic theory of appetite, and act to highlight a potential role for hepatic glycogen availability in post-exercise compensatory eating, but these findings do need to be replicated and the mechanisms linking hepatic carbohydrate utilization to post-exercise energy intake identified. While previous studies have inferred a role for carbohydrate utilization or availability in exercise-induced changes in appetite, the study of Edinburgh et al. (3) would appear to be the first to quantify carbohydrate utilization at the tissue-organ level to examine its potential impact on appetite. As such, this study provides a good example of how isotopic labelling and imagining techniques such as ^{13}C nuclear magnetic resonance could be applied to appetite research to provide new insight into how tissue-specific metabolism may influence homeostatic appetite control under conditions of varying nutrient and energy availability.

The liver is central to the regulation of whole-body glucose, lipid and amino acid metabolism, readily transitioning between the synthesis and degradation of energy stores and fuels to provide a constant supply of oxidizable substrates to tissues and organs during the fed and fasted state. In orchestrating such metabolism, there is significant cross-talk between the liver and extra-hepatic tissues such as skeletal muscle, adipose tissue and the gut. With this in mind, the liver would appear well placed to detect and respond to changes in peripheral nutrient and energy availability that occur during and

following exercise. However, whether exercise-induced perturbations to hepatic energy metabolism influence post-exercise compensatory eating behaviour has received little attention to date. Hepatic glycogen availability, which is perturbed with exercise, is tightly regulated in order to maintain euglycemia. Vagal afferent sensing of absorbed glucose in the hepatic portal vein has long been established (18), and some have linked hepatic glucose sensing in the portal vein to the control of food intake (although findings in humans are limited) (19). Furthermore, cross-talk between the liver and the brain can occur via the vagal nerve, and exercise-induced changes in liver glycogen content could potentially trigger hepatic afferent signalling to initiate hypothalamic responses in eating behaviour. A similar neural pathway has been proposed as part of the energostatic control of food intake, in which hepatic fatty acid oxidation is thought to alter the hepatocellular ATP/ADP ratio, and in turn, stimulate vagal afferent nerve activity in a manner that influences post-meal satiety (20)(21). However, it should be noted that there is limited hepatic vagal afferent innervation (22), and fatty acid oxidation in intestinal enterocytes rather than hepatocytes may have greater functional relevance for appetite (23).

When considered alongside the limited support for the glycogenostatic theory of appetite in humans, such findings do raise the question of how hepatic carbohydrate metabolism might be relayed to regions of the brain involved in the regulation of energy balance. As noted by Edinburgh et al. (3), there has been recent interest in the effects of the liver-derived hormone fibroblast growth factor 21 (FGF21) on appetite. Studies in mice and humans appear to indicate that FGF21 alters food preference, with lower FGF21 concentrations resulting in increased preference for sweet foods (24). While the specific role of FGF21 in human appetite control has yet to be clearly defined, the study of Edinburgh et al. (3) does highlight the potential to examine how macronutrient storage and/or oxidation at the tissue-organ level influences post-exercise compensation in energy intake using non-invasive techniques. When considered alongside gastrointestinal derived feedback (and psychological and environmental processes), such an approach may help provide a stronger account of the peripheral signals that underpin post-exercise compensation in energy intake.

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