



UNIVERSITY OF LEEDS

This is a repository copy of *Does Hepatic Carbohydrate Availability Influence Postexercise Compensation in Energy Intake?*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/147290/>

Version: Accepted Version

Article:

Hopkins, M orcid.org/0000-0002-7655-0215 (2019) Does Hepatic Carbohydrate Availability Influence Postexercise Compensation in Energy Intake? *Journal of Nutrition*, 149 (8). pp. 1305-1306. ISSN 0022-3166

<https://doi.org/10.1093/jn/nxz131>

(C) Copyright American Society for Nutrition 2019. All rights reserved This is an author produced version of a paper published in *Journal of Nutrition*. Uploaded in accordance with the publisher's self-archiving policy.

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

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

Dr Mark Hopkins

School of Food Science and Nutrition,

Faculty of Mathematics and Physical Sciences,

University of Leeds,

Leeds,

United Kingdom.

Tel: +44 (0) 11334 36990

Email: M.Hopkins@Leeds.ac.uk

Running Title:

Post-exercise compensation in energy intake

Disclaimers:

The author declares no conflicts of interest.

Funding:

The author reported no funding received for this commentary.

Abbreviations:

FGF21; fibroblast growth factor 21

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

14 Significant attention has been given to how transient changes in appetite-related hormones during
15 the post-exercise period influence energy intake (5), but such changes do not appear to fully account
16 for the changes in appetite and energy intake seen after exercise. This reflects a wider focus in the
17 field of appetite on the adipose and gastrointestinal derived peptide hormones that convey
18 information from the periphery concerning nutrient and energy availability to regions of the brain
19 thought to be involved in energy balance regulation (such as the hypothalamus) (6, 7). However, in the
20 1990s there was strong interest in the role of nutrient storage and oxidation in the control of food
21 intake, and whether perturbations to nutrient availability conferred properties on feeding behaviour.
22 In particular, JP Flatt's glycogenostatic theory (8-10) focused attention on glycogen availability as a
23 negative feedback signal in the control of food intake. Due to its tight regulation, Flatt suggested that
24 carbohydrate stores were strongly defended, and the depletion of endogenous liver and muscle
25 glycogen acted as a stimulus to increase food intake to replete these stores (8-10). This theory was
26 based around a negative relationship between carbohydrate balance and *ad libitum* feeding in mice

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

30 As a potent a metabolic stimulus that has the capacity, *inter alia*, to markedly perturb liver and muscle
31 glycogen (16), there has also been interest in whether carbohydrate utilization plays a role in exercise-
32 induced compensatory eating (17). However, such work has until recently been hampered by the lack
33 of non-invasive means of directly measuring tissue-organ carbohydrate utilization or availability.
34 Edinburgh et al. (3) demonstrated using 6, 6-²H₂ glucose infusion that hepatically derived plasma
35 glucose utilization was associated with post-exercise energy intake compensation, but no such
36 associations were seen for muscle glycogen utilization, whole-body lipid utilization or the exercise-
37 induced energy expenditure. These data are consistent with the glycogenostatic theory of appetite,
38 and act to highlight a potential role for hepatic glycogen availability in post-exercise compensatory
39 eating, but these findings do need to be replicated and the mechanisms linking hepatic carbohydrate
40 utilization to post-exercise energy intake identified. While previous studies have inferred a role for
41 carbohydrate utilization or availability in exercise-induced changes in appetite, the study of Edinburgh
42 et al. (3) would appear to be the first to quantify carbohydrate utilization at the tissue-organ level to
43 examine its potential impact on appetite. As such, this study provides a good example of how isotopic
44 labelling and imaging techniques such as ¹³C nuclear magnetic resonance could be applied to
45 appetite research to provide new insight into how tissue-specific metabolism may influence
46 homeostatic appetite control under conditions of varying nutrient and energy availability.

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

53 following exercise. However, whether exercise-induced perturbations to hepatic energy metabolism
54 influence post-exercise compensatory eating behaviour has received little attention to date. Hepatic
55 glycogen availability, which is perturbed with exercise, is tightly regulated in order to maintain
56 euglycemia. Vagal afferent sensing of absorbed glucose in the hepatic portal vein has long been
57 established (18), and some have linked hepatic glucose sensing in the portal vein to the control of food
58 intake (although findings in humans are limited) (19). Furthermore, cross-talk between the liver and
59 the brain can occur via the vagal nerve, and exercise-induced changes in liver glycogen content could
60 potentially trigger hepatic afferent signalling to initiate hypothalamic responses in eating behaviour.
61 A similar neural pathway has been proposed as part of the energostatic control of food intake, in which
62 hepatic fatty acid oxidation is thought to alter the hepatocellular ATP/ADP ratio, and in turn, stimulate
63 vagal afferent nerve activity in a manner that influences post-meal satiety (20)(21). However, it should
64 be noted that there is limited hepatic vagal afferent innervation (22), and fatty acid oxidation in
65 intestinal enterocytes rather than hepatocytes may have greater functional relevance for appetite
66 (23).

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

79

80 **ACKNOWLEDGEMENTS**

81 The sole author was responsible for the design, writing, and final content of this manuscript.

82 **REFERENCES**

- 83 1. Mayer J, Roy P, Mitra K. Relation between caloric intake, body weight, and physical work:
84 studies in an industrial male population in West Bengal. *American Journal of Clinical Nutrition*. 1956;4:
85 169-75.
- 86 2. Blundell J, Gibbons C, Caudwell P, Finlayson G, Hopkins M. Appetite control and energy
87 balance: impact of exercise. *Obesity Reviews*. 2015;16:67-76.
- 88 3. Edinburgh RM, Hengist A, Smith HA, Travers RL, Betts JA, Thompson D, Walhin J-P, Wallis GA,
89 Hamilton DL, Stevenson E. Skipping Breakfast Before Exercise Creates a More Negative 24-hour Energy
90 Balance: A Randomized Controlled Trial in Healthy Physically Active Young Men. *The Journal of*
91 *Nutrition*, nxz018, <https://doi.org/10.1093/jn/nxz018>.
- 92 4. Hopkins M, Beaulieu K, Myers A, Gibbons C, Blundell JE. Mechanisms responsible for
93 homeostatic appetite control: theoretical advances and practical implications. *Expert Review of*
94 *Endocrinology & Metabolism*. 2017;12:401-15.
- 95 5. Stensel D. Exercise, appetite and appetite-regulating hormones: implications for food intake
96 and weight control. *Annals of Nutrition and Metabolism*. 2010;57:36-42.
- 97 6. Schwartz MW, Woods SC, Seeley RJ, Barsh GS, Baskin DG, Leibel RL. Is the energy homeostasis
98 system inherently biased toward weight gain? *Diabetes*. 2003;52:232-8.
- 99 7. Keesey RE, Powley TL. Body energy homeostasis. *Appetite*. 2008;51:442-5.
- 100 8. Flatt J. Dietary fat, carbohydrate balance, and weight maintenance: effects of exercise.
101 *American Journal of Clinical Nutrition*. 1987;45:296-306.
- 102 9. Flatt J. The difference in the storage capacities for carbohydrate and for fat, and its
103 implications in the regulation of body weight. *The Annals of the New York Academy of Sciences*.
104 1987;499:104-23.
- 105 10. Flatt J. Glycogen levels and obesity. *International Journal of Obesity*. 1996;20:1-11.
- 106 11. Stubbs R, Murgatroyd P, Goldberg G, Prentice A. Carbohydrate balance and the regulation of
107 day-to-day food intake in humans. *American Journal of Clinical Nutrition*. 1993;57:897-903.

- 108 12. Shetty P, Prentice A, Goldberg G, Murgatroyd P, McKenna A, Stubbs R, Volschenk P.
109 Alterations in fuel selection and voluntary food intake in response to isoenergetic manipulation of
110 glycogen stores in humans. *American Journal of Clinical Nutrition*. 1994;60:534–543.
- 111 13. Stubbs R, Harbron C, Murgatroyd P, Prentice A. Covert manipulation of dietary fat and energy
112 density: effect on substrate flux and food intake in men eating ad libitum. *American Journal of Clinical*
113 *Nutrition*. 1995;62:316–329.
- 114 14. Stubbs R, O'Reilly L. Carbohydrate and fat metabolism, appetite and feeding behavior in
115 humans. In: Berthoud H, Seeley R, editors. *Neural and Metabolic Control of Macronutrient Intake*.
116 London: CRC Press; 2000. p. 165-88.
- 117 15. Blundell J, Stubbs R. Diet composition and the control of food intake in humans. In: Bray G,
118 Bouchard C, James W, editors. *Handbook of Obesity*. New York: Marcel Dekker Inc; 2004.
- 119 16. Richter E, Ruderman N. AMPK and the biochemistry of exercise: implications for human health
120 and disease. *The Biochemical Journal*. 2009;418:261-275.
- 121 17. Hopkins M, Jeukendrup A, King NA, Blundell JE. The Relationship between Substrate
122 Metabolism, Exercise and Appetite Control. *Sports Medicine*. 2011;41:507-21.
- 123 18. Nijijima A. Afferent impulse discharges from glucoreceptors in the liver of the guinea pig.
124 *Nutrition*. 1969;157:690-700.
- 125 19. Russek M. Participation of hepatic glucoreceptors in the control of intake of food. *Nature*.
126 1963;197:79-80.
- 127 20. Friedman M. Control of energy intake by energy metabolism. *American Journal of Clinical*
128 *Nutrition*. 1995;62:1096S–1100S.
- 129 21. Leonhardt M, Langhans W. Fatty acid oxidation and control of food intake. *Physiology &*
130 *Behavior*. 2004;83:645-51.
- 131 22. Berthoud H. Anatomy and function of sensory hepatic nerves. *The Anatomical Record Part A*.
132 2004;280:827-35.

- 133 23. Langhans W, Leitner C, Arnold M. Dietary fat sensing via fatty acid oxidation in enterocytes:
134 possible role in the control of eating. *American Journal of Physiology-Regulatory, Integrative and*
135 *Comparative Physiology*. 2010;300:R554-R65.
- 136 24. von Holstein-Rathlou S, Gillum M. FGF21: an endocrine inhibitor of sugar and alcohol.
137 *Appetite*. doi: 10.1113/JP277117.
- 138