Article:
Thivel, D, Metz, L, Julian, V et al. (7 more authors) (2021) Diet- but not exercise-induced iso-energetic deficit induces compensatory appetitive responses. European Journal of Clinical Nutrition, 75 (10). pp. 1425-1432. ISSN 0954-3007

https://doi.org/10.1038/s41430-020-00853-7

Diet- but not exercise-induced iso-energetic deficit induces compensatory appetitive responses

Thivel D[1,2], Metz L[1], Julian V[3], Isacco L[1], Verney J[1], Ennequin G[1], Charlot K[4], Beaulieu K[2], Finlayson G[2], King JA[5,6]

[1]Clermont Auvergne University, EA 3533, Laboratory of the Metabolic Adaptations to Exercise under Physiological and Pathological Conditions (AME2P), CRNH Auvergne, Clermont-Ferrand, France.

[2]School of Psychology, Faculty of Medicine and Health, University of Leeds, Leeds, LS2 9JT, UK

[3]CHU Clermont-Ferrand, Clermont-Ferrand, France.

[4]Institut de Recherche Biomédicale des Armées, Unité de Physiologie des Exercices et Activités en Conditions Extrêmes, Département Environnements Opérationnels, 1 place Général Valérie André, 91223, Bretigny-Sur-Orge, France. LBEPS, Univ Evry, IRBA, Université Paris Saclay, 91025, Evry, France.

[5] National Centre for Sport and Exercise Medicine, School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough LE1 3TU, UK.

[6]National Institute for Health Research (NIHR) Leicester Biomedical Research Centre, University Hospitals of Leicester NHS Trust and University of Leicester, LE5 4PW, UK.

Running title : Energy deficits and appetite

Corresponding Author :
Thivel David
Clermont University, EA 3533, Laboratory of the Metabolic Adaptations to Exercise under Physiological and Pathological Conditions (AME2P), BP 80026, F-63171 Aubière cedex, France
david.thivel@uca.fr
Phone and fax/ 0033 4 73 40 76 79

Abstract

Although physical exercise and dietary restriction can be both used to induce energy deficits, they have been suggested to favor different compensatory appetitive responses. While dietary restriction might favor increased subsequent energy intake and appetite sensations, such compensatory responses have not been observed after a similar deficit by exercise. The present work provides a first overview of the actual evidences discussing the effects of iso-energetic deficits induced by exercise *versus* dietary restriction on subsequent energy intake, appetite sensations and on the potentially involved hedonic and physiological mechanisms.

Introduction

The high worldwide prevalence of obesity and related comorbidities reinforces the need to better understand the mechanisms governing energy balance and associated perturbations. In a simplistic sense, energy balance is determined by the interaction between the energy ingested and expended. While energy intake corresponds to the consumption of food and drinks, total energy expenditure (TEE) is determined by the resting metabolic rate (RMR; ≈50-70% of TEE), diet-induced thermogenesis (DIT; ≈5-10% TEE) and physical activity energy expenditure (PAEE; ≈25% TEE). Interventions seeking to create an energy deficit and induce weight loss, therefore, require a reduction in energy intake and/or an increase in PAEE. Interestingly, while energy intake and energy expenditure were historically considered as two independent influences on energy balance, accumulating evidence has described a more complex interaction. In particular, physical exercise has been shown to indirectly contribute to the control of appetite and energy intake in healthy adults, youth and people with obesity (1, 2). Acute exercise, depending on its characteristics, can modulate appetite sensations, appetite-related hormones, energy intake, food preferences and reward (for review see (3-6)). Blundell et al. first summarized the effects of exercise on appetite and energy intake in the early 1990s (7) but have recently updated their working model which more clearly describes physiological and hedonic influences (8).

Briefly, as perfectly described in the authors' recent review (8), this model illustrates how energy expenditure is related to energy intake and particularly details the contribution from physical activity energy expenditure, which influences both tonic and episodic processes. It particularly illustrates how body composition influences appetite control through both a drive and an inhibitory system. It is proposed that fat-free mass, via resting metabolic rate, reflects the energy needs of our human body and then composes a drive to eat. In opposition, fat mass plays a tonic inhibitory role on eating. Both processes will dialogue with complex neuronal processes and once integrated will determine behaviors. These tonic pathways will be periodically interrupted by episodic signals from the

gastrointestinal system that will also be integrated in neuronal processes. This model then greatly presents how physical activity and acute exercise will impact the control of appetite and energy intake (for details and review see Blundell et al. (8)).

Interestingly, while single bouts of exercise do not commonly increase appetite or energy intake, even when energy expenditure is high (9-11), dietary energy restriction favors strong compensatory mechanisms with increased appetite and food ingestion (12, 13). Therefore, it appears that appetitive responses to short-term energy deficits is differentially mediated by the nature of the stimulus (exercise vs. diet-induced).

With the aim of stimulating further research and discussion in this important research area, this manuscript provides a narrative overview of the available studies that have directly compared the short-term appetitive responses (appetite sensations, energy intake and related hormones) to iso-energetic deficits induced by either acute exercise or dietary energy restriction, including the potential hedonic and physiological mechanisms.

Exercise versus diet-induced energy deficit

In 1997, Hubert and collaborators compared the appetitive response to similar energy deficits induced by either food restriction or physical exercise (13). In their study, the authors asked 12 healthy normal-weight women (aged 23 ± 2.7 years) to randomly perform four experimental conditions during which energy balance was manipulated by consuming either a low (≈251 KJ) or high (≈2,092 KJ) energy breakfast and by performing or not an acute bout of cycling (energy expenditure ≈1,326 KJ) (details are displayed in Table 1). According to their results, *ad libitum* energy intake was increased when the energy deficit was induced through the low energy breakfast, with or without exercise (increased of about 20%). These results were the first to suggest that energy restriction, but not exercise, led to a compensatory rise in food consumption (13). This was moreover accompanied by a higher pre-lunch sensation of hunger as well as higher end of day hunger, preoccupation with food, frequency and

strength of food cravings, when the energy deficit was induced through the low energy breakfast consumption, independently of exercise (13).

In a sample of healthy males, King and colleagues compared appetitive responses to relatively large (> 4,602 KJ) short-term energy deficits induced by exercise *versus* food restriction (14). In their exercise condition, the participants ran for 90 minutes on a treadmill at a moderate-to-vigorous intensity (≈70% VO_2max). Conversely, in the food-deficit condition, a proportional amount of energy was withheld from standardised breakfast and lunch meals. Supporting the previous findings of Hubert et al. (13), the researchers saw rapid and robust compensatory appetite responses to food restriction that were not observed in the exercise condition. Free choice energy intake mirrored this response when measured from a buffet meal at the end of the nine-hour trials. Notably, King et al (14) also showed that circulating concentrations of appetite-related peptides responded in a manner consistent with the appetite changes. Specifically, circulating concentrations of acylated ghrelin remained high after the consumption of small meals but were unaffected after exercise. Conversely, food restriction led to smaller postprandial PYY_{3-36} concentrations; again, not matched by exercise. These findings are consistent with the suggestion that appetite is sensitive to the passage of food through the gastrointestinal tract, but less so to acute energy balance perturbations (15). The same research group subsequently performed a similar study (using the same methodology as detailed in Table 1) among healthy normal-weight women, inducing a mean energy deficit of 3,500 KJ, and observed similar results for appetite, energy intake and appetite-related hormones (acylated ghrelin and PYY_{3-36} concentrations) (16) (Table 1).

To scrutinize the effects of more modest energy deficits (≈1,465 kJ), Deighton et al. studied appetite, energy intake and appetite-related hormone (acylated ghrelin and PYY_{3-36}) responses to an acute bout of cycling (30 min, 55% VO_2max) and matched energy restriction. Once more, exercise did not elicit any compensatory appetitive responses, whereas subtle energy restriction produced higher appetite ratings in comparison to control and exercise. Conversely, the smaller level of energy restriction did

not influence *ad libitum* energy intake or appetite-related hormones. These data suggest that appetite perceptions are sensitive to relatively minor reductions in food intake, whereas a larger energy deficit is required to alter *ad libitum* food intake and appetite-related hormones.

Appetitive response to a 24-h full energy deficit

More recently, the appetitive responses to a full 24-h fasting condition (as food restriction) have been compared with a similar deficit induced by exercise (17). On their exercise-induced deficit condition, 12 healthy lean males (21.5 ± 0.5 years) cycled for about 290 minutes at 70% VO_2max (they exercised on four different occasions during the day: twice in the morning and twice in the afternoon) to reach the deficit induced during the 24-h fast (11,209 ± 1,326 KJ). *Ad libitum* energy intake was assessed at lunch on the following day and was significantly increased after the 24-h fast but not after the exercise condition. Although the total self-reported intake for the rest of the day was not significantly different between conditions, the consumption of fat was found to be significantly higher in response to food restriction. As detailed in Table 1, the overall area under the curve (AUC) for hunger, desire to eat (DTE) and prospective food consumption (PFC) were significantly higher when the deficit was induced by dietary restriction while the AUC for fullness was lower. Using the Leeds Food Preference Questionnaire (LFPQ), the authors also found a higher pre-test meal fat bias in food choice after the fasting condition and a higher pre-test meal fat bias for implicit wanting on both energy depletion conditions (17), reinforcing the results observed by Cameron et al. concerning the potential role played by the hedonic system in response to energy deficit, particularly when induced by energy restriction (18).

Which responses to prolonged energy deficits (several days)?

While the previous studies characterized the effect of short-term energy deficits (several hours), Cameron and colleagues recently assessed the appetitive response to 3 days of energy depletion by diet or exercise in healthy young males (aged 23.7 ± 5.1 years) (18). In their study, the dietary-induced energy deficit was based on 25% of the participants' energy balance in the preceding 3-day control

condition, which corresponded to a mean deficit of 2,970 KJ per day. In the exercise condition, to reach this deficit, the participants had to run on a treadmill for approximately 65 minutes per day at 50% VO_2max. Once more, their results demonstrated an increase in *ad libitum* food intake at the buffet test meal in response to the food restriction compared to both the exercise and control conditions, without any difference between the latter two. This was accompanied by higher sensations of hunger, palatability and DTE during the diet-induced deficit condition compared with control. The authors however did not observe any difference between conditions for the plasma concentrations of total ghrelin, with also similar levels of leptin (18). Interestingly, Cameron et al. also assessed other aspects of the control of appetite and energy intake and compared the food reward and olfactory responses to such deficits. Concerning olfaction, while they did not show any difference regarding the level of odor discrimination, they observed a significantly higher odor detection threshold during the dietary-induced deficit condition compared with the control condition (18). These results suggest the implication of some sensory drivers in the compensatory rise in food intake and appetite sensations in response to dietary-induced energy deficit but not after an iso-energetic deficit induced by exercise.

Regarding their food reward results, the authors observed a higher relative-reinforcing value of food after the 3 days of dietary-induced deficit compared with the control condition. The reinforcing value was however also significantly higher in response to the exercise-induced deficit compared to both the control and diet-induced deficit conditions. While this might suggest a potential uncoupling between the response of the food reward system and the effective energy consumption in response to exercise, further studies are needed to better understand the effects of exercise, depending on its characteristics (intensity, duration, modality, etc.), on the hedonic control of food intake.

What do we know in patients with obesity?

While the previously mentioned studies enrolled healthy normal-weight young participants, we found one study that used the same methodology among adolescents with obesity (19). After a control condition during which the investigators assessed the overall daily energy intake and expenditure of

14 boys and girls with obesity (14.2 ± 1.0 years, z-BMI: 2.4 ± 0.29); a mean energy deficit of 1,062 ± 384 KJ (which individually corresponded to 25% of the lunch meal of the control condition) was induced once by dietary restriction on the lunch meal and once by a cycling exercise set at 65% VO_2max. Contrary to what was observed in healthy adults, both strategies of energy deficit (exercise and dietary restriction) prompted increased energy intake at the subsequent *ad libitum* buffet meal compared to the control session with however a significantly higher absolute consumption of fat in response to the dietary-induced deficit compared to the exercise and control conditions. This higher intake on both deficit conditions was accompanied by a higher sensation of hunger immediately before the test meal. Interestingly however, the authors observed significant correlations between the individual absolute degree of deficit induced (in KJ) and the total *ad libitum* intake; correlations that were in the opposite direction depending on the nature of the induced deficit. Indeed, the higher was the individual absolute energy deficit during the diet-induced deficit, the higher was the adolescent's energy compensation at the following meal (*ad libitum* intake); and inversely when the deficit was induced by exercise (the higher the deficit, the lower the intake compensation) (19).

Altogether, these results clearly point to the beneficial effects of exercise over dietary-restriction when it comes to the creation of an acute energy deficit, mainly through its anti-compensatory effects on energy intake. Although diet has been found to be more efficient for rapid and large weight loss, exercise becomes highly important for sustainable weight maintenance and its effects on the control of appetite, minimizing the compensatory responses produced solely by dietary restriction. Figure 1 summarizes these results.

Limitations and perspectives

These results must be interpreted with consideration of some limitations. The exercise intensities implemented in the previously detailed studies is one consideration. While moderate-intensity aerobic exercise ranging from 50% to 70% VO_{2max} was used, exercise at higher intensities has been shown to not only avoid compensatory responses but also favor anorexigenic responses (5, 20). Thus, higher-

intensity exercise may enhance the overall effect of exercise on energy balance. Similarly, the available studies induced short-term energy deficits, ranging from a few hours (9 hours) to 3 days, and additional studies are needed to characterize more long-term responses (which has more relevance to energy balance and weight management). In this regard, future studies also need to examine responses in a wider range of participant groups, including women, and individuals with overweight and obesity.

Another limitation of the studies reviewed is the inclusion of healthy adults only (except for one study that enrolled adolescents with obesity (19)). Energy deficits are mainly used among patients with overweight and obesity or elite athletes, who might show different responses to what was observed here. The results observed so far come from populations with quite similar characteristics and these responses to deficits should be also questioned among individuals with different metabolic profiles and physical capacities. Longer energy deficits should be induced in patients with weight issues to potentially take clinical advantages of these differentiated appetitive responses to energy depletion induced by exercise *versus* dietary restriction (21). Importantly, while exercise training alone might lead to less than expected weight loss, further studies should be conducted to explore to what extent the addition of exercise to dietary-induced energy deficits can optimize the reduction of energy balance through both energy depletion and the avoidance of nutritional compensatory responses.

Conclusion

To conclude, physical exercise seems to provide a double effect on energy balance by inducing an increase in energy expenditure while avoiding the activation of some physiological and hedonic mechanisms that have been shown to favor compensatory appetitive responses after similar energy deficits induced by dietary restriction alone. Further studies are required to characterize responses over a longer timeframe, among patients concerned with weight loss or weight maintenance.

Conflict of Interest

The authors have no conflict of interest to disclose.

Author Contributions

While DT and JK led the writing of this paper, all the co-authors significantly and equally contributed to this manuscript.

References

1. Thivel D, Finlayson G, Blundell JE. Homeostatic and neurocognitive control of energy intake in response to exercise in pediatric obesity: a psychobiological framework. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2019;20(2):316-24.
2. Blundell JE, Gibbons C, Caudwell P, Finlayson G, Hopkins M. Appetite control and energy balance: impact of exercise. Obes Rev. 2015;16 Suppl 1:67-76.
3. Schubert MM, Desbrow B, Sabapathy S, Leveritt M. Acute exercise and subsequent energy intake. A meta-analysis. Appetite. 2013;63:92-104.
4. Donnelly JE, Herrmann SD, Lambourne K, Szabo AN, Honas JJ, Washburn RA. Does increased exercise or physical activity alter ad-libitum daily energy intake or macronutrient composition in healthy adults? A systematic review. PLoS One. 2014;9(1):e83498.
5. Thivel D, Rumbold PL, King NA, Pereira B, Blundell JE, Mathieu ME. Acute post-exercise energy and macronutrient intake in lean and obese youth: a systematic review and meta-analysis. International journal of obesity (2005). 2016;40(10):1469-79.
6. Beaulieu K, Oustric P, Finlayson G. The Impact of Physical Activity on Food Reward: Review and Conceptual Synthesis of Evidence from Observational, Acute, and Chronic Exercise Training Studies. Curr Obes Rep. 2020;9(2):63-80.
7. Blundell JE, King NA. Physical activity and regulation of food intake: current evidence. Med Sci Sports Exerc. 1999;31(11 Suppl):S573-83.
8. Blundell JE, Gibbons C, Beaulieu K, Casanova N, Duarte C, Finlayson G, et al. The drive to eat in homo sapiens: Energy expenditure drives energy intake. Physiol Behav. 2020;219:112846.
9. King NA, Burley VJ, Blundell JE. Exercise-induced suppression of appetite: effects on food intake and implications for energy balance. Eur J Clin Nutr. 1994;48(10):715-24.
10. King NA, Lluch A, Stubbs RJ, Blundell JE. High dose exercise does not increase hunger or energy intake in free living males. Eur J Clin Nutr. 1997;51(7):478-83.
11. King JA, Miyashita M, Wasse LK, Stensel DJ. Influence of prolonged treadmill running on appetite, energy intake and circulating concentrations of acylated ghrelin. Appetite. 2010;54(3):492-8.
12. Green SM, Burley VJ, Blundell JE. Effect of fat- and sucrose-containing foods on the size of eating episodes and energy intake in lean males: potential for causing overconsumption. Eur J Clin Nutr. 1994;48(8):547-55.
13. Hubert P, King NA, Blundell JE. Uncoupling the effects of energy expenditure and energy intake: appetite response to short-term energy deficit induced by meal omission and physical activity. Appetite. 1998;31(1):9-19.
14. King JA, Wasse LK, Ewens J, Crystallis K, Emmanuel J, Batterham RL, et al. Differential acylated ghrelin, peptide YY3-36, appetite, and food intake responses to equivalent energy deficits created by exercise and food restriction. J Clin Endocrinol Metab. 2011;96(4):1114-21.

15. Borer KT, Wuorinen E, Ku K, Burant C. Appetite responds to changes in meal content, whereas ghrelin, leptin, and insulin track changes in energy availability. J Clin Endocrinol Metab. 2009;94(7):2290-8.
16. Alajmi N, Deighton K, King JA, Reischak-Oliveira A, Wasse LK, Jones J, et al. Appetite and Energy Intake Responses to Acute Energy Deficits in Females versus Males. Med Sci Sports Exerc. 2016;48(3):412-20.
17. Thivel D, Finlayson G, Miguet M, Pereira B, Duclos M, Boirie Y, et al. Energy depletion by 24-h fast leads to compensatory appetite responses compared with matched energy depletion by exercise in healthy young males. The British journal of nutrition. 2018;120(5):583-92.
18. Cameron JD, Goldfield GS, Riou ME, Finlayson GS, Blundell JE, Doucet E. Energy depletion by diet or aerobic exercise alone: impact of energy deficit modality on appetite parameters. Am J Clin Nutr. 2016;103(4):1008-16.
19. Thivel D, Doucet E, Julian V, Cardenoux C, Boirie Y, Duclos M. Nutritional compensation to exercise- vs. diet-induced acute energy deficit in adolescents with obesity. Physiology & behavior. 2017;176:159-64.
20. Ueda SY, Yoshikawa T, Katsura Y, Usui T, Fujimoto S. Comparable effects of moderate intensity exercise on changes in anorectic gut hormone levels and energy intake to high intensity exercise. J Endocrinol. 2009;203(3):357-64.
21. Franz MJ, VanWormer JJ, Crain AL, Boucher JL, Histon T, Caplan W, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. J Am Diet Assoc. 2007;107(10):1755-67.

Table 1. Description of the methods and main results of the included studies.

Figure 1. Appetitive (subsequent energy intake, appetite sensations, food reward and appetite related hormones) responses to iso-energetic energy deficits induced either by dietary restriction (Def-EI) or exercise (Def-EX), compared to a control condition (CON). **EE: Energy Expenditure; EI: Energy Intake; PFC: Prospective Food Consumption; DTE: Desire To Eat; FR: Food Reward; PYY: Peptide YY; AG: Acylated Ghrelin; ↔: unchanged; ↓: decreased; ↑: increased.**