Title: Carbohydrate availability as a regulator of energy balance with exercise

Short title: Carbohydrates and energy balance

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Abstract

We explore the novel hypothesis that carbohydrate availability is involved in the regulation of energy balance with exercise, via hormonal and neural signals. We propose that carbohydrate availability could play a direct mechanistic role and partially explain previously-documented relationships between a more active lifestyle and tighter control of energy balance.

Summary

Low carbohydrate availability may stimulate increased energy intake via decreasing leptin secretion and hepatic glycogen content.

Key points

- Reductions in adiposity require a chronic energy deficit, but this is defended against by declining leptin concentrations.
- Leptin concentrations are also lowered in response to decreasing carbohydrate availability, independent of energy balance.
- Exercise transiently reduces carbohydrate availability via the utilization of endogenous glycogen stores, which could contribute to the lower leptin response apparent following exercise.
- The reduction in hepatic glycogen stores with exercise may also contribute directly to appetite control via the vagal nerve.
- Exercise training reduces the relative reliance on carbohydrate utilization during exercise, which could explain why endurance trained individuals may be less susceptible to post-exercise dietary compensation.

Key words

appetite; carbohydrate; energy balance; glycogen lipid; metabolism; physical activity

INTRODUCTION

Obesity represents an excessive accumulation of adipose tissue and is common amongst humans in modern societies. The causes of obesity are undoubtedly complex (involving biological, psychological, societal and environmental factors), yet the root cause at the individual level is a chronic positive energy balance, culminating in a change in the availability of stored energy (1). This is relevant because the consequence of sustained positive energy balance (i.e. excess adiposity) and the individual components driving that imbalance (e.g. excessive dietary intake of certain nutrients and/or a sedentary lifestyle) are all independent risk factors for chronic diseases (e.g. type 2 diabetes, cancer and cardiovascular disease) representing global public health challenges.

Energy intake is the product of the mass of energy-providing nutrients (macronutrients) ingested and absorbed, multiplied by the energy-density specific to each macronutrient (i.e. carbohydrate, fat, protein and alcohol). Energy exiting the system (post-absorption) is the total accumulated thermogenesis via components of energy expenditure. These include: resting metabolic rate (which is proportionate to energy required to sustain various bodily tissues under basal conditions (2)); diet-induced thermogenesis (reflecting the increment in energy expenditure above the fasted-state necessary to process ingested nutrients (2)); and physical activity thermogenesis (encapsulating all metabolic costs above resting-state necessary to exert physical forces on our environment (2)).

A change in any component on either side of the energy balance equation has potential to interact with any one, or all other components, via highly-evolved feedback mechanisms designed to preserve energy balance. A clear example is that food ingestion can be acutely sensed and rapidly elicit compensatory responses to limit further energy intake (i.e. satiation). Such interactions between different components of energy balance can also operate across the two sides of the equation (in either direction), as evidenced by the fact that prescribed exercise can stimulate appetite (3) whereas extended fasting can limit spontaneous physical activity (2), which partly explains why either exercise or dietary interventions in isolation are generally ineffective. In the longer-term, a sustained shift in stored energy availability and therefore tissue mass introduces a

further dynamic aspect to energy balance regulation, whereby energy requirements are continually adjusted and adaptive responses such as non-shivering thermogenesis can serve to offset any ongoing energy imbalance (4).

Theoretically, the homeostatic mechanisms that enable energy intake to mirror energy expenditure under variable circumstances can maintain energy balance across a large range of energy flux (i.e. energy turnover). In modern times, however, energy balance is much more likely to occur at higher levels of energy flux – as evidenced by the observations that habitually active individuals typically exhibit a leaner phenotype than those with a sedentary lifestyle (5). This pattern was attributed over 60 years ago to a "J-shaped" relationship between energy intake and energy requirements whereby mirroring between the two sides of the energy balance equation is only regulated at 'normal' (i.e. moderate to high) levels of physical exertion, whereas sedentary activities paradoxically increase appetite in excess of requirements, producing weight-gain of ~15 kg on average compared to moderate-to-high levels of activity (5). This idea is consistent with more recent cross-sectional observations that individuals who are objectively classified as more habitually active are able to more appropriately modify energy intake at a second meal after energy intake has been covertly manipulated at an earlier eating occasion (6). Moreover, whilst further randomised controlled trials are required for definitive causality, this relationship between physical activity and appetite regulation is strengthened from a recent non-randomized trial where 12 weeks of exercise improved the accuracy of appetite (7).

Understanding the regulation of energy balance adjustments with physical activity is important in order to maximise the potential for exercise to induce fat loss and thus further improve metabolic health. This review will consider the metabolic responses to exercise which may have implications for the relative lack of weight loss sometimes seen with exercise training, but also may explain the potentially improved sensitivity of the appetite regulatory system in highly physically active individuals. In particular, we will first consider the established regulation of endogenous fat stores – which are the reflection of long-term energy balance (8), before highlighting the relatively neglected role of carbohydrate availability in the potential regulation of energy balance behaviours.

We propose the novel hypothesis that the relatively limited availability of endogenous carbohydrate reserves (mainly comprising muscle and liver glycogen) can be considerably altered by physical exercise, especially in less-well-trained individuals, and that this energy store is involved in energy balance regulation *via* hormonal and neural signalling (**Figure 1**).

***** Figure 1 *****

LEPTIN IS A PRIMARY ADIPOSE SIGNAL SENSING ENERGY DEFICIT

Adipocytes secrete hundreds of proteins involved in multiple physiological processes. One especially important protein for the regulation of energy balance is leptin. Leptin plays a key role in appetite and energy intake during an energy deficit. Normally, systemic leptin concentrations tend to be positively associated with fat mass (9). A reduction in energy intake results in a profound reduction in leptin concentrations (10). This disproportionately large fall in leptin concentration may not simply be a 'starvation' signal due to reduced energy intake *per se* but rather is largely a response to the net negative energy balance, so is a signal for compensatory feeding stimulated by energy deficit (10). Thus, a fall in leptin is an attempt to preserve fat stores, with leptin functioning as the afferent signal in a negative feedback loop to maintain the stability of adipose tissue mass. A fall in leptin is associated with increased sensations of hunger (11) and an increase in 'reward-related' behaviours (10). Leptin has direct effects on the hypothalamic arcuate nucleus (10) and also affects the sensitivity to other appetite-regulatory hormones such as cholecystokinin (12). Furthermore, the replacement of leptin in humans during caloric restriction (via subcutaneous leptin administration) helps maintain weight loss through reduced energy intake (13).

LEPTIN RESPONDS TO ENERGY EXPENDITURE

Leptin concentrations can similarly be reduced if negative energy balance is instead achieved via increased energy expenditure rather than reduced energy intake. Indeed, fasting leptin concentrations are 20-50% lower following exercise interventions, despite only modest reductions in fat mass (3). Notably, an exercise-induced reduction in leptin can be prevented if additional food (as mixed macronutrients) is provided (14). Therefore, the fall in leptin concentrations with exercise may

be entirely due to an energy or relative macronutrient deficit, rather than the increase in energy expenditure *per se*. It is currently unknown whether this fall in leptin can be prevented by the specific preservation of either carbohydrate or fat balance. The fall in leptin with exercise, and the corresponding compensatory increase in hyperphagia, likely plays a role in explaining the less-than-predicted weight loss with exercise interventions (3). Thus, it appears that exercise and/or an exercise-induced caloric deficit provoke a suppression of leptin as a clear attempt to maintain energy stored as adipose triglycerides (**Figure 2**).

***** Figure 2 *****

The cause(s) of reduced circulating leptin concentrations with increased physical activity or exercise is unclear. Leptin secretion is regulated at both the transcriptional and post-transcriptional level. Rodent studies indicate that the fall in leptin with an expenditure-induced energy deficit represents a relatively sustained shift in basal gene expression (15), although some human studies report no change in leptin mRNA after exercise training (16). The interval between the last exercise bout and blood sampling could be an important consideration and one study in women reported adipose leptin gene expression to be reduced by 25% after 7-weeks of training when the adipose sample was collected 15-24 h after the last exercise bout (17). Our own data indicate that leptin gene expression is only modestly reduced after a large energy deficit from combined caloric restriction and exercise (with adipose tissue sampled ~48h post-exercise), even though serum leptin concentrations were reduced by 40-50% at the corresponding time point (18). Thus, reduced leptin concentrations following exercise seem to be the product of both reduced leptin gene expression and reduced leptin secretion, with perhaps the relative reduction in leptin secretion being particularly important.

LEPTIN RESPONDS TO CARBOHYDRATE AVAILABILITY

Leptin secretion appears to be at least partly regulated by glucose availability. Adipocytes ‘sense’ glucose and energy flux (19) and infusion studies in humans show that even a small amount of glucose (~4 g/h) can prevent the profound fall in leptin normally seen during extended (72-h) fasting (20). An acute bout of exercise reduces adipose tissue glucose uptake in humans (21) and increases

adipose AMPK phosphorylation (22). Since AMPK is a negative regulator of mTOR-dependent leptin secretion, reduced adipose glucose metabolism may be one factor responsible for an exercise-induced reduction in adipose leptin secretion. Interestingly, an exercise intervention coupled with a high carbohydrate diet led to an impressive 5-kg weight-loss over 14 weeks without sensations of increased hunger (23). Furthermore, reductions in carbohydrate availability over 3 days, whether achieved by either daily physical activity or by low-carbohydrate diets, can reduce fasting leptin concentrations relative to a high carbohydrate diet under sedentary conditions (24). This has been confirmed by a metabolic ward study showing that 4 weeks of a low-carbohydrate, ketogenic diet lowers plasma leptin concentrations by ~20% compared to an isocaloric high-carbohydrate diet (25). Therefore, changes in carbohydrate availability potently alter circulating leptin concentrations, independent of energy balance. Since transiently lowering carbohydrate availability via exercise or dietary intake each reduce insulinemia (25,26), and prolonged hyperinsulinemia is thought to stimulate leptin secretion (27), the mechanism(s) by which carbohydrate availability may influence leptin concentrations could involve prolonged changes in insulinemia and related adipose carbohydrate metabolism (27).

EXERCISE ALTERS SUBSTRATE AVAILABILITY

Carbohydrates in the form of muscle and liver glycogen are major fuel sources during almost all forms of prolonged exercise. The contribution of carbohydrate to exercise metabolism can be altered by the intensity and duration of exercise, in addition to fitness status and recent diet, such as prior carbohydrate intake (28,29). When total energy expenditure is fixed, any shift in carbohydrate oxidation is typically replaced with a reciprocal change in fat oxidation (30). In other words, a 100-kcal reduction in carbohydrate oxidation would typically be replaced by a 100-kcal increase in fat oxidation. However, due to the size of body energy stores (**Figure 1**), a 100-kcal carbohydrate deficit represents a much greater proportion of the endogenous carbohydrate pool than does a 100-kcal fat deficit relative to the available endogenous fat pool.

CARBOHYDRATE STATUS REGULATES ENERGY BALANCE

Carbohydrates (primarily stored as glycogen) are drastically limited in their storage capacity. A typical (untrained) healthy individual, is likely to store less than 1200 kcal of energy as

carbohydrate, compared to more than 100,000 kcal of energy as fat (31). Carbohydrate stores typically represent 1-3% of the energy in fat stores, even amongst endurance trained individuals who have an elevated capacity to store muscle glycogen (31). This finite capacity to store carbohydrate, combined with the homeostatic imperative of maintaining euglycemia, potentially implicates carbohydrate availability as a key regulatory factor in energy balance (32). Whilst the hypothesis that glycogen stores may regulate energy balance has been speculated upon for decades, largely pioneered by Flatt (32–35), with contributions from others (36–38), much of that work did not support the role of glycogen in regulating appetite (36–39). However, it has only been recently that the tissue-specific (liver and muscle) relationship between glycogen stores and energy balance have been assessed (40), which may reveal relationships that are otherwise obscured when determining total glycogen stores and energy balance behaviours.

Whilst some studies have employed exercise as a means to deplete glycogen stores and assess appetite responses (39), direct relationships between muscle or liver glycogen concentrations and appetite have not yet been reported in humans. However, there is increasing evidence that whole-body carbohydrate availability, and/or tissue-specific utilisation rates, may contribute to the regulation of energy balance behaviours (40,41). Furthermore, there is some direct evidence in rodents that liver glycogen concentrations in particular can regulate energy balance behaviours (42). In humans, whole-body carbohydrate utilisation has been independently associated with energy intake compensation after exercise (41). Specifically, carbohydrate oxidation during a bout of exercise designed to expend 400 kcal was positively associated with post-exercise energy intake (41). This suggests that individuals who utilise carbohydrate more rapidly during exercise may be more likely to erode the energy deficit created by exercise through post-exercise dietary compensation. However, it is unclear from this work whether muscle or liver glycogen utilisation were stronger predictors of post-exercise energy intake.

TISSUE-SPECIFIC GLYCOGEN STORES AND APPETITE

Recent work has explored the role of tissue-specific (skeletal muscle and liver) carbohydrate utilization on energy balance behaviours (40). When participants exercised at 50% of maximum

power output, the rate of endogenous glucose appearance (and endogenous glucose disappearance) positively correlated with exercise-induced energy intake compensation (the difference between energy intake after an exercise bout compared to after rest (40)). In other words, those who displayed a higher rate of hepatically-derived glucose utilization during exercise were more likely to attenuate the exercise-induced energy deficit via increasing energy intake. Importantly the rate of muscle glycogen utilization during exercise did not correlate with post-exercise energy intake compensation (in fact, the correlation between muscle glycogen oxidation and energy intake compensation tended to be negative (40)). Since endogenous glucose appearance rates primarily represent rates of hepatic glycogenolysis (29), these data support the hypothesis that hepatic glycogen metabolism during exercise may be an important regulator of post-exercise energy balance behaviours.

Muscle Glycogen:

The availability of carbohydrate to peripheral tissues such as muscle has been suggested to drive food intake based on correlations between capillary-venous differences in glucose concentrations (as a marker of tissue glucose uptake) and food intake (43). However, the available evidence regarding muscle metabolism during exercise and appetite is indirect, and does not suggest a major role for low muscle glycogen concentrations driving increased appetite. For example, interleukin-6 (IL-6) is a muscle-derived peptide secreted when muscle glycogen is depleted yet a *negative* correlation between post-exercise plasma IL-6 concentrations and appetite ratings has been reported (44). Moreover, IL-6 blockade during 12 weeks of exercise training abolishes the loss of visceral fat mass, with total fat mass displaying a similar tendency (45). Furthermore, muscle IL-6 secretion to a degree that is meaningful for appetite regulation is likely to require substantial difference in muscle glycogen stores, which is unlikely to be the case in explaining variance across relatively sedentary individuals beginning exercise training for weight loss. Therefore, there is currently no direct evidence to indicate that low muscle glycogen concentrations regulate post-exercise energy intake.

Liver Glycogen:

Teleologically, hepatic glycogen availability would be more tightly defended than skeletal muscle glycogen, since hepatic glycogen is the primary, direct source of glucose for the circulation, and thus the brain. Skeletal muscle, on the other hand, is deficient in glucose-6-phosphatase, and thus the major fates of glucose within skeletal muscle are either storage (as glycogen), oxidation or conversion to lactate. This may explain why hepatic carbohydrate utilization correlates with post-exercise energy intake, as a behavioural mechanism to restore liver carbohydrate stores. Furthermore, in contrast to skeletal muscle, the liver benefits from a logical direct link to the brain in the form of the vagal nerve, so could (theoretically) more precisely regulate energy balance behaviours proportionate to hepatic glycogen content (42). Data from non-human models provide further support for the idea that hepatic carbohydrate status regulate energy balance behaviours but also help reveal some of the mechanisms involved. Two potential mechanisms include the vagal nerve and the peptide hormone, fibroblast growth factor 21 (FGF21):

Neural Signalling - Protein targeted to glycogen (*Ptg*) acts on both glycogen synthase and glycogen phosphorylase to double hepatic glycogen concentrations under both fasted and fed conditions. Mice with hepatic overexpression of *Ptg* display reduced energy intake, increased energy expenditure, and lower subcutaneous fat masses compared to wild-type mice (42). Importantly, vagotomy abolished all of these responses without affecting the higher liver glycogen concentrations seen in the mice with hepatic overexpression of *Ptg* (42). This provides strong causal evidence for a role of hepatic carbohydrate status in the regulation of energy balance in mice, and also suggests that the vagal nerve is one key link connecting liver glycogen to energy balance behaviours. However, it is still unknown whether it is absolute quantity of liver glycogen, or the rate of liver glycogen utilization that is sensed. This could have implications for energy balance responses to exercise versus fasting, since exercise (at least at moderate-intensity) would provide a more rapid decline in liver glycogen stores than fasting or low-carbohydrate diets (30,31). Nevertheless, the relevance of this mechanism to humans is still unclear, with potential variance in the species-specific hepatic glycogen metabolism and hepatic innervation (31).

Endocrine Signalling - FGF21 is primarily produced by the liver, with smaller contributions from skeletal muscle and adipose tissue (46). FGF21 has been reported to regulate nutrient-specific intake and appears to also be responsive to (hepatic) carbohydrate availability (47). FGF21 can decrease meal size and sweet-seeking behaviour in rodents, resulting in reduced body mass (47), and so (at least in rodents) FGF21 may impact both hunger and satiety. Furthermore, human genetic variants in the *FGF21* locus are associated with reported intakes of sweet foods in the Danish population and dietary carbohydrate increases hepatic *FGF21* mRNA and plasma FGF21 concentrations in rodents (47). This appears to be primarily a response to fructose-containing sugars and/or insulin availability (47,48), which suggests hepatic glycogen status is a key regulator of hepatic FGF21 secretion, since fructose-containing sugars are more potent stimulators of liver glycogen synthesis than glucose-only sources of carbohydrates (49,50), and insulinemia also stimulates liver glycogen accumulation (31). However, there is little evidence to date supporting a role for FGF21 in linking hepatic glycogen availability to post-exercise energy balance adjustments. Exercise increases splanchnic FGF21 secretion in humans, which has been shown by some to be enhanced by glucagon and suppressed by insulin (51), in contrast to findings from others (48). In this scenario, greater hepatic glycogenolysis would be expected under the conditions of higher splanchnic FGF21 release (i.e. a high glucagon-to-insulin ratio). Furthermore, exercise performed in the overnight fasted-, versus the fed-state, which is very likely to result in *lower* liver glycogen concentrations (30), appears to modestly *increase* post-exercise FGF21 concentrations (40). The evidence for FGF21 in linking hepatic carbohydrate availability to energy balance is, therefore, currently unclear. Nevertheless, these data are consistent with the notion that increased FGF21 may be involved in the increase in reward for low-calorie foods (i.e. a shift away from sweet, energy dense food preferences) during the post-exercise state (52). Furthermore, it may be that FGF21 functions in humans primarily to protect against nutrient overload, rather than detect a nutrient deficit, and therefore the role of FGF21 in energy balance may be more important in preventing weight gain than during weight loss.

CAN CARBOHYDRATE AVAILABILITY EXPLAIN RELATIONSHIPS BETWEEN PHYSICAL ACTIVITY STATUS, FAT-FREE MASS AND APPETITE CONTROL?

Carbohydrate availability could provide the mechanistic explanation for the proportional (physiological) increase in energy intake in individuals increasing physical activity from a moderate to a high level, and also the disproportionate (dysregulated) energy intake at low levels of physical activity that lead to weight gain (5).

It has been suggested that fat-free mass (FFM) may regulate energy intake via resting metabolic rate, potentially explaining increased fasting appetite in response to exercise training (53). The mechanistic explanation for this relationship could be partially-related to interactions between organ sizes (muscle relative to liver), as FFM is more variable than is liver size within individuals, especially in response to changes in physical activity status. An increase in FFM could increase the requirements on liver glycogen to provide glucose to the FFM during fasting periods (**Figure 3A**). Importantly the relative demand on the liver should theoretically only increase with changes in FFM and not adiposity, since the downregulation of adipose glucose uptake is directly proportional to expanding adipose tissue mass (54).

A high physical activity level and associated changes in fitness result in numerous changes to carbohydrate and fat metabolism. Individuals with a high aerobic capacity have a greater capacity to store muscle glycogen, and to utilize muscle glycogen more sparingly during exercise (29,31). Whilst liver glycogen storage appears to be unaffected by physical activity status when measured in the overnight fasted state (31), individuals with type 2 diabetes (and thus insulin resistance) can display lower postprandial liver glycogen synthesis (55), and during exercise liver glycogen is utilized more sparingly in individuals with a high aerobic capacity (29). Therefore, if carbohydrate availability is a regulator of energy balance, then this could explain why individuals with a higher physical activity level (and greater insulin sensitivity) display better compensatory reductions in food intake following prior high energy intake (6), and may also be less likely to erode the energy deficit of exercise by subsequently increasing energy intake . Consistent with this notion, individuals who display a greater increase in the respiratory quotient after eating a standardized meal (indicative of greater metabolic flexibility, and a consequence of physical activity) also display a greater decrease in hunger after a standardized meal (39). Therefore, the increase in carbohydrate storage following feeding could be

a factor that dictates postprandial satiety (**Figure 3B**), and decreased reliance on carbohydrate as a fuel during exercise could explain why trained individuals may compensate less following exercise with dietary intake (**Figure 3C**).

***** Figure 3 *****

OTHER FACTORS THAT MAY CONTRIBUTE TO ENERGY BALANCE REGULATION WITH EXERCISE

The novel hypothesis proposed in this review suggests that carbohydrate availability regulates energy balance behaviours in the context of exercise. It should be acknowledged that this is very likely occurring on a background of many other physiological factors also contributing to energy balance regulation. Moreover, these additional factors could be at play in either an independent or interactive way with carbohydrate availability. Whilst not the focus of this review, there is potential for leptin to be regulated by specific amino acids such as leucine (56). Finally, gut hormones such as glucagon-like peptide-1 (GLP-1), ghrelin and peptide tyrosine tyrosine (PYY) clearly play important roles in energy balance (57).

SUMMARY & FUTURE DIRECTIONS

Energy balance is regulated by a variety of factors. The physiological drivers of appetite and energy intake are wide ranging, and include hormones secreted by the gut and adipose tissue. Leptin is a key hormone secreted by adipose tissue that suppresses appetite, and reductions in leptin with a negative energy balance may contribute to the lack of effectiveness of diet and exercise for long-term weight loss. The role of carbohydrate availability in the regulation of energy balance has been speculated upon for years, yet the mechanistic links between carbohydrate availability and energy balance remained elusive. There is now increasing evidence that carbohydrate availability regulates leptin secretion, independent from energy balance. Carbohydrate availability may also regulate energy balance more directly, since hepatic glycogen content can be detected by the vagal nerve to control energy intake and expenditure in rodents (**Figure 4**). High hepatic glycogen content suppresses food

intake and increases energy expenditure. In humans there is now observational evidence supporting a link between energy intake and hepatic glycogen content, since individuals who oxidise hepatic carbohydrate sources more slowly during exercise also display less energy intake compensation post-exercise. This may partly explain why individuals who are highly physically active and/or aerobically fit are better able to control appetite than people with very low physical activity levels.

Future work should explore the mechanisms by which carbohydrate availability may affect secretion of hormones such as leptin and GLP-1, and potential interactions with other nutrients such as leucine. Further work is also needed to examine the causal nature of the relationship between hepatic glycogen availability and energy balance in humans, alongside potential mechanisms. This information could be important for understanding the compensation of energy intake with exercise training and caloric restriction. An understanding of these relationships can be used to develop strategies targeting carbohydrate availability via nutrition, exercise modalities or pharmacological agents, and could hold promise in maximising the potential of exercise to induce fat loss.

*****Figure 4*****

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Figure Legends – Figures to be printed in black and white only.

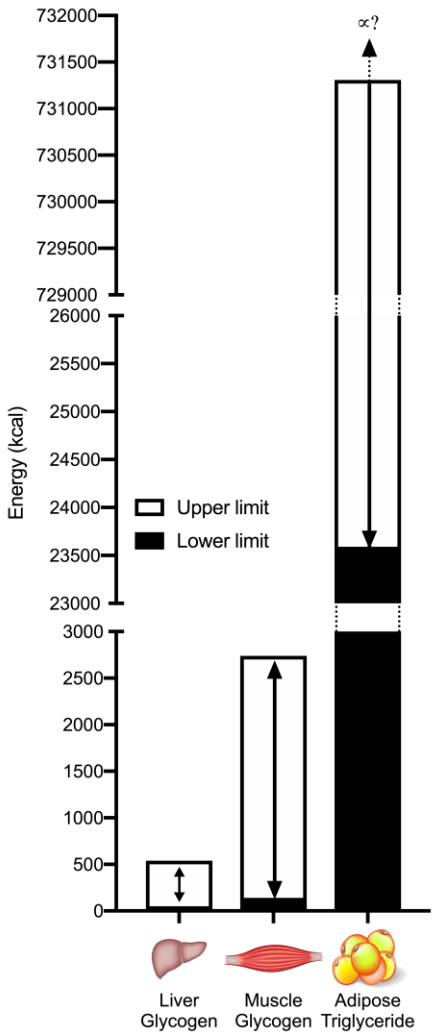

Figure 1. Upper and lower limits of energy stores in humans. Energy is primarily stored in humans in the form of liver and muscle glycogen and adipose tissue triglycerides. The lower limits of liver (~13 g) and muscle glycogen (~35 g) are observed with 2-7 days of fasting, and prolonged, exhaustive exercise, respectively. Upper limits of liver (~125 g) and muscle (~650 g) glycogen are seen after a high carbohydrate diets consumed by endurance-trained individuals. The lower limit of fat mass is thought to be ~2.5 kg as observed with 6 months of starvation, whereas the upper limit of adipose tissue is theoretically limitless, but observations of ~75 kg is an observable fat mass in many obese individuals.

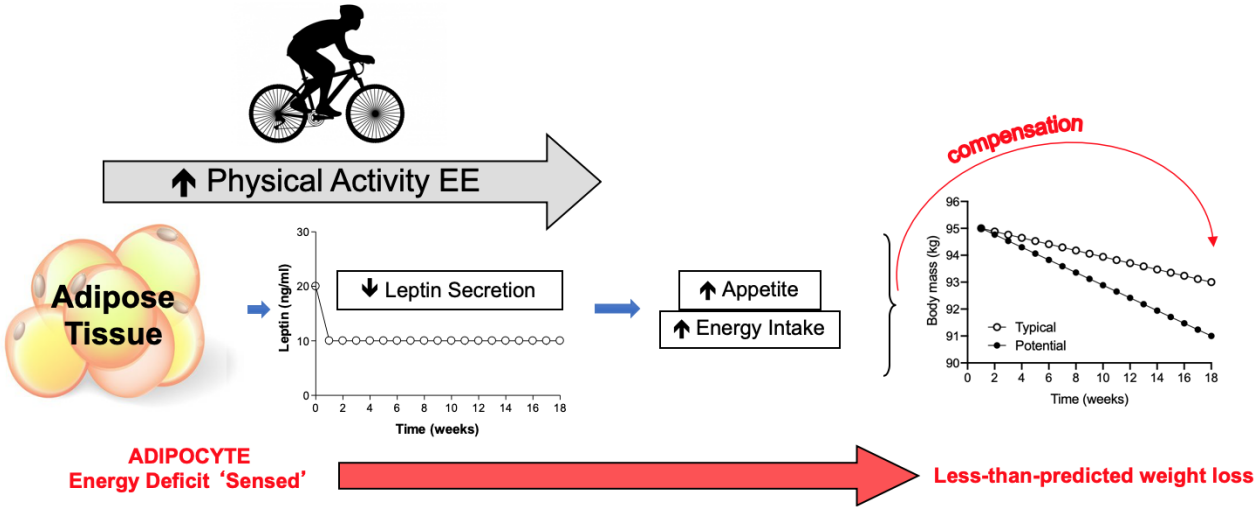

Figure 2. Leptin responds to exercise-induced energy deficits to defend against weight loss. An increase in energy expenditure by exercise that results in an energy deficit is sensed by adipose tissue, which results in a decline in leptin secretion. The reduction in leptin concentrations stimulate increases in appetite, resulting in compensatory increases in energy intake. The increase in energy intake erodes the potential energy deficit created by exercise, producing weight loss that is less than would be predicted based on the energy expended by exercise alone.

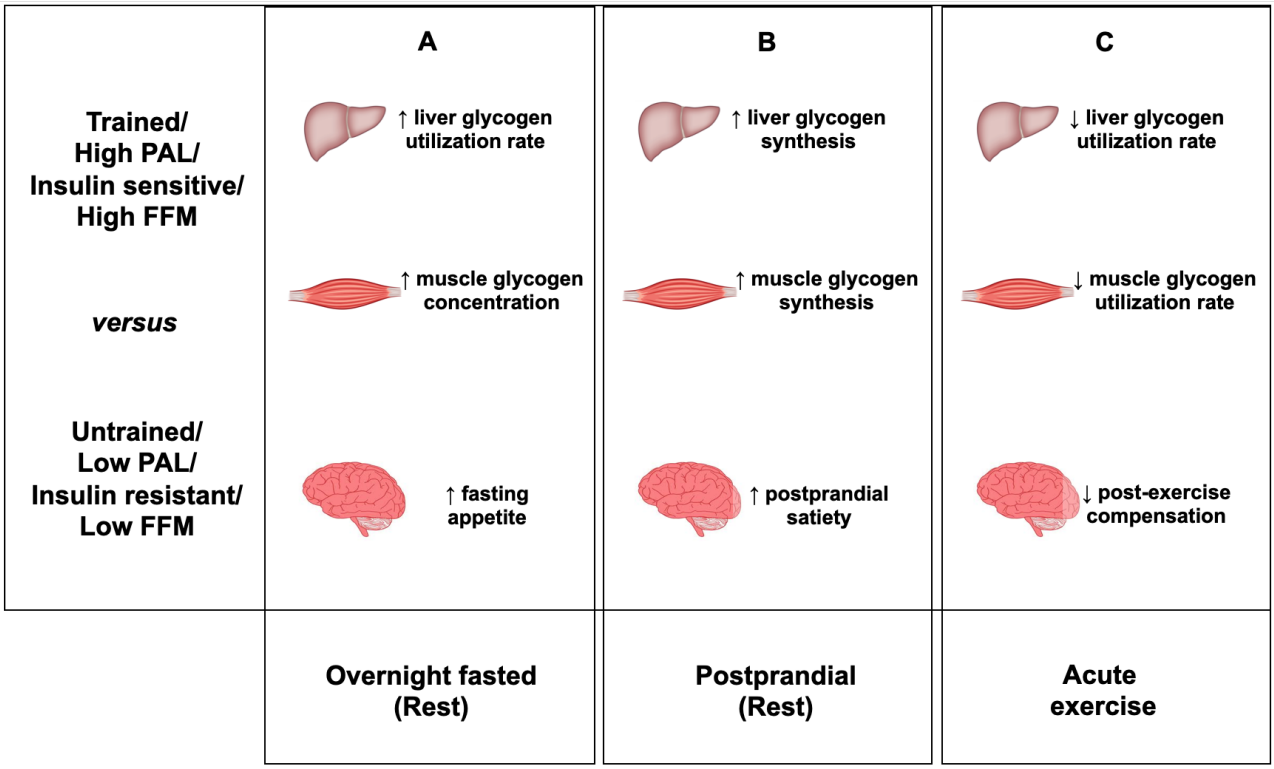

Figure 3. Putative mechanisms by which changes in carbohydrate metabolism may link physical activity status to appetite control. A high physical activity level (PAL) clusters with increases in training status, increased insulin sensitivity and higher fat-free mass (depending on the mode of physical activity), relative to a lower physical activity. A high PAL and the associated phenotype could result in an increase in the relative demand for liver glycogen during fasting periods if liver size is unchanged, which could result in higher fasting appetite due to more rapid liver glycogen depletion, even in the presence of similar or higher muscle glycogen concentrations (**A**). In the postprandial state, the high PAL phenotype is associated with greater muscle and liver glycogen synthesis, which could increase postprandial satiety (**B**). During acute exercise (in the fasted state), a high PAL phenotype is associated with slow rates of liver and muscle glycogen utilization, which may result in less post-exercise dietary compensation due to less of a depletion of endogenous carbohydrate stores (**C**).

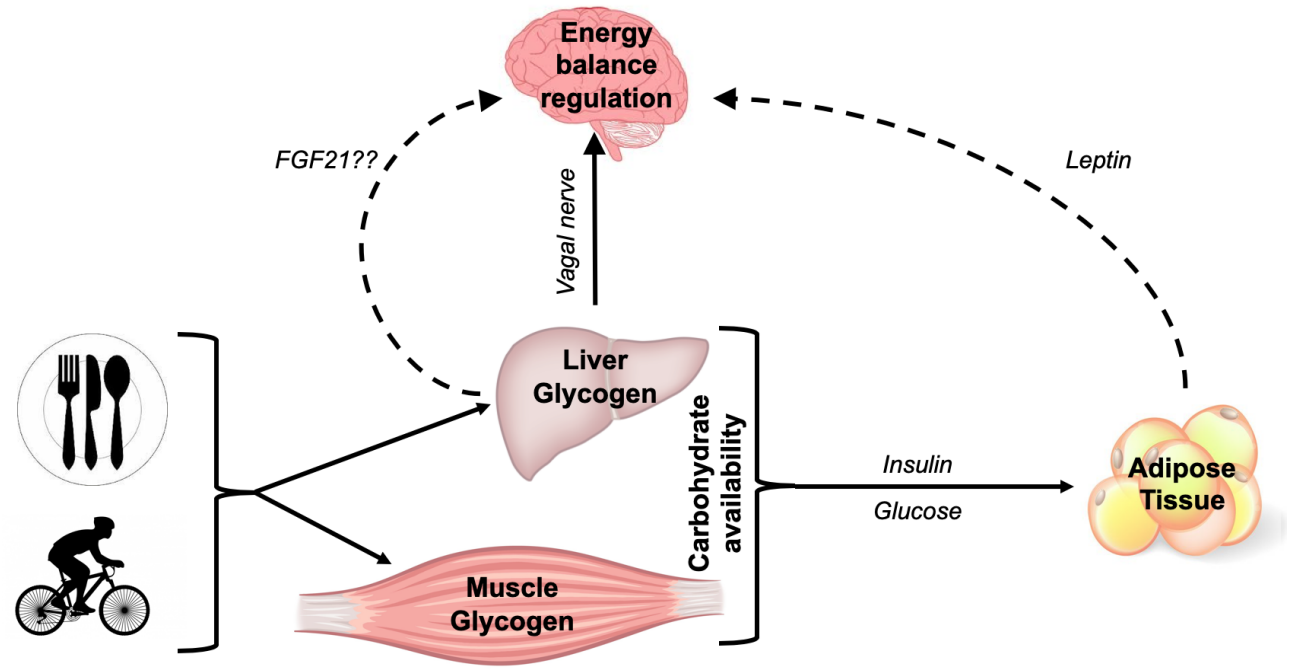

Figure 4. Potential hormonal and neural mechanisms linking carbohydrate availability to energy balance regulation. Diet and exercise can each influence carbohydrate availability by modulating rates of liver and muscle glycogen synthesis and utilization. Leptin is well-established as a hormonal link between adipose tissue mass and energy balance regulation. When adipose tissue stores are low, lower leptin concentrations result in increases appetite and energy intake. Increasing evidence suggests lower carbohydrate availability can also reduce leptin secretion in humans, independent from energy balance, and low liver glycogen concentrations can also directly stimulate energy intake in rodents via the vagal nerve. Fibroblast-growth factor 21 (FGF21) has been implicated in linking hepatic metabolism to energy balance, but the evidence for this link is currently less clear.