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Abstract

Hyperglycaemia is the defining feature of type 1 (T1D) and type 2 (T2D) diabetes and results from deficient insulin production, impaired insulin-stimulated glucose uptake, or both. It is now well established that hyperglycaemia results in profound metabolic complications, but the effect of diabetes and its associated metabolic effects on homeostatic and hedonic appetite control has received less attention. Inappropriate food choices and excess food intake may promote weight gain, further exacerbating the metabolic consequences of T1D and T2D. The need to control blood glucose through diet, physical activity and/or medication as a consequence of impaired insulin secretion and/or sensitivity adds a further level of physiological and behavioural complexity to the processes underlying food choice and appetite control. Alterations in appetite-related processes have been noted in those with T2D, but the effect of T1D on appetite is largely unexplored. Peripheral neuroendocrine signalling appears disrupted in those with T2D, while brain regions involved in the central modulation of appetite may display central insulin resistance. However, it is difficult to isolate the consequences of T2D from that of obesity. Healthcare policy advocates the use of physical activity as a means of preventing and treating T2D via the promotion of weight loss and its independent influence on insulin sensitivity. Exercise-induced perturbations to energy balance can elicit biological and behavioural compensation that attenuates weight loss, and diabetes pathophysiology may alter the strength of such compensation. However, the effect of exercise on appetite in people living with diabetes has yet to be fully explored.

INTRODUCTION

Understanding the processes influencing eating behaviour in health and disease are important as they underpin the overconsumption of food and are implicated in the metabolic responses that impede weight loss. These processes involve complex interactions between the homeostatic and hedonic systems governing energy balance. Overconsumption is now widely regarded as arising from the strength and abundance of cues to eat in the environment that cause a hedonic response which, in turn, overcomes the capacity of the homeostatic processes to inhibit food seeking and ingestion. The prevention and treatment of diseases such as obesity and type 2 diabetes (T2D) through restricting energy intake (EI) or increasing physical activity are challenged by the willingness of people to relinquish a major source of pleasure in their lives, and by physiological and behavioural responses opposing weight loss. In the case of diabetes, the need to control blood glucose through diet, physical activity and medication as a consequence of impaired insulin secretion or insulin sensitivity adds a further level of physiological and behavioural complexity to food choice and appetite control. Therefore, this narrative review examines the consequences of diabetes on the mechanisms of appetite control and how exercise impacts on these processes.

HOMEOSTATIC APPETITE CONTROL

The homeostatic perspective on appetite control embodies feedback signals that reflect acute (episodic) and long-term (tonic) energy availability and needs. Tonic mechanisms exert stable influence over appetite and provide a link between metabolic requirements, stored energy, and day-to-day EI. This feedback has traditionally been attributed to the inhibitory action of leptin and insulin, but it is now recognised that the metabolically active lean tissues also provide an enduring signal to eat [1]. Episodic signals respond to the presence or absence of nutrients in the gastrointestinal tract. Anorexigenic gastrointestinal hormones such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1) and peptide tyrosine tyrosine (PYY), along with the orexigenic peptide ghrelin are released according to the structure, composition and quantity of ingested foods and manage the uptake of nutrients into the peripheral circulation and tissues and provide direct and indirect stimulation of receptors in key brain regions such as the hypothalamus [2].

The Drive to Eat - A Need Based System

Modern theories of human appetite control embody the view that adipose and gastrointestinal derived signals inhibit a motivational drive to eat. However, until recently, the biological origins of this drive have been poorly defined. Recent studies examining components of body composition and energy expenditure (EE) as putative signals of appetite have demonstrated that fat-free mass and resting metabolic rate are positively associated with hunger and EI in weight stable individuals [1]. These findings have led to the suggestion that the metabolic activity of fat-free mass creates a tonic drive to eat that ensures EI meets basal energy requirements [1]. In line with this, the effect of fat-free mass on EI has been shown to be mediated by resting metabolic rate [3], suggesting that EE *per se* may exert influence over day-to-day EI. This model shifts scientific focus from the mechanisms that inhibit appetite to those that drive appetite, and when considered alongside signals stemming from adipose tissue and gastrointestinal hormones, provides a stronger account of whole-body peripheral signals involved in the tonic control of human appetite. Questions remain over the molecular pathways that translate obligatory energy needs into behavioural feeding patterns, and how the strength of the associations between body composition, EE and EI are altered in health and disease. Evidence suggests that associations between fat-free mass, hunger and EI are weaker in those with obesity [4], but while ectopic fat accumulation is a key feature of insulin resistance, how such associations are altered in diabetes is unknown.

The Inhibition of Eating

Hormones secreted from adipose tissue, the pancreas and the gastrointestinal tract act to inhibit appetite on a meal-to-meal (episodic) and day-to-day (tonic) basis. Gastrointestinal hormones such as CCK, GLP-1, PYY and oxyntomodulin, released on the sight and smell of food and the presence of nutrients in the gastrointestinal tract, initiate a cascade of neural and hormonal signals that act both peripherally and centrally to promote meal termination (satiation) and supress hunger during the post-prandial period (satiety) [2]. These anorexigenic hormones act alongside the orexigenic hormone ghrelin in the episodic control of food intake. Hormones such as leptin and insulin also exert tonic feedback on appetite by

adjusting the strength of episodic signalling to reflect longer-term energy storage and requirements in meal-to-meal feeding patterns [2].

Mechano- and chemo-sensitive vagal afferent neurons are stimulated by gastric distension and the secretion of gastrointestinal hormones such as CCK, GLP-1, PYY and oxyntomodulin following food consumption. Vagal afferent signalling is detected by interoceptive areas of the brainstem (e.g. nucleus tractus solitarii; NTS), and in turn, relayed to areas such as the hypothalamus to provide feedback concerning the volume, energy content and macronutrient composition of nutrients consumed [5]. Vagal afferent sensitivity to CCK is enhanced by the release of gastric leptin upon meal consumption (an effect separate to the tonic influence of adipose-derived leptin) [5]. These 'satiety' hormones act synergistically with their co-secretion enhancing their individual anorexigenic properties [6]. The orexigenic hormone ghrelin, secreted by gastric cells in the absence of nutrients in the gastrointestinal tract, inhibits vagal afferent sensitivity to gastric distention and CCK to promote hunger [2]. Ghrelin, insulin, and leptin are also able to cross the blood-brain barrier, acting directly on the brain stem to mediate feeding behaviour [7]. It is worth noting however that these gastrointestinal hormones have a range of functions associated with gastrointestinal motility and nutrient digestion and absorption [6], and their effect on appetite may be a secondary function which provides a modulation rather than a causal inhibition.

Peripheral neuroendocrine signals are integrated in the hypothalamus, and in particular, the arcuate nucleus. Once relayed to the arcuate nucleus via the NTS, these signals stimulate the orexigenic AgRP- and NPY-expressing neurons, and the anorexigenic POMC neurons which release α-melanocyte stimulating hormone [7]. The balance of secretion of these functionally antagonistic neuropeptides confer acute properties of satiation and satiety based on the neuroendocrinal feedback from the periphery [8]. The orexigenic NPY/AgRP neurons in the arcuate nucleus are stimulated by ghrelin and inhibited by glucose, insulin and leptin. In contrast, the POMC/CART neurons are stimulated by insulin, leptin, and glucose, and inhibited by activation of NPY/AgRP neurons [8].

In bringing satisfaction of long-term energy needs through daily EI, hormones such as leptin, and to a lesser extent, insulin [7], also exert tonic feedback on appetite by adjusting the strength of meal-to-meal episodic signalling to reflect long-term energy storage (e.g. adipose tissue). This is achieved by altering central sensitivity to satiety signals. Reductions in circulating leptin and insulin with adipose tissue loss reduces the sensitivity of the NTS to CCK-mediated vagal afferent stimulation, reducing satiation on a meal-to-meal basis [2]. Weight loss-induced reductions in leptin are also thought to promote hunger via a down-regulation in POMC/CART neuron expression, and an up-regulation in NPY/AgRP expression [2].

HEDONIC APPETITE CONTROL

The hedonic perspective on appetite control accounts for eating behaviour motivated by the expectation or experience of pleasure from consuming specific foods and involves dissociable processes of 'wanting' and 'liking'. The 'liking' component refers to the subjective experience of pleasure elicited by the sensory perception of food and is associated with the release of endogenous opioids acting on localised clusters of neurons termed 'hedonic hotspots' [9]. The 'wanting' component of reward refers to the process by which food is assigned motivational significance or 'incentive salience attribution', and is associated with the release of the neurotransmitter dopamine in the mesocorticolimbic pathway. This latter component can be activated by thoughts or cues signalling food and often precedes the actual receipt of food [10].

In human neuroimaging studies, regional differences in the neural activation to food stimuli during either anticipatory or consummatory phases of reward processing are broadly supportive of the distinction between liking versus wanting. Response to passive viewing of high- versus low-calorie foods or cues signalling the imminent receipt of a tasty food are more reliably observed in the amygdala and ventral striatum whereas the response to the actual taste and consumption of a palatable food is associated with activation in the primary taste cortex in the insular/opercular cortices [11]. Some researchers have proposed that differences between individuals who are lean and with obesity in neural activation to palatable food can be understood as a dissociation in both the direction and region of

responding during the anticipatory and consummatory phases of food intake; with greater striatal activation in individuals with obesity compared to lean controls when a food is wanted but lower activation in liking-related regions when a food is actually tasted [12]. However, a number of inconsistencies in the brain imaging literature have been noted [13] and further research is needed to substantiate this hypothesis.

Liking and wanting for food are often viewed in relation to subjective states or explicit feelings that refer to the everyday understanding of these terms in the context of food choice and food intake [14]. Wanting may describe subjective states of desire, craving, or perceived deprivation of pleasure. While liking is characteristically understood as the perceived hedonic impact of a food, the appreciation of its sensory properties, or some evaluative judgment of its potential to give pleasure. As the subjective sensations of liking and wanting often overlap and are subject to interference or misinterpretation, their relationship with behaviour is often difficult to discern [14]. However, liking and wanting responses to food are not necessarily consciously monitored or even always accessible to the individual. While people tend to be very good at estimating and reporting their liking for food, they are often unable to accurately gauge their implicit wanting for food (i.e. why they are unconsciously drawn to one food over another).

The hedonic approach primarily accounts for the natural appetite for pleasure, so essential in a well-functioning homeostatic system for the supply of nutrients and energy, but also for forms of dysregulated eating. Increasingly, evidence for the interplay between liking and wanting with hunger and satiety is helping to clarify the role of hedonics in the control and loss of control over food intake [15]. This extension to the conventional homeostatic model recognises that hedonic processes are affected by acute nutritional need states, and may modulate food intake through their interaction with other physiological processes involved in satiation and satiety. Likewise, cognitive and sensory inputs implicated in food liking and wanting can modulate the metabolic processes associated with homeostatic control over food intake [16]. In addition to the effect of liking and wanting on episodic appetite responses, more recent evidence is emerging to suggest that tonic signals of nutritional status

may affect liking and wanting for food to influence food preference and the composition of the diet [15].

GLUCOSE AND INSULIN HOMEOSTASIS AND THE CONTROL OF APPETITE

The glucostatic theory of appetite, proposed by Jean Mayer [17], suggested that changes in peripheral and central glucose utilization were key in encoding perceptions of hunger in the short-term control of EI, with 'metabolic hypoglycaemia' acting as cue for meal initiation. While recent scientific advances have shown the glucostatic theory to be overly simplistic as a 'stand-alone' model of appetite, animal models indicate that insulin can influence appetite by activating insulin receptors that increase the hypothalamic expression of anorexigenic peptides, and acts on other neurons to inhibit the expression of orexigenic peptides. In support of this, some studies have assessed the link between glycaemic load, glycaemic responses and appetite e.g. [18], and suggest that lower glycaemic loads and glycaemic responses result in lower postprandial appetite and EI. Interestingly, Flint *et al.* [19] reported that post-prandial insulin concentrations were inversely correlated with hunger, satiety and *ad libitum* EI in individuals with normal weight. This 'satiety' effect was blunted in individuals with overweight and obesity, an effect attributed to insulin resistance. Post-prandial blood glucose concentrations were not associated with subjective appetite in individuals with normal weight or with obesity. More recent studies are examining how differences in glycaemic control can be used to inform 'personalised nutrition' interventions e.g. [20], while the PREDICT study reported that individuals who demonstrated larger post-prandial dips in glucose during a 13-day period of continuous glucose monitoring (n=1070) experienced greater hunger sensations 2-3h post-meal and greater subsequent EI [21].

Feeding Responses to Hypoglycaemia

While glucose and insulin likely act alongside other gastro-intestinal hormones in the episodic control of food intake, there may be certain circumstances in which glucose homeostasis plays a more prominent role in influencing eating behaviour. Due to the need to deliver a constant supply of glucose to the brain, glucose homeostasis is tightly regulated. Hypoglycaemia, common in those with diabetes

[22], is met with potent neuroendocrine and autonomic counter-regulatory responses to restore euglycemia [23]. Hypoglycaemia is also characterised by hyperphagia. In individuals without diabetes, hypoglycaemia has been shown to enhance selective attention toward food stimuli [24] and increase EI [25]. While the counter-regulatory responses to hypoglycaemia are impaired in those with diabetes [26], hypoglycaemia also increases food cravings in those with T1D [27]. This hypoglycaemia-induced feeding, termed glucoprivic feeding [7], is thought to ensure the repletion of peripheral fuel stores, and in particular, glucose. Numerous peripheral and central glucose-sensing mechanisms play a role in detecting hypoglycaemia and initiating counter-regulatory responses [28]. The hypothalamus again plays a role in glucoprivic feeding, with hypoglycaemia increasing the activity of hypothalamic NPY/AgRP and decreasing the activity of POMC/CART neurons [29]. However, hypothalamic NPY/AgRP activity may not be required to initiate this response [30], and in contrast to 'normal' day-to-day feeding, the norepinephrine and epinephrine neurons in the hindbrain have been suggested to be those primarily involved in hypoglycaemia-mediated feeding [28]. It has been suggested that hypoglycaemia may activate neuronal feeding pathways as part of an 'emergency response' that are distinct to that activated during 'normal' periods of fasting [7].

DYSREGULATION OF APPETITE AND FOOD REWARD IN DIABETES

Central and peripheral differences in appetite have been noted in individuals with and without diabetes. However, research specifically examining appetite control in those with diabetes, and especially T1D, is limited and it is difficult to isolate the effects of obesity from those of diabetes *per se*. In addition to its peripheral action, insulin provides central modulation of neuronal activity in brain regions implicated in eating behaviour, sensory processing and reward [31]. It has been suggested that brain insulin resistance occurs alongside peripheral resistance in regions key to appetite and motivational behaviours [32]. Central insulin signalling also regulates metabolic pathways in peripheral tissues, with modulation of vagal nerve activity providing cross-talk between the hypothalamus and peripheral organs (e.g. liver and adipose tissue) [5]. Mechano- and chemo-sensitive vagal fibres innervating the gut are central to the gut-brain axis, but vagal gastrointestinal hormone receptor expression and sensitivity to peripheral stimuli may be reduced in those with obesity and diabetes [33]. This may occur in part due to neuropathy

[34], but vagal afferent sensitivity to CCK has been shown to be attenuated in rodents fed a high-fat rather than low-fat diet [35], and vagal neurons may develop leptin resistance in individuals with obesity [36]. These data suggest that excess fat mass, as typically seen in T2D, may disrupt vagal sensing of peripheral appetite signals and their detection and integration in brain regions key to the central modulation of appetite.

Evidence also indicates that circulating concentrations of peripheral gastrointestinal hormones maybe altered in those with T2D. Individuals with T2D demonstrate reduced concentrations of fasted acylated ghrelin [37], which may be a consequence of prolonged hyperglycaemia and hyperinsulinemia [38]. Attenuated post-prandial responses to meal ingestion have also been noted for acylated ghrelin [39], and ghrelin and insulin resistance are inversely associated [40]. Post-prandial GLP-1 concentrations are also impaired in those with T2D following meal ingestion [41], while fasting and post-prandial PYY concentrations have also been reported to be lower [42]. Increased concentrations of pro-inflammatory cytokines such as IL-6 and TNF-α, as seen in those with T2D, may also modulate the secretion of gastrointestinal hormones [43]. However, the functional relevance of these alterations on subjective appetite and EI is not clear, especially given the multiple physiological roles these hormones play within the gastrointestinal tract. It is also difficult to disassociate the effects of excess fat mass from the pathophysiological effects of diabetes *per se*. The aforementioned changes in appetite-related hormones mirror those reported with obesity, and studies that attempt to dissociate the effects of diabetes and obesity on gastrointestinal hormones are inconsistent e.g. [39, 44].

Studies suggest that obesity is associated with preferences for foods high in fat and sugar and with reward in response to food intake and food cues [14]. Research on food reward in diabetes is lacking but results from small brain imaging studies have suggested altered activity in central reward circuits in response to visual food stimuli and food intake in individuals with T2D compared to healthy controls [45]. Insulin-reward pathways may be affected in T2D as insulin resistance in the periphery is associated with insulin resistance in brain regions involved in appetite control and food reward [32]. An interesting hypothetical mechanism for altered appetite and food reward in diabetes may emanate from the

hippocampus. Hippocampal insulin resistance in diabetes is associated with impaired cognitive function [46] and damage to the hippocampus has been shown to have a range of appetitive consequences such as loss of interoception of hunger and fullness sensations, poor mental imagery of food, and weak inhibition of food-cue-elicited reward responding to food [47]. In an examination of persons with T2D during a 12-month weight management trial, improvements in hedonic eating scores on the Power of Food Scale were related to percentage weight loss and an improvement in glycaemic control [48]. Another 3-month weight loss trial with GLP-1 analogue liraglutide examined food reward in patients with overweight and T2D with poorly controlled glycaemia [49]. An improved taste threshold detection for sweet along with decreased wanting and recalled liking for high-fat food was observed alongside decreases in body weight and HbA1c. An important consideration for clinical practice is how the dietary prescriptions for diabetes management, and weight loss *per se*, influence eating behaviour and food reward. While most diabetes associations now recognize that there is no specific one-size-fits-all 'Diabetes Diet', benefits of reducing overall carbohydrate intake for blood glucose management has been shown [50]. The long-term implications for appetite control and compensatory appetite behaviours from these clinical dietary recommendations remain to be fully understood.

PHYSICAL ACTIVITY, ENERGY BALANCE AND DIABETES

Alongside diet, healthcare policy advocates the use of physical activity as a first-line treatment in individuals at high-risk of developing or with T2D. As this approach centres on the promotion of both weight loss and insulin sensitivity, it is important to understand how exercise and/or physical activity impacts on components of energy balance and processes of appetite control. Perturbations to energy balance via dietary restriction and/or exercise training can elicit biological and/or behavioural compensation that offsets the prescribed energy deficit and minimises weight loss [51]. Diet and/or exercise-induced reductions in non-exercise EE have been suggested as a behavioural means through which weight loss is opposed, but evidence for such a response is not strong [52]. Indeed, while EE and its components change in response to weight loss (e.g. resting metabolic rate), compensatory changes in EI may have a greater capacity to counter perturbations to energy balance and body composition [53]. Therefore, the following section will provide a brief overview of the effects of acute and chronic

exercise on appetite and food reward in individuals who are lean and with obesity, before examining the research pertaining specifically to exercise and appetite in those with diabetes.

Exercise and Appetite Control

The effect of acute bouts of aerobic exercise on subjective appetite, gastrointestinal hormones and EI has been studied extensively in healthy lean, and to a lesser extent, in adults with obesity. Studies typically demonstrate that a single bout of moderate-to-vigorous intensity aerobic exercise transiently suppresses appetite during and immediately following exercise [54]. This suppression is short-lived (~30-60 minutes post-exercise), but coincides with reductions in acylated ghrelin and increased concentrations of PYY, GLP-1 and pancreatic polypeptide [55]. However, these post-exercise changes in subjective appetite and gastrointestinal hormones display marked inter-individual variability and do not typically translate into changes in EI [54]. When objective measures of EI and EE have been used, partial compensation in EI equal to ~30% of the exercise-induced energy expenditure have been observed following 7-14 days of exercise e.g. [56]. These findings are consistent with some longer-term interventions which demonstrate that compensatory eating can mediate exercise-induced weight loss in some individuals e.g. [57]. However, compensation is again often partial with weight loss still seen. Indeed, it has been proposed that long-term exercise training has a positive effect on appetite control and promotes a stronger coupling between EI and EE [58].

One of the perceived barriers for engaging in exercise is its potential to promote hedonic eating. Observational studies show that habitual exercise is associated with lower liking and wanting for high-fat/high-energy food, and higher liking for low-fat/low-energy food e.g. [59]. These findings may reflect improved appetite control and are supported by evidence from exercise training interventions. Where exercise training leads to successful weight loss, it appears to be accompanied by a dissociation between liking and wanting evidenced by a reduction in wanting for high-energy food but increase in liking for low-energy food [60]. Acute bouts of exercise tend to only impact behavioural indices of food reward in less active individuals or those with poor appetite control, where it tends to result in reduced food reward e.g. [61]. Food reward therefore does not counteract the benefit of physical activity for

management of obesity. Rather, exercise appears to accompany positive changes in food preferences in line with improvements in appetite control.

The Impact of Exercise on Appetite in Individuals with Diabetes

Limited research exists examining the effect of exercise on appetite in those with diabetes. In studies in those with overweight and obesity, glycaemic control is not typically well characterised, and those with clinically defined T2D are normally excluded from participation. Studies performed in those with diabetes rarely compare between individuals with and without diabetes, are limited to small samples, and post-exercise measures of EI are not always included alongside measures of gastrointestinal hormones and subjective appetite. Heden et al. [62] reported that a 45-minute bout of resistance exercise in 12 individuals with obesity and T2D reduced subjective hunger and increased fullness (measured ~20-30 minutes post-exercise) in comparison to a non-exercise control condition, and these changes coincided with a reduction in acylated ghrelin. Pancreatic polypeptide concentrations were also reduced immediately after exercise, but were not different to the non-exercise control condition ~20-30 minutes post-exercise. Müller et al. [63] reported that ad libitum meal intake and self-reported EI did not change 4-36 hours after one hour of continuous (~70% peak maximal aerobic capacity) or intermittent walking (intervals of 3 minutes slow [~55% of peak maximal aerobic capacity] & 3 minutes fast walking [~90% of peak maximal aerobic capacity]) in 13 individuals with T2D. Interestingly, it has been reported that individuals with overweight and T2D (n=8) displayed reduced post-prandial fullness in response to a 75-g oral glucose load as compared to those without T2D (n=7) [37]. When one hour of cycling (50% of maximum work capacity) was performed immediately before an oral glucose load, post-prandial fullness did not differ between groups and this was taken as evidence that acute exercise could 'restore' glucose-induced satiety in those with T2D.

Although reduced fasting and post-prandial ghrelin concentrations have been noted in those with T2D, the effect of exercise training on this orexigenic hormone in those at risk of or with T2D is unclear. Adults with obesity and prediabetes, defined as impaired fasting glucose (100–125 mg/dl) and/or impaired glucose tolerance (2-hour plasma glucose; 140–200 mg/dl), performed 14-days of work-

matched continuous (*n*=14) or interval (*n*=14) aerobic exercise [64]. Exercise did not alter fasting or post-prandial concentrations of acylated or de-acylated ghrelin, or subjective appetite. However, a reduction in post-prandial insulin was noted in both groups, while an increase in fasting GLP-1 was noted in the continuous group. There was also a tendency for self-reported food intake (3-day food logs) to decline with exercise training (*P*=0.09). More recently, the same authors have demonstrated in women with obesity (*n*=26) that 14-days of interval exercise combined with a low-calorie diet enhanced the post-prandial suppression of acylated ghrelin and attenuated the changes in fasting hunger as compared to a low-calorie diet only [65]. These data indicated that 14 days of exercise training, with or without energy restriction, failed to elicit compensation in markers of appetite in those at risk of T2D, but the short-term nature of these studies limits interpretation. Interestingly, women with T2D (*n*=17) were shown to increase fasting total ghrelin concentrations in the absence of significant weight loss following 12 weeks of aerobic exercise (4 times/week, 45–60 minutes/session) [66]. However, no effect was seen in men (*n*=9), and as subjective appetite or EI were not measured, the functional relevance of these changes for appetite control are unknown. In individuals with overweight/obesity and prediabetes (fasting glucose 95–125 mg/dl and/or 2-h blood glucose 140–199 mg/dl), 15 months of resistance training reduced daily EI (albeit with no overall changes in diet quality measured using the Healthy Eating Index) [67]. These authors suggested that exercise training – specifically resistance training – may exert spillover effects and influence other health behaviours such as food intake and food choices among this population. Therefore, exercise in people with (pre)diabetes may not only be strategy to improve insulin sensitivity, but also to improve eating behaviour.

As proposed above, impaired hippocampal function in diabetes and its association with executive function and appetite may also be of therapeutic relevance for exercise training in people with diabetes. In older adults, the hippocampus tends to be larger in those with higher cardiovascular fitness, and physical activity training increases hippocampal perfusion [68]. A large randomised control trial in older adults demonstrated that aerobic exercise training increases hippocampus size, leading to improvements in spatial memory; furthermore, higher pre-intervention fitness attenuated the decline hippocampal volume observed in the control group [68]. These findings together with the hypothesis

of Stevenson [47], linking hippocampal function to eating behaviour, suggest that exercise may be a specifically effective intervention for improving appetite control in those with diabetes, especially where the hippocampus is compromised such as in older adults or those with poor glucose control.

Impact of Exercise and Meal Timing

From a clinical diabetes management perspective, the timing of exercise in people with insulin resistance represents an interesting avenue of research relevant for glycaemic control, and potentially appetite control. The beneficial effects of a single bout of exercise on post-prandial lipidaemia and glycaemia are well established, but there is growing interest in how the timing of exercise, both in terms of its timing across the day and relative to meal intake, influence these metabolic responses in individuals with T2D [69]. An inverted circadian pattern has been reported in individuals with T2D, with the improved insulin sensitivity noted in the evening declining overnight, manifesting in abnormal fasting glucose levels in the morning. Interestingly, 2 weeks of high-intensity interval exercise performed later in the day reduced glucose concentrations (measured via continuous glucose monitoring) on exercise and rest days compared to baseline and to exercise performed in the morning in individuals with T2D [70]. Furthermore, performing exercise after a meal appears to reduce post-prandial glycaemia and lipemia more than when exercise is performed immediately before a meal in individuals with T2D [69]. Exercise timing is an important consideration for clinical diabetes management because most exercise prescriptions follow the 'FITT' principle i.e. frequency, intensity, time (duration) and type, and don't necessarily focus on the 'when'. It remains unknown whether this enhancement in insulin sensitivity with acute exercise timing also promotes an enhancement in the sensitivity of the appetite control system in people with impaired glucose tolerance. In people with T2D, exercise could indirectly influence appetite control via an improvement in insulin sensitivity, but this remains to be examined in future research.

CONCLUSIONS

Alterations in appetite-related processes have been noted in those with T2D, but the effect of T1D on appetite control appears largely unexplored. Neuroendocrine appetite signalling from the periphery may be disrupted in those with T2D, alongside interoceptive detection and integration in brain regions

involved in the central coordination of appetite. However, it is difficult to isolate the consequences of T2D *per se* from those of obesity. Although advocated as a primary means of preventing and managing diabetes, research examining the effect of exercise on appetite in those with T1D and T2D is limited. Existing studies are often of short duration and fail to measure objective food intake alongside measures of gastrointestinal hormones and subjective appetite. Further research is needed to dis-associate the effects of diabetes on appetite from that of obesity, and examine how the pathophysiology of diabetes interacts with the metabolic and behavioural responses to exercise in the control of appetite.

Author Contributions

MH, KB and GF contributed equally to the writing and reviewing of the manuscript and provided final approval for its publication.

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