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Review

The Lipids and Volume in Satiation and Satiety (LIVES) Hypothesis: A Proposed Alternative Model for the Pathogenesis of Obesity

Andrew Warrilow [1,2], Kate Pumpa [3,4], Shawn Somerset [1,†] and Nenad Naumovski [1,2,5,*]

[1] Discipline of Nutrition and Dietetics, Faculty of Health, University of Canberra, Canberra, ACT 2601, Australia
[2] Functional Foods and Nutrition Research (FFNR) Laboratory, University of Canberra, Canberra, ACT 2601, Australia
[3] Discipline of Sport and Exercise Science, Faculty of Health, University of Canberra, Canberra, ACT 2601, Australia
[4] Research Institute for Sport and Exercise (UCRISE), University of Canberra, Canberra, ACT 2601, Australia
[5] Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University, 10431 Athens, Greece
* Correspondence: nenad.naumovski@canberra.edu.au; Tel.: +61-6206-8719
† Deceased.

Abstract: Obesity is one of the most important factors responsible for the marked increase in both the incidence and prevalence of type 2 diabetes mellitus (T2DM) in recent decades. Addressing the lifestyle factors associated with the progression to T2DM would present a potential rational early prevention strategy. The current evidence suggests that excessive energy intake is mediated via dietary fat. Biochemical signals released in response to the ingestion of food require supportive signalling from the presence of food in the stomach. The degree of supportive volume signalling emanating from the stomach influences both the satiation and satiety phases. The Lipids and Volume in Satiation and Satiety (LIVES) Hypothesis proposes that the biological feedback from fat intake appears to be influenced by the other macronutrients with which it is consumed. By identifying the various possible macronutrient combinations with fat, it is possible to construct a matrix of food composition/volume scenarios, which may help elucidate dysfunction in the human food energy regulation system within the context of the modern food environment.

Keywords: obesity; type 2 diabetes; satiation: satiety; fat; volume; cholecystokinin; peptide tyrosine tyrosine

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1. Introduction

Obesity is one of the most important factors responsible for the increase in both the incidence and prevalence of type 2 diabetes mellitus (T2DM) in recent decades [1]. The increase in the prevalence of obesity continues worldwide with the more recent locus of change moving from developed to developing countries as living standards improve and diet preferences change. Globally, the prevalence of obesity has doubled since 1980 [2] with serious consequences for both health systems and individuals. It is estimated that over 2 billion people currently suffer adverse health effects as a result of excessive body weight [3]. Despite these alarming facts, a clear link to the causes of the sudden spike in overweight and obese people and the development of effective prevention strategies still remains elusive.

Addressing the lifestyle factors associated with the progression to diabetes would present a rational early prevention strategy. Normal circulating fasting blood glucose levels (3.9–5.6 mmol/L) [4] and β-cell functioning can be restored by weight loss [5] utilising a low calorie diet and/or physical exercise. Furthermore, this weight loss can

result in normalisation of both β-cell function and hepatic insulin sensitivity in individuals living with T2DM. These changes are also associated with decreased pancreatic and liver triglyceride stores, while increased adiposity may also interfere with the proper functioning of organs. The twin cycle hypothesis [6] postulates that the pathogenesis of ectopic fat accumulation is chronic, excessive energy intake with eventual 'spill-over' into the pancreas. These self-reinforcing cycles between the liver and the pancreas eventually cause metabolic inhibition of insulin secretion after meals and onset of hyperglycaemia suggesting that T2DM is a reversible condition of intra-organ fat excess.

2. Regulation of Dietary Energy Intake

2.1. Satiation and Satiety

The dietary energy intake is governed by a system that consists of two distinct phases—satiation and satiety. Whereas satiation refers to physiological responses to food intake during the consumption of food, which leads to a cessation of eating, satiety refers to the signals which inhibit eating prior to the subsequent meal [7]. The ability of foods to mediate satiation and satiety can be successfully determined in the controlled laboratory setting where potential confounders, such as palatability of the test food, may be well managed [8]. The methodology for measuring satiation is for the energy of food consumed to be calculated up to the point of satiation and after the food concerned has been consumed ab libitum in the fasted state. The ability of a food to mediate satiety may also be measured in the laboratory environment where a test food is given as a meal or preload, and the effect on energy intake of the subsequent meal is measured [7].

2.2. Physiological Regulation of Dietary Energy Intake

The gastrointestinal system continuously relays the information to the brain regarding the quality and quantity of ingested food and nutrients, which is important for satiation, meal termination, appetite and timing of meals. By acting on the brainstem and the hypothalamus, this stream of sensory information from the gut to the brain (and vice versa) generates sensations of satisfaction observed after a satiating meal [9]. The infundibular nucleus located at the base of the hypothalamus is the site of the receptors for many of the digestive hormones known to regulate food intake. Furthermore, the paraventricular nucleus, located in the anterior hypothalamus, interacts with the thyroid and the pituitary and adrenal glands to regulate metabolism [10]. The hypothalamus receives biochemical signals released from the gut in response to food, whereas the brain stem serves as a recipient of nerve signals travelling from the gut via the afferent vagus nerve [11]. The system for receiving feedback from the gut, which provides information crucial for regulating eating behaviour, therefore, is comprised of two separate systems interacting with each other (Figure 1).

Nerves known as vagal afferents transmit information to the relevant sections of the brain from a variety of organs including the gastrointestinal tract, pancreas and liver. Vagal efferent nerves travelling from the brain together with the sympathetic nervous system and hormonal mechanisms act as communication pathways for the brain to control digestion and other functions. These vagal sensory mechanisms play a crucial role in the neural mechanism of satiation [12].

When food is ingested, its presence and volume is detected by vagal afferent nerves in the external muscle layers sensitive to stretch and tension. Intra-ganglionic laminar vagal afferent endings are responsible for detecting muscle tension generated by both passive stretch and active contraction of the muscle layers [9]. Studies in animal models have uncovered an abundance of receptors of the digestive hormone cholecystokinin (CCK) in the vagal afferent nerves [13]. Therefore, digestive hormones may communicate with the brain directly through the bloodstream or via such receptors. Furthermore, it has been proposed that a digestive hormone could use different paths to produce physiological effects, such as changes in eating behaviour or interference with gastrointestinal functions.

Nevertheless, for many pathways there is still conflicting evidence concerning which digestive hormone is responsible for what effect [9].

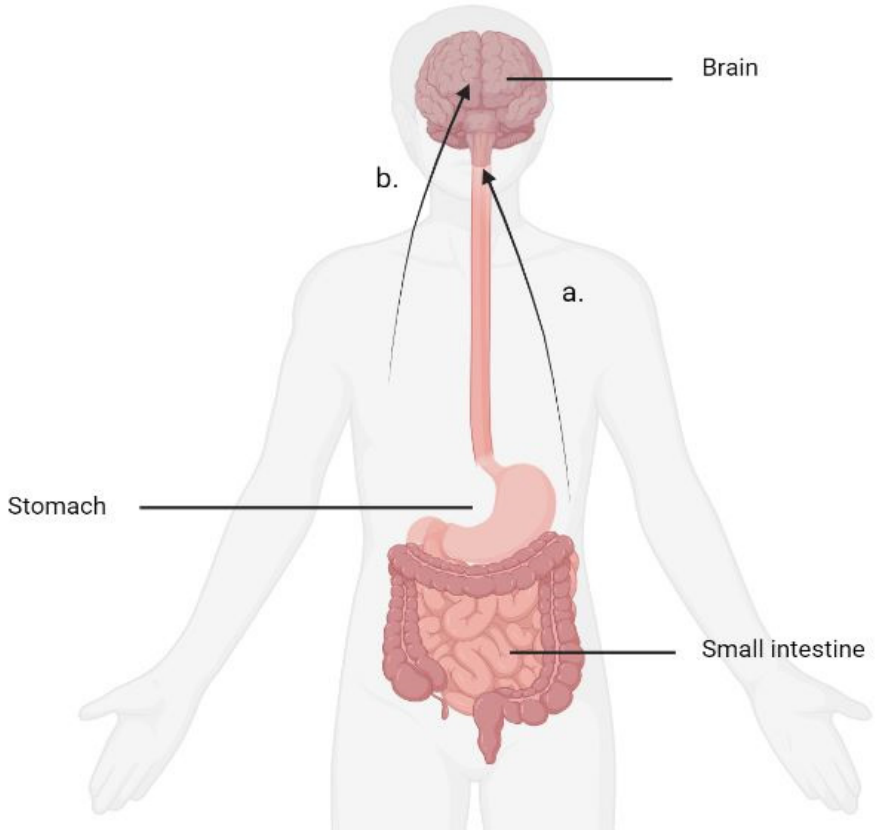

Figure 1. Mechanisms for digestive feedback. (a) The afferent vagus nerve delivers chemical signals produced by baroreceptors located in the stomach to the brainstem. (b) Biochemical signals emanating from the digestive tract are referred to the brain through the circulation. The infundibular nucleus located at the base of the hypothalamus is the site of many of these receptors.

2.3. Biochemical Signalling

Biochemical signals play a crucial role in energy regulation and their function both has an influence on and is influenced by the development of obesity. Peptide tyrosine tyrosine (PYY) is a digestive hormone produced in the endocrine L cells of the ileum, large intestine and rectum [14]. PYY is found in the body in both PYY1-36 and PYY3-36 forms with the latter having an effect on energy intake and the former no effect [15]. The release of PYY peaks around 90 min postprandially and remains elevated for up to 6 h [16]. PYY is secreted in the distal areas of the gut and the amount of PYY released is proportional to the amount of food energy consumed [17], suggesting a role in satiety as opposed to satiation. In animal studies, increased feeding of protein to mice resulted in an increase in plasma PYY levels, decreased food intake and reduced adiposity [18]. Furthermore, PYY null mice have been shown to develop obesity, which was only reversed by the administration of endogenous PYY [18]. In humans, PYY has been shown to reduce food intake by 30% when administered before a subsequent meal [19].

PYY levels peak well before nutrients reach the location where the majority of secreting cells reside in the distal section of the digestive tract [20]. In research conducted on rats, vagotomy was performed completely halting the secretion of PYY in the distal gut. The idea that the signalling responsible for PYY secretion could occur via the vagus nerve is strongly suggestive of mechanisms for PYY release emanating not in the distal gut but in the stomach. Other influences on this transfer of signalling from the proximal to the distal gut include nicotinic synapses and nitric oxide (NO) release [20].

Ghrelin is the hormone responsible for the hunger sensation and is commonly referred to as the 'hunger hormone'. The primary site of ghrelin secretion is in the stomach. The stomach contains ten to twenty times more ghrelin per gram of tissue than the duodenum, and the concentrations of ghrelin decline with increasing distance from stomach along the gastrointestinal tract [21]. Ghrelin secretion results in an increase in meal size [22]. Therefore, the process of satiation is linked to suppression of the secretion of ghrelin.

Insulin has been found to be is essential for meal-induced plasma ghrelin suppression [23] and, therefore, it plays a role in appetite regulation. Insulin is produced in the β cells of the pancreas and acts to regulate carbohydrate, lipid and protein metabolism [24]. Infusions of insulin have shown mixed results on appetite control with some early studies reporting an increase [25] or no increase in appetite [26]. There is evidence for endogenous insulin mediating a reduction in appetite [27]. However, this effect could potentially be due to the influence of glucose as no changes in appetite or food intake were apparent when glucose levels were maintained at constant levels [26].

Recently, the function of the incretin hormones in the suppression of appetite has become more fully elucidated in the scientific literature. Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are the two primary incretin hormones secreted from the intestine on the ingestion of glucose or nutrients to stimulate insulin secretion from pancreatic β cells [28]. GLP-1 is co-secreted with PYY in response to nutrients in the gut [10], and it plays a role in both peripheral and central pathways mediating satiation [29]. GLP-1 is produced in the ileum in the presence of carbohydrate and stimulates the pancreas to increase the production of insulin [30]. GLP-1 is proposed to play an important part in the 'ileal brake' mechanism, and this is believed to be directly related to the means by which GLP-1 influences appetite [31]. GLP-1 has been shown to reduce ad libitum energy intake [32] in a dose dependent manner [33], and its rapid degradation by dipeptidyl peptidase IV (DPP4) and short duration of action suggests a role in satiation as opposed to satiety.

The incretin hormone GIP is released in the presence of either glucose or fat [34]. Studies concerning GIP's role in appetite regulation have shown mixed results with some studies demonstrating its secretion resulting in a reduction in appetite [35] and others failing to find an effect [36]. The insulinotropic effect of GIP is lost in persons living with T2DM [37].

CCK was one of the first digestive peptides to be discovered [38] and was subsequently shown to play an important role in appetite control in animal models [39]. Although CCK is released very quickly into the blood stream (it has been detected at 15 min postprandially) [40], it is also relatively quickly removed. The elimination half-life of the octapeptide variant of CCK is 18 min [41]; however, there are a multitude of variants and concentrations of bioactive CCK variants with larger molecules may remain elevated in the blood plasma for several hours after a meal in healthy humans [42]. Due to its rapid entrance into the blood plasma and short period of action, any effect of CCK on eating behaviour is more likely to be found within a meal rather than between meals and is, therefore, known as the digestive peptide most associated with satiation.

CCK is secreted by duodenal and ileal cells when fat and protein enter the lumen [38] and causes the release of digestive enzymes and bile from the pancreas and gallbladder, respectively [43]. The release of CCK into the blood stream acts on CCK receptors causing gastric emptying to slow [44]. The highest concentrations of CCK may be found in the proximal section [45] of the small intestine. CCK receptors are located in the pancreatic nerves, the gallbladder muscularis, the nerves and muscle along the gastrointestinal tract and in several areas of the brain [46].

The administration of exogenous CCK at pharmacological doses causes smaller meals to be consumed, whereas blocking the action of endogenous CCK or other satiety signals causes larger meals to be consumed [22]. At physiological doses, a preload consumed before the test meal was a necessary condition to achieve this result [47–49]. Initially, it was thought that the effect of CCK was due to the hormone's ability to slow gastric emptying,

but it was observed that the resultant reduction in food intake was greater than that expected from the reduction in gastric emptying, suggesting another potential mechanism of action. The enhancement of signals of stomach distention from the afferent vagus was proposed to be responsible for this effect [48,50–52]. CCK activates CCK-A-type receptors in the pyloric region of the stomach, and this signal is then transmitted via vagal afferent neurons to the nucleus of the tractus solitarius where it is relayed to the hypothalamus [53].

The hormone leptin is secreted by white adipose tissue and has an influence on eating behaviour and the metabolism [54]. Leptin is a mediator of energy regulation over the long term [55] and is thus outside the scope of this review.

2.4. Macronutrients and Regulation of Dietary Intake

2.4.1. Protein and Dietary Energy Intake

Several studies have suggested the effect of adhering to a high protein diet on mediating weight loss [56–59]. Some of the proposed mechanisms include: an increase in the secretion of digestive hormones, such as CCK, GIP and GLP-1; a reduction in secretion of the ghrelin; an increase in thermogenesis caused by the conversion of protein to energy; and protein-induced alterations in gluconeogenesis to improve glucose homeostasis [60].

Protein can influence appetite regulation through either affecting the satiation or satiety (or both) [61]. Protein has been found to deliver both greater satiation and satiety at equivalent levels of energy to carbohydrate and fat [62]. Biochemical signals released from the small intestine in the presence of protein are carried to the brain via the blood plasma [63]. Meals high in protein content suppressed levels of the digestive hormone ghrelin greater than meals high in carbohydrate or fat [64].

2.4.2. Carbohydrate and Dietary Energy Intake

In terms of the regulation of energy intake from the perspective of mediation of satiety and satiation, carbohydrates are proposed to be less efficacious than protein but more efficacious than fat [65]. These findings should be taken with caution as many studies assessed an effect on satiety for different foods after an interval of only two or three hours after ingestion [62] when the effects of carbohydrate were at their peak, but the effects of fat and protein were yet to fully register. A satiety effect peaking so soon after ingestion would be unlikely to have an effect on energy intake at the next meal [66]. Furthermore, the degree of efficacy is dependent upon the type of carbohydrate consumed. The absence of water and fibre in higher energy dense starchy carbohydrates consequently results in a substantial reduction in its satiating properties.

Dietary fibre is the fraction of the edible part of plants or their extracts, or analogous carbohydrates, that are resistant to digestion and absorption in the human small intestine, usually with complete or partial fermentation in the large intestine [67]. Dietary fibre has been shown in epidemiological studies to be associated with lower body weight [68], but it's effect on weight in acute studies is controversial [68–70]. Fibre is also associated with improved satiation, satiety and reduced food intake [71]. Fibre has been shown to improve the ability of those on a low energy diet to maintain compliance [72]. Conversely, in observational studies, the consumption of diets which are low in fibre content, but incidentally high in dietary fat, have been shown to be associated with increased levels of overweight [73,74].

2.4.3. Fat and Dietary Energy Intake

The high energy density of fat makes it an ideal source for the storage of excess energy, and it is used for this purpose in both animals and plants [75]. The consumption of some quantity of fat is necessary to maintain overall health [76,77]. The diets of a number of hunter gatherer groups were heavily dependent on energy-dense, if at times scarcely available, animal-based foods [78]. Historical and anthropological studies have shown hunter-gatherers generally to be healthy, fit and largely free of the degenerative cardiovascular diseases common in modern societies [79].

Fat is highly desirable to humans and this may be due to various factors beyond its nutritional properties, such as cultural and psychological influences [80]. As economic development progresses, consumers consistently make dietary choices which incorporate increased levels of fat, and this behavior is most clearly evident today in the changing dietary choices of consumers in developing countries [81,82]. Furthermore, high dietary fat intake is also considered to be a significant contributing factor to increasing rates of overweight and obesity over recent decades [83]. High-fat diets have been shown to promote the development of overweight and obesity in animal [84–86] and human studies [86–88], although health effects have been shown to vary depending on the type of dietary fat consumed [89]. The high energy density of food makes excessive energy intake occur more easily in foods containing high levels of fat. Improvements to texture and flavour of foods containing fat also increase the risk of overconsumption. In some of the previous studies, it was reported that participants can consume much greater quantities of energy from a range of high-fat foods than from foods high in general carbohydrates or sucrose, commonly associated with the passive overconsumption of fat [90].

On the one hand, fat in the intestine appears to generate potent feedback signals, yet exposure to high-fat foods leads to a form of passive overconsumption suggesting a weak feedback effect on eating behaviour. This contradiction between the strong sensory signaling following the ingestion of fat and failure of these signals to influence eating behavior is commonly referred to as The Fat Paradox [91]. It has been shown that the satiation ability of fat can be made similar to that of carbohydrate by the addition of substances to lower energy density, such as water [92]. More recently, it has been suggested that the feedback from fat intake may be variable depending on the food with which it is consumed [93].

3. Discussion

3.1. LIpids, Volume in Satiation and Satiety (LIVES) Hypothesis Proposal

The system of regulation of energy intake in humans is composed of two aspects—satiation and satiety. It is proposed that the process of satiation appears to more closely resemble an estimate of energy intake, taken rapidly while the meal is being consumed and adjusted during the satiety phase post-ingestion after a more accurate estimate of energy intake may be obtained. For the system of energy regulation to work, it is necessary for either only the satiation phase or the satiety phase to function properly. Conversely, for energy regulation to fail, both phases must be dysfunctional.

Both physically and indeed functionally, satiation and satiety systems are dual faceted—'gastric satiation is volumetric; intestinal satiation is nutritive' [94]. The volume of food is of relevance in satiation and satiety [95]. For the purposes of this review, it is necessary, therefore, to divide carbohydrates into two classes: more voluminous and lower energy dense fruit and vegetables (F&V); and less voluminous, higher energy dense non-Fruit and Vegetable carbohydrates (N-F&V), such as carbohydrates containing starch. Accordingly, there are three possible combinations of fat with other macronutrients: fat with F&V; fat with N-F&V; and fat with protein.

That CCK requires a gastric volume signal to optimise satiation has been demonstrated in a recent systematic review [95], and this is also true of other digestive hormones [96]. The amount of PYY released in the distal gut is controlled by mechanisms in the proximal gut, and these signals are delivered by the vagus nerve [20] suggesting an origin in the stomach. PYY signalling peaks around 90 min post ingestion [16]. It is important to note that carbohydrates rapidly transit the stomach, having a gastric half emptying time of approximately 50 min post ingestion [97,98]. Thus, the degree of supportive stimulus to PYY secretion would be dependent on the quantity of fat and, more specifically, protein in the meal. PYY's connection to the ingestion of protein has been noted in other research [18].

It is now known that the efficacy of Roux-en gastric bypass surgery depends upon this principle. Roux-en gastric bypass surgery is one of the most effective therapies for lowering dietary energy intake and thereby assisting in the treatment of both obesity

and T2DM. The mechanism of action was originally believed to be that the changes after surgery physically restricted food intake or caused nutrient malabsorption. However, such mechanical effects do not play a role in the efficacy related to gastric bypass with a growing amount of evidence pointing to altered neuroendocrine signalling [99]. Gastric bypass surgery creates an increase in pressure in the gastric fundus and PYY levels are elevated after gastric bypass surgery [100]. Therefore, it would be plausible to propose a supportive role for gastric volume in the proper functioning of PYY as well.

3.2. Macronutrient Combinations-Satiation Phase

When fat intake is combined with F&V, greater volume enhances signals of stomach fullness from the afferent vagus nerve via CCK [95]. Further, mastication and other processes involved in the digestion of complex carbohydrates slow digestion, allowing more time for the feedback mechanisms elicited in response to the ingestion of fat to take effect [93]. When fat intake is combined with protein, although the presence of both elicits a strong satiation response, the energy intake may or may not be excessive depending on the fat content of the meal. When intake of fat is combined with N-F&V, the lack of fibre, water and cellulose matrix present in F&V results in loss of volume relative to F&V. Loss of volume and faster ingestion results in a large reduction in satiating power. N-F&V are more quickly ingested, allowing less time for feedback mechanisms to take effect.

3.3. Macronutrient Combinations-Satiety Phase

When fat intake is combined with F&V, the carbohydrate component exits the stomach rapidly leaving only a small volume in the stomach and chemo-signalling not optimised. However, as proposed above, for this combination of macronutrients the satiation phase has already prevented the excessive intake of energy. When fat and protein intake is combined, they remain in the stomach providing volume to positively influence the amount of PYY secreted in the distal gut and ensuring a strong satiety response. Any excessive energy intake via fat and protein is thereby corrected in the satiety phase. When fat intake is combined with N-F&V, as in the case of F&V, the carbohydrate component is emptied from the stomach relatively rapidly and satiety signalling is relatively poor. However, unlike in the case of fat with F&V, this has been accompanied by a failure to prevent excessive energy intake in the earlier satiation phase. For excessive energy intake to occur, it is necessary for both satiation and satiety phases to fail to prevent excessive energy intake. In this case, both phases have failed to regulate energy intake properly resulting in potential excessive energy intake (Table 1). The various possible outcomes of the different combinations are summarised in the matrix in Table 1.

The above proposed model provides a potential new explanation for several dietary challenges hitherto unexplained and is supported by other research. A study by Rolls et al. [92] found that fat was as satiating as carbohydrate at the same level of energy density and the improved signalling via CCK derived from fat when accompanied by F&V offers itself as a potential explanation for this phenomenon. Persons on high-protein diets report an increase in satiety [101], and the presence of protein remaining in the stomach and increasing stomach distention during the crucial period of PYY signalling may explain the positive influence on satiety reported by those on high-protein diets. Diets combining both low fat and high fibre have been found to be the most effective for weight loss [102,103], whilst those high in fat content and low in fibre are most strongly associated with weight gain [73] and the development of T2DM [104].

Table 1. Proposed outcomes of the different combinations for energy regulation and paired macronutrient matrix.

Macronutrient Combination	Satiation Phase	Satiety Phase	Outcome
Fat + F&V [1]	CCK [2] signalling optimised with F&V.	PYY [3] signal not optimised due to energy intake; rapid emptying of carbohydrate.	Non-excessive.
Fat and Protein	Strong satiation signal due to the action of CCK but potential for energy intake to be excessive depending on fat content.	PYY signal optimised due to slow gastric emptying during PYY release and resultant volume signal from the stomach.	Non-excessive energy intake.
Fat and N-F&V [4]	CCK signal not optimised with N-F&V.	PYY signal not optimised due to rapid gastric emptying of carbohydrate.	Excessive energy intake.

[1] Fruit and Vegetables; [2] Cholecystokinin; [3] Peptide Tyrosine Tyrosine; [4] Non-Fruit and Vegetable carbohydrates.

4. Conclusions

The current evidence suggests that excessive energy intake is predominately mediated via dietary fat although with varying effects depending on the type of dietary fat. The biological feedback from fat intake appears to be influenced by the other macronutrients with which it is consumed. Feedback is delivered in two phases—satiation and satiety. Numerous studies have identified the importance of stomach distension to the proper signalling of the digestive hormone CCK, and it is highly plausible that stomach distension plays a similarly important role in the proper functioning of other digestive hormones, such as PYY. Classifying carbohydrates into voluminous/less voluminous types and combining each class with fat and, in addition, combining protein with fat, there is a plausible proposal to construct a matrix of possible food composition/volume scenarios, which may help elucidate dysfunction in the food energy regulation system within the context of the modern food environment. These proposals warrant further assessment by clinical trials.

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