Appetite Regulatory Hormones – A Novel Target for Prevention, Management, and Treatment of Obesity

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ABSTRACT: The World Health Organization has described obesity as one of the today's most neglected public health problems worldwide. The main factor contributing to excessive weight gain is the impaired balance between energy intake and expenditure. This review aims to highlight the role of appetite regulatory hormones in obesity and to discuss a few evidence-based researches dealing with interventions targeting these hormones. Appetite regulatory hormones such as leptin and ghrelin are known to affect the development of obesity by influencing food intake, fat metabolism, and gastrointestinal function. Interventional studies conducted across the globe targeting these appetite regulatory hormones have proven to be impactful in altering the serum concentrations of these hormones and thus improve appetite regulation, thereby regulating energy homeostasis leading to desirable weight loss. Within this framework, it is expected that exploiting the body's own appetite regulatory signals through a conceptual strategy involving lifestyle, behavioral, public health, and medical interventions would appear to be a promising platform in prevention, management, and treatment of obesity.

KEYWORDS: appetite, hormones, obesity

CITATION: Lizia and Hemamalini. Appetite Regulatory Hormones – A Novel Target for Prevention, Management, and Treatment of Obesity. *Clinical Medicine Reviews in Therapeutics* 2016:8 7–13 doi: 10.4137/CMRT.S32424.

TYPE: Review

RECEIVED: August 03, 2015. **RESUBMITTED:** August 09, 2016. **ACCEPTED FOR PUBLICATION:** August 13, 2016.

ACADEMIC EDITOR: Garry M. Walsh, Editor in Chief

PEER REVIEW: Four peer reviewers contributed to the peer review report. Reviewers' reports totaled 613 words, excluding any confidential comments to the academic editor.

FUNDING: Authors disclose no external funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

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Introduction

All over the world, obesity has more than doubled since 1980. In 2014, more than 1.9 billion adults, aged 18 years and older, were overweight. Of them, over 600 million were obese; 39% of adults aged 18 years and older were overweight, and 13% were obese. A majority of the world's population live in countries where overweight and obesity leads to the morbidity of more people than underweight. A total of 42 million children under the age of five years were overweight or obese in 2013.[1] The main drivers of obesity in the developing countries are foods of low cost with high content of sugar and fat, sedentary lifestyle, and rapid nutritional transitions as a result of increasing affluence, socioeconomic transition, urbanization, mechanization, and rural-to-urban migration.[2] "Endocrinology is experiencing a wave of newly identified signaling peptides illuminating the gut–brain axis regulating the body's energy balance, or more thoroughly described as the gut–central and peripheral nervous systems – accessory organs (eg, pancreas and liver) axis.[3]" Molecules released by the enlarged adipose tissue, most of which are pro-inflammatory, have been named adipokines. More than 600 adipokines have been identified so far and molecules such as leptin, visfatin, resistin, and retinol-binding protein may serve as informative markers for metabolic and cardiovascular diseases and play important roles in maintaining glucose homeostasis, insulin sensitivity, and metabolic regulation of energy expenditure.[4] Gut hormones have been found to interact with brain centers that influence the mechanisms of energy intake and storage. With respect to obesity, the mechanism to reduce overweight becomes complicated as the evolutionary species-protecting mechanisms of energy balance result in an escalating level of body fat. Hence, understanding the changes and nuances that occur in the regulators of homeostasis such as hormones and peptides and their roles in weight reduction is pivotal to understand the causal mechanism of obesity. This review aims to highlight the role of appetite regulatory hormones in obesity and discuss a few evidence-based researches dealing with interventions targeting these hormones.

Appetite Regulatory Hormones

Appetite regulation is a complex process involving communication between the hypothalamus within the brain, various gastrointestinal organs (including the stomach, the pancreas, and the intestines), and adipose tissue. Satiation (the signal that causes one to stop eating) may be initiated by neural input from the stomach to the brain, signaling gastric distension after food consumption. This is quickly followed by the release of various hormones sensing the digestion and absorption of nutrients and initiate satiety (the feeling of fullness that persists after eating).

Hormones like cholecystokinin (secreted from the duodenum and jejunum), glucagon-like peptide-1 (GLP-1), oxyntomodulin (OXM) and peptide YY (PYY) (all secreted from the small and large intestines), and pancreatic polypeptide (PP) and amylin (both secreted from the pancreas) act as short-term or episodic signals because they occur in unison with episodes of eating. They signal satiation and satiety either via the vagus nerve (which connects the gut to the brain) or via blood perfusing the hypothalamus. In addition to the episodic hormonal signals, tonic hormonal signals are also present, indicating the level of energy storage in the body. Two of the important tonic satiety hormones are insulin (released from the pancreas) and leptin (released from adipose tissue). These hormones aid the regulation of energy balance over long term.[5]

All of the hormones mentioned above act as satiety signals, ie, high concentrations of each hormone in the blood suppress appetite. In contrast to the satiety inducing hormones, the hormone ghrelin, which is released predominately from the gastric cells of the stomach, is known to have appetite-stimulating effects.[6]

Appetite Regulation and Energy Balance

Appetite is the internal driving force for the search, choice, and ingestion of food. Appetite in humans can be measured by two ways – (i) with the help of subjective ratings such as rating scales and (ii) by actual food intake – the amount of food eaten within a measurable limit.[7] Appetite is a complex process involving numerous internal and external signals. Energy status within the body influences circulating hormones and feedback signals that regulate appetite and eating behavior.[8] The physiologic measures that have an impact on the subjectively rated appetite, actual food intake, or both are defined as biomarkers of satiety and satiation. These markers can be indicators of appetite or causal factors of appetite.[7] The pursuit of the body's own satiety signals as therapeutic targets promises effective weight reduction with minimal effect on other systems.

> "Energy balance is tightly regulated by several neural and hormonal pathways. Much of the research into the control of energy intake focuses on the following aspects:
>
> - hunger and satiety control centres in the brain;
> - brainstem–hypothalamic neurotransmitters involved in feeding regulation;
> - hunger and satiety signals from the periphery, in particular, the gut–brain axis and peripheral adiposity signals.
>
> Centres located in the hypothalamus that are involved in control of feeding behavior include:
>
> - the arcuate nucleus (ARC);
> - the paraventricular nucleus;
> - the ventromedial hypothalamic nucleus;
> - the lateral hypothalamic nucleus;
> - the perifornical area.[9]"

These centers integrate neural (vagal) and circulatory (via nutrients and hormones) signals related to the control of food intake. Neuropeptide Y (NPY) and agouti-related peptide (AgRP), expressed by NPY/AgRP neurons, stimulate food intake (Fig. 1).

The Gut–Brain Axis in Appetite and Body Weight Regulation

The passage of food through the gut initiates a number of satiety signals. The vagus nerve carries afferent signals from stretch receptors and the chemoreceptors to the hindbrain. Endocrine signals from the gut that play a part in appetite regulation are summarized in Table 1. Several peptides such as orexin, apolipoprotein A-IV, bombesin-like peptides, enterostatin, PP, obestatin, and gastric leptin have been reported to play some part in appetite regulation, and further research regarding their actions is needed.[10]

In the central nervous system, the hypothalamus is the key region involved in the regulation of appetite. It had previously been hypothesized that satiety was controlled by the ventromedial hypothalamic nucleus and that feeding was controlled by the lateral region. This early hypothesis has, however, evolved into a much more comprehensive and complex understanding of the integrated neural network responsible for the regulation of appetite, involving discrete pathways within specific nuclei of the hypothalamus, and various regulatory modulators. The regulation of feeding, energy intake and expenditure, and body weight is a homeostatic process (Fig. 2).[10]

The processes such as meal initiation and termination are believed to be regulated through short-term signals, such as neural signals from the brain and humoral signals from the gut. The receipt and integration of these signals occur mainly in the hypothalamus and are largely regulated by the ARC. Gut hormone receptors are located in the neuronal areas of the ARC, which is also partially accessible to circulating appetite modulators due to its incomplete isolation from the blood–brain barrier. Within the ARC, two distinct populations of neurons responsible for appetite regulation such as the proopiomelanocortin appetite-inhibiting neurons and the NPY and AgRP appetite-stimulating co-expressing neurons are present. Signals from the periphery cause changes in the relative activity of these two neuronal subpopulations and the release of their respective neuropeptides, subsequently influencing feeding behavior and energy expenditure. Thus, these hormones regulate the process of appetite and body weight.[10]

Appetite Regulatory Hormones and Obesity

The gastrointestinal tract is the largest endocrine organ in the body and plays an important appetite-regulating role as a source of numerous regulatory peptide hormones. Postprandial

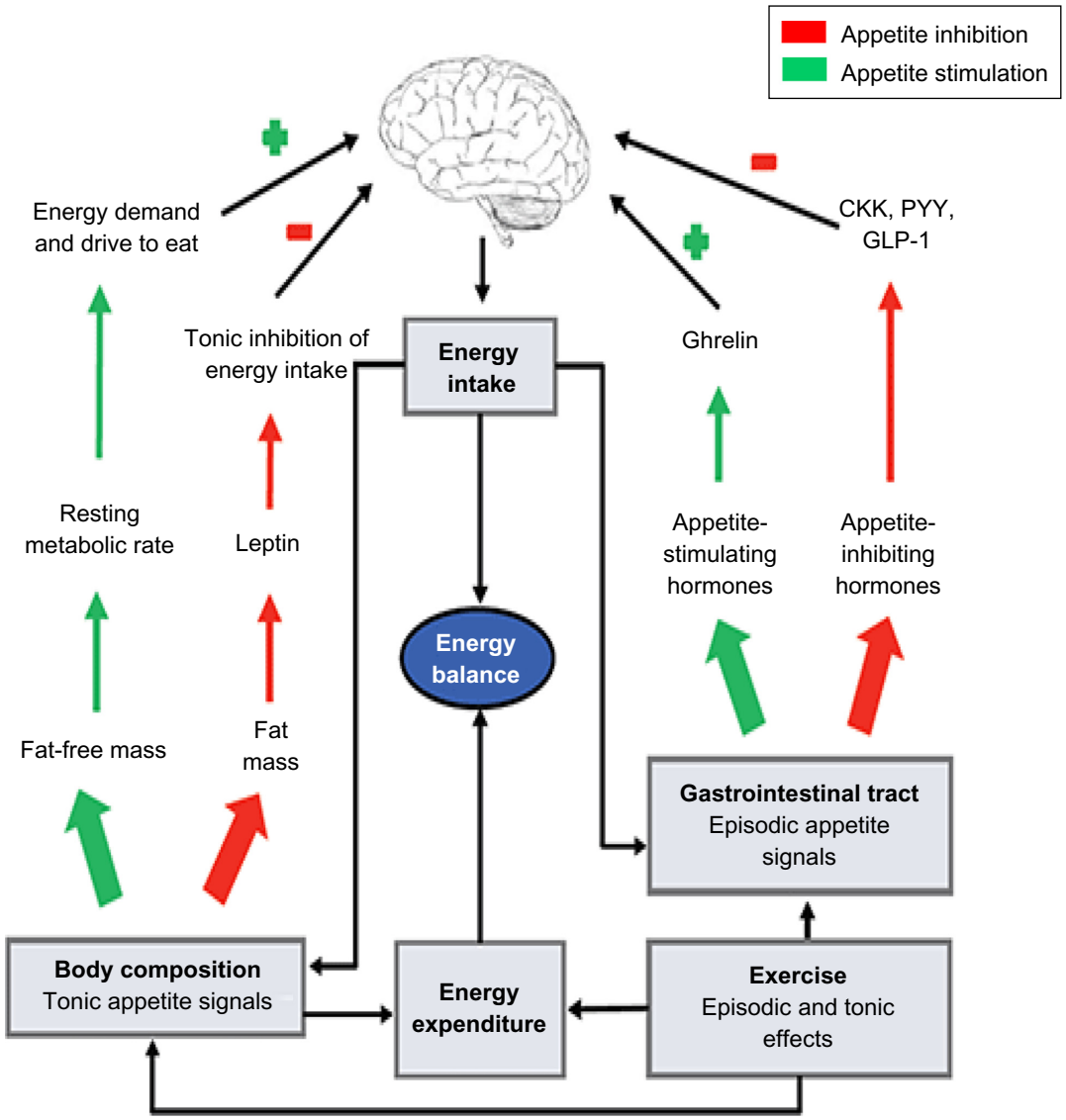

Figure 1. Appetite regulation and energy balance.
Note: The main energy balance control signals in human body. Reused with permission from Blundell et al.[34]

satiety is believed to be regulated by a sensory system that communicates between the gut and appetite-regulating centers in the brain, with the hypothalamus being responsible for nutrient and energy sensing and corresponding adjustments in food intake. When the circulating levels of the hormones inducing hunger in the blood increase, the demand for food intake increases, thereby contributing to excess energy storage and increased levels of fat, all of which sum up to the cause of obesity.

Definitions of Obesity

Obesity is defined as excessive fat accumulation that presents health risks (World Health Organization.[11] Multiple measures such as body mass index (BMI), waist circumference, waist-to-hip ratio, skinfold thickness, bioelectric impedance analysis, underwater weighing (densitometry), air displacement plethysmography, dilution method (hydrometry), dual-energy X-ray absorptiometry, computerized tomography, and magnetic resonance imaging are employed to assess obesity.[12] BMI is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his/her height in meters (kg/m^2). BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and for all ages of adults. Classification based on BMI is tabulated in Table 2.

Obesity is a multifaceted problem with many contributing factors including genetics, hormone levels, overconsumption of food, and sedentary lifestyle. Dietary adherence has been found to be negatively associated with the degree of caloric restriction. Based on this evidence, development of strategies to promote weight loss in the absence of purposeful caloric restriction could be advantageous in combating obesity.[13]

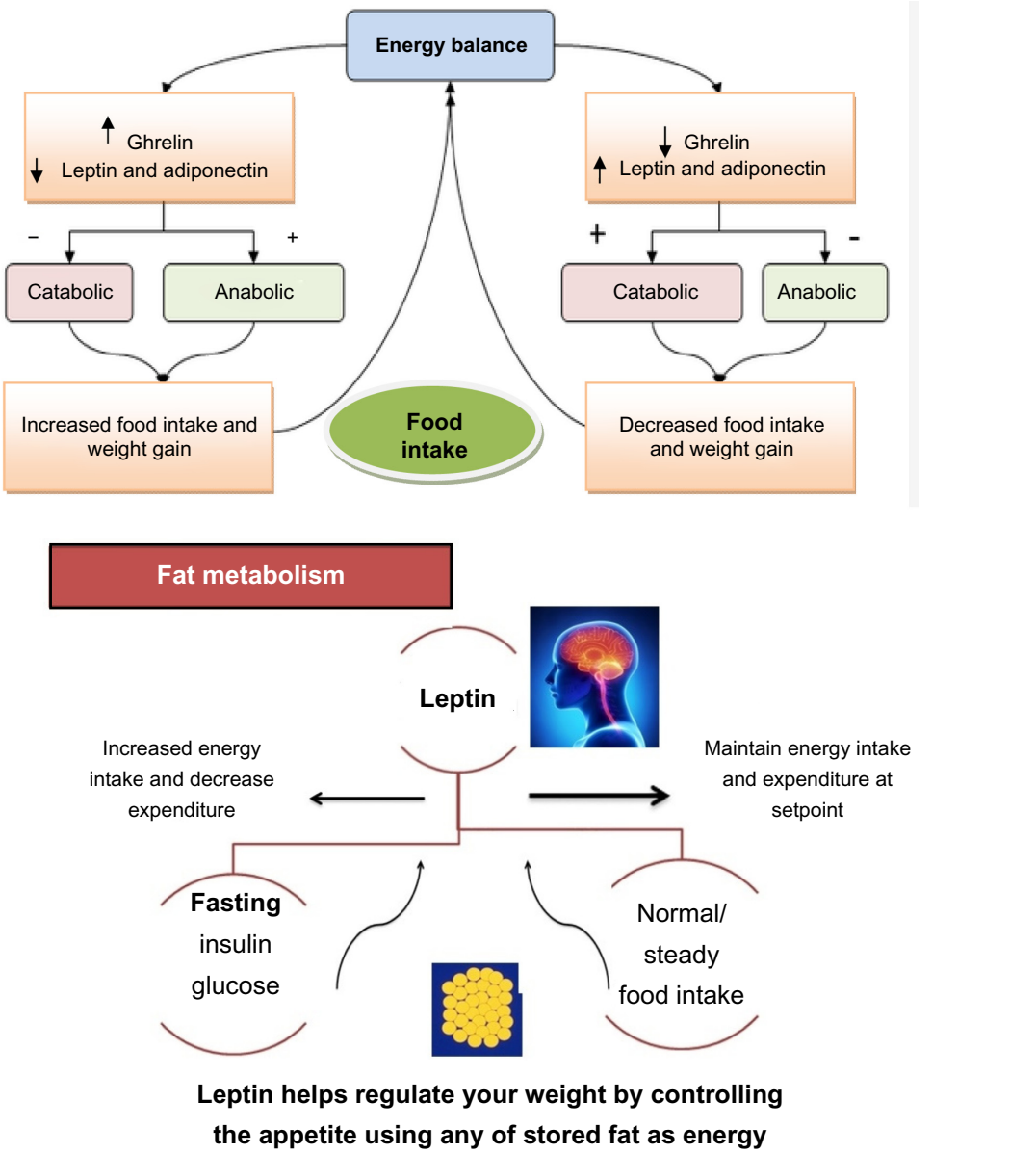

Figure 2. Role of appetite regulatory hormones in food intake and fat metabolism.

Table 1. Gut hormones linked to appetite regulation.

PERIPHERAL EFFECTS OF SELECTED FOOD INTAKE – REGULATING GUT HORMONES			
GUT HORMONE	**SITE OF SYNTHESIS**	**FOOD INTAKE – REGULATING RECEPTOR**	**PERIPHERAL EFFECT ON FOOD INTAKE**
CCK	Intestinal L-cells	CCKA	Decrease
Ghrelin	Stomach	GHS	Increase
PP	Pancreas/colon	Y4R	Decrease
PYY	Intestinal L-cells	Y2R	Decrease
GLP-1	Intestinal L-cells	GLP1R	Decrease
OXM	Intestinal L-cells	GLP1R?	Decrease

Note: Reused from Hu FB[10], under the terms of a CC-BY-NC-ND 3.0 license.
Abbreviations: CCK, cholecystokinin; CCKA, cholecystokinin receptor subtype A; GHS, growth hormone secretagogue receptor; GLP-1, glucagon-like peptide-1; GLP1R, GLP-1 receptor; OXM, oxyntomodulin; PP, pancreatic polypeptide; PYY, peptide YY; Y2R, PYY Y2 receptor; Y4R, PP Y4 receptor.

Although heredity explains some cases of obesity with identified causative gene mutations, the contributions from lifestyle factors such as satiety, diet, and physical activity may be predominantly responsible for the increase in the prevalence of obesity. Appetite regulatory hormones are crucial mediators of satiety and hunger signals and energy balance, where ghrelin stimulates appetite and leptin decreases it. Although there are several studies in both children and adults on the causes of obesity, only very little is known about appetite regulatory hormones' physiological role in humans. Hence, there is ample scope for research in this area.

Impact of Lifestyle Intervention on Appetite Regulatory Hormones

Since obesity is considered to be a multifaceted problem, different lifestyle factors may be modified in order to contribute

Table 2. Body weight classification based on BMI.

WHO CLASSIFICATION	WHO BMI CUT-OFF POINTS FOR DEFINITION (Kg/m^2)	CARDIO-VASCULAR DISEASE RISK	ASIAN BMI CUT-OFF POINTS FOR ACTION (Kg/m^2)
Underweight	<18.50		<18.50
Normal range	18.50–24.99	Low	18.50–22.99
Overweight	≥25.00		
Pre-obese	25.00 to 29.99	Moderate	23.00–27.40
Obese class I	30.00–34.99	High risk	>27.5
Obese class II	35.00–39.99		
Obese class III	≥40.00		

Note: Reprinted from WHO Fact Sheet 311.[1]

to weight reduction in the absence of caloric restriction. These lifestyle factors are macronutrient composition of meals, meal frequency, exercise, sleep, and psychological stress.

Studies have analyzed the relationship between appetite regulatory hormones and metabolic risk factors according to weight status. Few studies have reported that the concomitant variations of these factors after an intervention of lifestyle factors may positively or negatively influence ghrelin, glucocorticoids (in particular, cortisol), insulin, and leptin to promote weight loss. The need for novel approaches to control rates of obesity is warranted. Various lifestyle factors can help attenuate the hormonal responses normally associated with appetite control and regulation. The planning, development, and action of an effective gut hormone-based therapy will not absolve patients from responsibility for their own lifestyle. As with current medical therapies for obesity, the greatest weight loss is likely to be seen within the context of a multidisciplinary approach, which includes objectives targeting the modification of lifestyle factors contributing to energy imbalance. Particularly, eating more frequent and smaller meals comprising moderate protein levels and lower fat, obtaining normal sleep of eight hours a day, and controlling stressors and levels of psychological stress could more readily control the levels of appetite hormones. In addition to this, it is recommended that exercise, both endurance and resistance training, should be incorporated into any lifestyle or behavior enhancement program. Development of a weight loss program requires an integrative approach of many professionals including physicians, psychologists, nutritionists, and exercise physiologists who can as a team propose an optimal personalized strategy taking into account all aspects of obesity.[14]

Weight loss achieved by dietary or exercise treatment initiates compensatory changes in appetite and energy expenditure that hinders maintenance of the reduced body weight. A substantial average weight reduction of ≥0.5 Body Mass Index-Standard Deviation Scores (BMI-SDS) would have more explicit effects on (average) gut hormone concentrations. This postulate is based on the principle that the amount of weight loss is correlated with counter-regulatory changes of plasma appetite regulatory hormones, contributing to

Table 3. Sources and functions of key adipokines.

	SOURCES	OBESITY	PRINCIPAL FUNCTION	RELEVANCE
Leptin	Adipocytes	Increase	Decreases appetite; improves hypertrigliceridemia and insuln sensitivity	Marker of body fat mass; treatment of lipodystrophy; treatment of genetic leptin deficency
NAMPT/ Visfatin	Adipocytes	Increase	Improves glucose metabolism	Putative marker of systemic inflammation and atherosclerosis
Resistin	Monocytes Macrophages	Increase	Contributes to systemic inflammation and induces insulin resistance	Putative marker for metabolic disease in humans, particularly type 2 diabetes, myocardial infarct, atherosclerosis
Vaspin	Adipocytes Macrophages	Increase	Improves glucose metabolism; reduces food intake	Possible target for obesity and type 2 diabetes
Apelin	Adipocytes Macrophages	Increase	Improves insulin sensitivity and glucose metabolism	Possible target for obesity and type 2 diabetes
RPB4	Adipocytes Macrophages	Increase	Improve insulin resitance and systemic inflammation	Putative marker of adipose tissue inflammation
Adiponectin	Adipocytes	Decrease	Insulin sensitizer; anti-inflammatory	Promising candidates for further development as therapeutics for insulin resistance.

Note: Reused from Di Raimo T et al[4], under the terms of a CC-BY 4.0 license.

maintenance of the lost weight. Thus, appetite regulatory hormones may help the obese to lose weight in response to lifestyle measures and also maintain the weight loss effectively (Table 3).[15]

Lifestyle interventions targeting the appetite regulatory hormones have been proven to create an effective change in the body weight of obese children. Reinehr et al discussed the effects of different gut and adipose tissue hormones on food intake and their changes in childhood obesity and after weight loss.[16] The orexigenic hormone ghrelin was found to increase or remain stable after weight loss in obese children,[17–19] indicating the energy demand after weight loss. A few of the anorexigenic hormones, peptide YY (PYY), pancreatic polypeptide (PP) and adiponectin also increased after weight loss,[20–23] affecting the food intake of obese children by inducing satiety. On the other hand, anorexigenic hormones such as insulin, amylin and leptin were found to decrease after weight loss among obese children,[22,24–27] highlighting the energy demand post weight loss. Weight loss research on hormones such as glucagon-like peptide-1 (GLP-1), oxyntomodulin (OXM) and cholecystokinin (CCK) among obese children[28–33] still remains ambiguous and controversial. Hence, more evidence is required to understand the complex nature of these hormones and their roles in causing or curing obesity, offering a prospective scope for research in the future.

Conclusion

Research on acclimatization of energy homeostasis is gaining more importance as obesity is one of the most important risk factors for the development of various noncommunicable diseases. Appetite regulatory hormones are known to affect the development of obesity by influencing food intake, fat metabolism, and gastrointestinal function. Serum levels of one or more of these hormones have been found to correlate with obesity measures such as BMI, amount of fat mass, and waist circumference, as well as with insulin concentration and insulin resistance. Thus, they appear to offer promise for the development of new strategies to treat obesity in both children and adults. Development of effective treatments will require more complete knowledge about the production, regulation, and functions of these hormones. Investment in a strategy that involves lifestyle, behavioral, public health, medical, and, where appropriate, surgical interventions would appear to be the most practical course to adopt. Within that framework, by exploiting the body's own satiety signals, interventions based on the actions of gut hormones will undoubtedly have a crucial role to play. The changes of these hormones and adipocytokines will allow answering the questions whether the alterations of these hormones are a cause or consequence of overweight and thus offer a platform to prevent, treat, and manage obesity.

Author Contributions

Wrote the first draft of the manuscript: SML. Contributed to the writing of the manuscript: SML, AJH. Agree with manuscript conclusions: SML, AJH. Jointly developed the structure and arguments for the paper: SML, AJH. Made critical revisions and approved final version: AJH. Both authors reviewed and approved of the final manuscript.

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