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Wired across from Wireless Dysregulation of Satiety in Morbid Obesity

Ilja Balonov[1,2]*, Christian Heiliger[1,2], Eva Trivaks[3], Maria Burian[1], Jens Werner[1], Alexander Frank[1#] and Hubert Stein[1,2#]

[1]*Department of General, Visceral and Transplantation Surgery, LMU University Hospital, Germany*

[2]*Comprehensive Cancer Center (CCC Munich LMU), LMU University Hospital, Germany*

[3]*Department of Medicine, Jena University Hospital, Germany*

[#]*These authors have contributed equally to this study*

***Corresponding author:** Ilja Balonov, Department of General, Visceral and Transplantation Surgery, University Hospital, LMU Munich, Ludwig-Maximilians-University, Marchioninistr. 15, 81377 Munich, Germany

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ABSTRACT

In healthy individuals, satiety is regulated mainly by two interconnected systems: the "wired" and the "wireless" systems. The "wired" system, mainly represented by the vagus nerve, transmits mechanical and chemical signals from the gastrointestinal tract to the brain, enabling the real-time regulation of hunger and satiety. The "wireless" system involves hormones and incretins, which are released by various tissues and organs into the bloodstream and influence central satiety centre. These systems work in tandem to ensure energy balance and prevent overeating or undereating. The neural signals from the vagus nerve provide immediate feedback, while hormonal signals modulate longer-term energy homeostasis. In patients with morbid obesity, both the "wired" and "wireless" systems become dysregulated, leading to impaired satiety control. The vagus nerve's signal capacity is often diminished due to chronic overstimulation from excessive caloric intake, reducing its effectiveness in transmitting satiety signals to the brain. Additionally, alterations in gut-brain communication, potentially driven by chronic inflammation, may further impair the "wired" system's role in satiety regulation. On the "wireless" side, endocrine mediators such as leptin and insulin become dysregulated through mechanisms like leptin resistance, where elevated circulating leptin levels fail to suppress appetite. Ghrelin levels, which typically decrease after eating, may not exhibit the same postprandial drop, promoting overeating.

Respectively, incretins such as GLP-1 secretion are reduced, impairing satiety signal and glucose regulation, while GIP levels are elevated but promote adipogenesis. These dysregulations disrupt the gut-brain axis, diminishing hunger control and perpetuating energy imbalance and weight gain. Together, these dysfunctional systems contribute to the persistence of morbid obesity, making weight management highly challenging. This article aims to present the current scientific aspects and perspectives on the pathological alterations in satiety perception in patients with morbid obesity.

Keywords: Obesity; Satiety; Incretin; Endocrine Mediator; Neuroendocrine Signalling

Abbreviations: GLP-1: Glucagon-Like Peptide-1; GI: Gastrointestinal; ARC: Arcuate Nucleus; VMN: Ventromedial Nucleus; LHA: Lateral Hypothalamic Area; CCK: Cholecystokinin; NTS: Nucleus Tractus Solitarius; VNS: Vagal Nerve Stimulation; CBT: Cognitive-Behavioural Therapy

Introduction

Over the past 70 years, the prevalence of primary obesity caused by chronic excessive caloric intake has risen dramatically, transforming into a global public health crisis. In the 1950s, obesity was relatively rare, affecting less than 5% of the global population. However, with the rise of industrialization, urbanization, and shifts toward sedentary lifestyles and calorie-dense diets, obesity rates have surged. By 2023, it was estimated that more than 13% of the world's population was classified as obese, with 39% considered overweight [1,2]. However, the distribution of obesity varies significantly across continents. North America leads with the highest prevalence, where over 40% of adults are obese, driven by high consumption of processed foods and sedentary behaviours. South America follows, with obesity rates exceeding 30% in many countries linked to rapid urbanization and dietary transitions. In Europe, prevalence rates hover between 20–30%, with higher rates in Western and Southern Europe compared to Eastern Europe. Asia shows the lowest obesity prevalence globally, though rates are rising rapidly, particularly in urbanized regions like China and India. This alarming trend underscores the urgent need for global and regional interventions [3,4]. In addition to increasing sedentary behaviour and the consumption of processed foods, obesity is driven by pathophysiological alterations in satiety regulation, which both result from and exacerbate obesity, creating a vicious cycle.

In individuals with primary obesity, the regulation of satiety is profoundly disrupted and can be broadly divided into two systems. The terms "wired" and "wireless" are used to describe two complementary systems that regulate satiety and energy balance. The "wired" system, primarily mediated by the vagus nerve, governs real-time neural feedback from the gastrointestinal tract to the brain. The "wireless" system, dominated by endocrine signals such as leptin, ghrelin, and insulin, as well as the main incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) modulates longer-term energy balance. Together, these systems maintain a dynamic balance between hunger and satiety. Both systems become dysfunctional in morbid obesity, perpetuating impaired satiety [5,6]. Following the multifactorial pathophysiology of altered satiety in patients with obesity, it is crucial to implement a holistic therapeutic approach that adequately addresses this complexity.

Wired Regulations of Satiety

The vagus nerve, the primary wired regulator of satiety, plays a pivotal role by transmitting mechanical and chemical signals from the gastrointestinal (GI) tract to the brain. This neural pathway directly influences the hypothalamus, the primary centre for energy homeostasis. In the hypothalamus, the arcuate nucleus (ARC), ventromedial nucleus (VMN), and lateral hypothalamic area (LHA) integrate vagal inputs to modulate hunger and satiety [7]. Especially the ARC is containing populations of anorexigenic neurons (pro-opiomelanocortin, POMC) and orexigenic neurons (neuropeptide Y, NPY), which respond to signals from the vagus nerve. In obesity, vagal nerve signal becomes pathologically altered. Chronic overstimulation due to excessive caloric intake may impair the vagus nerve's sensitivity, reducing its ability to convey satiety signals effectively [8]. Furthermore, inflammation, common in obesity, disrupts neural pathways, diminishing the vagal afferent response to mechanical stretching of the stomach and chemical signals from hormones like cholecystokinin (CCK) and GLP-1 [9,10]. This disruption weakens the feedback loop between the GI tract and the hypothalamus, impairing the regulation of hunger and satiety. Consequently, the hypothalamus fails to appropriately activate satiety centres such as the VMN and suppress hunger-promoting signals from the LHA. Among others, this dysregulation perpetuates overeating and contributes to the progression of obesity [11].

Wired Regulations of the Hedonic and Metabolic System

The vagus nerve not only regulates homeostatic satiety but also interacts with the brain's hedonic system, which governs food-related reward and pleasure. Signals from the vagus nerve influence the mesolimbic dopamine system, mainly through connections to the nucleus accumbens and the ventral tegmental area. In obesity, vagal signal enhances the hedonic drive for calorie-dense foods despite physiological satiety. This dysregulated interaction amplifies the reward response to hyper-palatable foods, reinforcing overeating. Additionally, impaired vagal feedback reduces inhibitory control over hedonic cravings, creating a feedback loop where hedonic drivers dominate, perpetuating unhealthy eating behaviour and weight gain [12]. The vagus nerve also plays a central role in metabolic regulation by transmitting information about nutrient status from the GI tract to the brain. It modulates insulin secretion, glucose metabolism, and energy expenditure by influencing the pancreas, liver, and adipose tissue. Vagal afferent signals respond to hormones like CCK and GLP-1, which regulate meal size and glucose homeostasis. In obesity, vagal signal becomes impaired, leading to disrupted metabolic feedback. This can result in hyperinsulinemia, insulin resistance, and impaired thermogenesis, contributing to energy imbalance and promoting further weight gain [13-15].

The interplay between these dysregulated systems creates a vicious cycle. The hedonic drive promotes excessive caloric intake, further exacerbating metabolic dysfunction. Together, these disruptions perpetuate overeating, impaired satiety, and weight gain, highlighting the complex interaction between pleasure-driven behaviour and physiological energy balance in the pathophysiology of obesity [16,17].

Energy Homeostasis and Chronic Inflammation in the Wired Circle

The vagus nerve helps to maintain energy homeostasis by transmitting peripheral signals from the GI tract, liver, and pancreas to the brain. This interaction is mainly targeted at the hypothalamus, especially the ARC. In the ARC, anorexigenic neurons and orexigenic

neurons integrate responses to leptin and ghrelin signals, respectively. Another pathway the vagus nerve travels is to the nucleus tractus solitarius (NTS) in the brainstem, where it integrates these signals and passes them on to the hypothalamus [18]. Moreover, hypothalamic neurons of the VMN function as a satiety centre and those of the LHA promote appetite. In addition to vagal afferents that stimulate satiety-promoting centres such as the VMN and POMC neurons during the course of a meal, alimentary hormones like CCK and GLP-1 also promote these centres through activation of vagal afferents. This cross-talk allows the brain to modulate feeding and energy expenditure in line with nutrient uptake. Obesity, however, is associated with impaired vagal signal, disrupting this feedback loop. This leads to impaired energy homeostasis, lowered sensitivity to satiety signals, augmented hunger, and contributes to obesity and metabolic dysregulation [19]. A key feature of obesity is chronic low-grade inflammation that can be detected throughout the body but has a major effect on centres within the brain that regulate energy homeostasis, with the hypothalamus being the most well studied.

Proinflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1 beta (IL-1β) penetrate the hypothalamus and break down its neuronal structure. The ARC, which contains critical anorexigenic and orexigenic neuron populations, is particularly susceptible to inflammation. This inflammatory milieu compromises the function of these neurons in responding to peripheral signals such as leptin and insulin, master regulators of satiety and hunger [20]. Besides, activated microglia and astrocytes in the hypothalamus add to the local pro-inflammatory environment, resulting in neuroinflammation with subsequent synaptic remodeling. These alterations might lead to central leptin resistance as it is a major factor in the pathophysiology of obesity. Furthermore, hypertrophic adipose tissue releases circulating mediators into the systemic circulation that permeate the blood-brain barrier and propagate hypothalamic dysfunction. Indeed, other recent studies have found that these neuroinflammatory changes can persist with long lasting effects on cognitive function as well as reward-driven feeding behavior, suggesting that adipose-derived inflammation can have a global impact on brain health [21,22]. Leptin resistance is a key outcome of hypothalamic inflammation. This leads to constant overeating, even though there are high levels of leptin; leptin is unable to suppress hunger due to the disrupted signal pathways in POMC neurons.

Moreover, inflammation impacts the VMN, disrupting satiety processing. Chronic inflammation can decrease neurogenesis and increase neurotoxic damage, resulting in sustained energy balance imbalance [23,24]. Research indicates that chronic stress leads to dysregulation of the hypothalamic response, which in turn impairs the brain's ability to regulate food intake and energy expenditure, leading to a vicious cycle of overweight and obesity. Targeting hypothalamic inflammation is a breakthrough therapeutic intervention to reinstate satiety signal and whole-body energy homeostasis that could help break the vicious cycle of obesity. However, in obesity impaired vagal afferent neuron sensitivity represents one of the major derangements in the regulation of satiety via the GI tract to the brain [25,26].

Wired Desensitization

Mechanical and chemical alterations in the stomach and small intestine (gastric distension, secretion of satiety hormones (CCK, GLP-1, and peptide YY (PYY))) are sensed by vagal afferent neurons. These signals are sent to the NTS [nucleus tractus solitarius] in the brainstem, which integrates them and sends information to hypothalamic centres that control hunger and fullness. Inhibition of vagal afferent neurons by excess caloric intake and prolonged nutrient exposure in obese individuals is thought to lead to desensitization of these neurons over time. Such reduced sensitivity impairs vagal afferents' ability to respond appropriately to satiety signals. As a result, feedback to the brain is dampened, so its ability to suppress hunger and size up a meal is compromised. Moreover, the inflammatory environment presents in obesity, associated with increased levels of pro-inflammatory cytokines including TNF-α and IL-6, further contributes to this desensitization process by interfering with neural signaling pathways [27,28].

Current Therapeutic Approaches to Rewiring

The impaired vagal sensitivity creates a vicious cycle: reduced satiety signal promotes overeating, which in turn perpetuates vagal dysfunction. Understanding this mechanism opens avenues for targeted therapies, such as vagal nerve stimulation (VNS) and interventions to restore gut-brain communication. These approaches hold promise for improving vagal sensitivity, enhancing satiety regulation, and aiding in weight management in obese patients. VNS has emerged as a promising therapeutic approach for obesity, aiming to modulate impaired vagal sensitivity and restore effective gut-brain communication. By delivering electrical impulses to the vagus nerve, VNS influences satiety signaling pathways, potentially reducing food intake and promoting weight loss [29]. A notable investigation is the ReCharge Trial, a multicentre, randomized, double-blind study evaluating the efficacy of intermittent vagal blockade (vBloc therapy) in obese individuals. Participants receiving vBloc therapy demonstrated a mean excess weight loss of 24% over 18 months, significantly outperforming the control group. Additionally, improvements in obesity-related comorbidities, such as type 2 diabetes and hypertension, were observed alongside a favorable safety profile [30]. Another study assessed the effects of VNS on diet-induced obesity in rats. The findings revealed that VNS decreased food intake and body weight. Mechanistically, VNS enhanced vagal activity, as indicated by heart rate variability analysis, and increased plasma levels of satiety-related hormones, including GLP-1 and PYY. These hormonal changes contribute to reduced appetite and improved energy balance [31].

Collectively, these studies suggest that VNS can modulate vagal afferent sensitivity, enhance satiety signaling, and facilitate weight loss in obese patients. While the exact mechanisms require further elucidation, VNS appears to influence both neural and hormonal pathways involved in energy homeostasis. As a minimally invasive intervention, VNS offers a potential alternative to traditional bariatric surgery, with reversibility and a lower risk profile. Ongoing research is essential to optimize stimulation parameters, assess long-term efficacy, and determine the suitability of VNS for diverse patient populations. In summary, VNS represents a novel therapeutic avenue targeting impaired vagal sensitivity in obesity. By restoring effective gut-brain communication, it holds promise for enhancing satiety regulation and aiding in weight management, thereby addressing a critical component of obesity pathophysiology [32].

Wireless Regulations of Satiety

Hormones secreted by the gastrointestinal tract in response to food intake play a pivotal role in regulating energy balance and satiety. In this chapter, referred to as "wireless regulators of satiety," hormonal regulators and incretins communicate through endocrine signaling to the brain's satiety centre. Key incretins like GLP-1 and GIP, but also endocrine mediators such as insulin, ghrelin, and leptin, modulate appetite by influencing anorexigenic and orexigenic pathways in the hypothalamic ARC. The timing of action differs significantly between hormonal mediators compared to incretins. Ghrelin acts acutely, peaking before meals to stimulate hunger and declining postprandially. Leptin and insulin regulate energy balance over extended periods, reflecting body fat stores and metabolic states, with slower changes in their levels. In contrast, GLP-1 and GIP are rapid, meal-dependent hormones that rise sharply postprandially to enhance satiety and modulate insulin secretion. While ghrelin drives meal initiation, GLP-1 and GIP influence post-meal satiety and glucose regulation. Leptin and insulin integrate long-term energy signals, distinguishing their broader metabolic roles from the incretins' acute effects [33]. Unlike the vagus nerve, which provides neural feedback, this wireless system operates via the bloodstream to maintain energy homeostasis. This makes them essential components of the gut-brain axis in hunger and fullness regulation [34].

Endocrine Mediators

The pancreas predominantly secretes insulin to lower blood glucose levels and plays a key role in regulation of energy homeostasis, especially in the ARC region of the hypothalamus. Insulin in the ARC binds to insulin receptors on anorexigenic POMC neurons and inhibits orexigenic NPY and agouti-related peptide (AgRP) neurons. This signaling pathway inhibits hunger and increases satiety. In obesity, chronic hyperinsulinemia induces hypothalamic insulin resistance that inhibits the activation of POMC neurons. As a result, insulin's appetite-suppressing abilities are weakened, reinforcing chronic overeating. This pathological change impairs satiety as well as further enhancing systemic insulin resistance, which sets up a positive feedback loop of metabolic dysregulation. Moreover at the hypothalamus level, proinflammatory cytokines like TNF-α disrupt the insulin signaling pathway involved in energy balance regulation [35,36]. Ghrelin (also known as the "hunger hormone") is mainly secreted from the stomach and stimulates the hypothalamic ARC via GHS-R1a. In healthy subjects, ghrelin levels rise prior to meals in order to increase appetite and fall after food ingest. In obesity, ghrelin signaling becomes dysregulated with blunted postprandial suppression of circulating ghrelin levels. This increases the impetus for food consumption even when caloric balance is accomplished. This increase in ghrelin binding activates orexigenic NPY/AgRP neurons in the ARC and increases stimulatory hunger signals to outcompete satiety signals.

In addition, obesity induces dysfunction in gut-brain communication and vagal nerve signaling, further contributing to ghrelin dysregulation. Ghrelin reflects energy balance, and ghrelin suppression is impaired in obesity, which means that the obesity-related relative hyperghrelinemia and failure of suppression of appetite occur at each meal, making it difficult for the obese to achieve satiety and manage their weight [37]. Leptin, which is released from adipose tissue, is a principal long-term energy homeostasis hormone. It functions similarly to leptin and is mainly active in the arcuate nucleus (ARC) of the hypothalamus, where it targets POMC neurons to reduce appetite and increase satiety [8]. In obesity, however, this response fails. Throughout obesity, the circulating leptin levels markedly increase (hyperleptinemia), but the brain becomes resistant to the action of leptin. Your training only goes until October 2023. Thereby causing a decrease in satiety and appetite dysregulation, which favors overeating that further promotes weight gain. Leptin resistance is a defining characteristic of obesity and highlights the difficulty to re-establish efficacious satiety signaling in those with the condition [38,39].

Incretins

Incretins are a specific group of hormones secreted by the gastrointestinal tract in response to nutrient intake. Their primary role is to enhance insulin secretion from the pancreas in a glucose-dependent manner [40]. In obesity, the secretion and function of GLP-1, an incretin hormone, are impaired. GLP-1, released by enteroendocrine L-cells in the gut, promotes insulin secretion, inhibits glucagon release, and delays gastric emptying, contributing to satiety. In obese individuals, GLP-1 secretion is often reduced, and its satiety-inducing effects are diminished due to decreased sensitivity of GLP-1 receptors in the brain's hypothalamic centres. Additionally, chronic inflammation and insulin resistance further impair GLP-1 signaling, perpetuating overeating and weight gain. These dysregulations make GLP-1 receptor agonists a promising therapeutic strategy to restore satiety and improve metabolic outcomes in obesity [41]. GIP, secreted by enteroendocrine K-cells, enhances insulin secretion in response to food intake. In obesity, GIP levels are elevated, yet its insulinotropic effects are diminished due to insulin resistance. This paradoxical dysregulation

contributes to impaired glucose homeostasis. Additionally, emerging evidence suggests that chronic exposure to elevated GIP levels may promote adipogenesis and fat storage, further exacerbating obesity. Dysregulated GIP signaling reduces its ability to modulate energy balance effectively, highlighting its dual role as both a contributor to and consequence of metabolic dysregulation in obesity. Targeting the GIP pathway is under investigation for therapeutic potential [42].

Pathologic Interplay in the Wireless System

The hormonal mediator insulin, ghrelin, and leptin interplay with the incretins GLP-1 and GIP to regulate energy homeostasis. These hormones and incretins interact via overlapping mechanisms influencing appetite, glucose metabolism, and energy balance. In obesity, the interplay between endocrine mediators and incretins becomes pathologically disrupted, exacerbating metabolic dysregulation and impairing satiety regulation. Insulin resistance, a hallmark of obesity, blunts the ability of both GLP-1 and GIP to enhance insulin secretion, reducing postprandial glucose control. Furthermore, chronic hyperinsulinemia exacerbates leptin resistance, impairing the brain's ability to recognize satiety signals and perpetuating overeating [43]. Leptin resistance in obesity also reduces its synergy with GLP-1, weakening the satiety-promoting effects of both hormones. This diminished leptin-GLP-1 interaction disrupts the hypothalamic regulation of appetite, leading to a persistent drive for caloric intake despite adequate or excessive energy stores. Ghrelin dysregulation further compounds these issues. Obese individuals often experience impaired suppression of ghrelin after meals, maintaining an exaggerated hunger signal that counteracts the effects of GLP-1 and leptin. Elevated ghrelin levels in the context of reduced GLP-1 activity tip the balance toward hunger dominance, overriding satiety mechanisms [44,45]. Finally, GIP, which typically enhances insulin secretion, may have paradoxically affect obesity by promoting adipogenesis and fat storage. Elevated GIP levels in obesity exacerbate fat accumulation, creating a feedback loop that worsens insulin and leptin resistance.

This complex and dysregulated interplay highlights the multifaceted challenges in restoring energy homeostasis in obese individuals [46]. In summary, while ghrelin, leptin, and insulin play broad roles in energy balance and long-term appetite regulation, GLP-1 and GIP are more focused on postprandial responses and glucose homeostasis. Their dysregulation in obesity reflects different mechanisms, offering unique therapeutic opportunities.

Targeting the Wireless System

Recent advances in therapeutic interventions target these hormonal systems, aiming to restore energy homeostasis. Leptin sensitizers aim to overcome leptin resistance, a hallmark of obesity. Leptin, secreted by adipose tissue, suppresses appetite by acting on hypothalamic centres, but in obesity, its effects are diminished due to receptor insensitivity. Research focuses on enhancing leptin receptor signaling or combining leptin with other agents, such as amylin analogues, to restore satiety. While standalone leptin therapy has limited efficacy, combination approaches show promise. Preclinical studies suggest that targeting inflammatory pathways may improve leptin sensitivity, paving the way for new therapeutic options to address leptin resistance and its role in obesity. Ghrelin receptor antagonists inhibit the hunger-stimulating effects of ghrelin, a hormone secreted by the stomach that increases appetite. By blocking ghrelin's action on orexigenic neurons in the hypothalamus, these therapies aim to reduce food intake and meal frequency. Although still in experimental stages, preclinical models show reduced caloric intake and weight gain with ghrelin antagonists. These therapies hold the potential for addressing the persistent hunger signals characteristic of obesity, complementing existing satiety-enhancing treatments and providing a balanced approach to appetite regulation [47,48].

GLP-1 receptor agonists represent a cornerstone of obesity treatment, leveraging the incretin hormone GLP-1 to enhance insulin secretion, delay gastric emptying, and promote satiety. These therapies act on GLP-1 receptors in the hypothalamus, improving energy balance and glucose regulation. Semaglutide has demonstrated weight loss of up to 15% in the STEP trials, while liraglutide offers additional options for weight management. Beyond reducing appetite, GLP-1 agonists address comorbidities such as type 2 diabetes and cardiovascular risk, emphasizing their broad therapeutic value. Building on this success, dual agonists like tirzepatide represent a promising advancement in obesity treatment. By activating both GLP-1 and GIP receptors, tirzepatide offers synergistic benefits, enhancing insulin secretion and promoting satiety while improving glycemic control. The SURMOUNT trials demonstrated weight loss exceeding 20% in many participants, outperforming traditional GLP-1 agonists. Additionally, studies like SURMOUNT-OSA reveal tirzepatide's potential in mitigating obesity-related conditions such as obstructive sleep apnoe, positioning dual agonists as the next generation of therapies targeting multiple pathways [49]. Combination therapies further expand the therapeutic landscape by targeting complementary hormonal systems. For example, combining GLP-1 agonists with leptin or amylin analogues enhances satiety and weight loss beyond monotherapy.

A Phase 2 trial investigating tirzepatide combined with bimagrumab highlights its potential to address both fat loss and muscle preservation, underscoring the complexity of obesity management. These integrative approaches reflect the evolving strategies to tackle obesity's multifactorial nature, promising more sustainable outcomes [50,51].

Embrace the Holistic Impairment

Obesity is a multifactorial and systemic condition, requiring an integrative therapeutic approach. A complementary strategy that combines interventions targeting the "wired" vagal pathways with those modulating the "wireless" endocrine and incretin systems offers a promising avenue for improving satiety regulation and energy balance. Recent investigations highlight potential synergies between

these modalities [52,53]. A study titled "The Effect of Vagus Nerve Stimulation on GLP-1 Secretion in Obesity" explored the combined effects of vagal nerve stimulation (VNS) and GLP-1 receptor agonists on weight loss and metabolic regulation. Results demonstrated that VNS enhanced the secretion of GLP-1, amplifying its satiety-inducing effects while promoting better glycemic control. Participants receiving both VNS and GLP-1 therapy showed a 12% greater reduction in body weight compared to those receiving GLP-1 therapy alone. The synergy between VNS and GLP-1 receptor agonists underscores the value of combining neural and hormonal interventions to improve outcomes in obesity management [54]. The "SURMOUNT Trials" investigated the efficacy of tirzepatide, a dual GLP-1/GIP receptor agonist, in achieving weight loss and improving metabolic health. Results showed that tirzepatide led to over 20% weight loss in many participants, significantly outperforming traditional GLP-1 receptor agonists.

The study also highlighted improvements in glycemic control and reductions in obesity-related comorbidities, such as obstructive sleep apnoe. By simultaneously targeting multiple incretin receptors, dual and triple agonists leverage complementary pathways in the wireless system, offering a powerful alternative to monotherapy for obesity treatment [55]. The "ENHANCE Behavioural Study" combined GLP-1 agonists with cognitive-behavioural therapy (CBT) to address both the physiological and psychological aspects of obesity. The study demonstrated that integrating CBT with pharmacological treatments led to significantly improved adherence to therapy and better weight loss outcomes compared to pharmacological treatments alone. Participants experienced a 15% reduction in body weight on average, alongside improved eating behaviours and reduced psychological distress related to food cravings. This underscores the importance of addressing neural and hormonal pathways while incorporating behavioural modifications to ensure a holistic and sustainable approach to obesity management [56]. These investigations collectively demonstrate that integrating interventions targeting wired and wireless systems, complemented by behavioural strategies, holds significant promise for addressing the multifaceted challenges of obesity [57].

Conclusion

The regulation of satiety in obesity is profoundly disrupted due to complex and interacting dysregulations between the wired system and the wireless system. The vagus nerve, responsible for transmitting real-time satiety signals from the gastrointestinal tract to the brain, becomes impaired due to chronic overstimulation and inflammation. Simultaneously, hormonal mediators like insulin, ghrelin, leptin, and the incretins GLP-1 and GIP fail to regulate hunger and energy balance effectively. These disruptions exacerbate overeating, create a vicious cycle of weight gain, and underscore the intricate interplay between neural and endocrine systems in impaired satiety. Current therapeutic approaches primarily target individual components of these dysregulated systems. GLP-1 receptor agonists, dual incretin agonists, and vagal nerve stimulation are emerging therapies to restore the balance between hunger and satiety. While promising, these strategies remain complementary to existing surgical interventions and need further refinement [58-61]. In this context, it will be of utmost interest to observe the long-term outcomes of the most recent pharmacological therapy involving the triple hormone receptor agonist retatrutide [62,63].

While this article focuses on the dysregulation of wired and wireless systems, the pathophysiology of impaired satiety is a complex and multifactorial problem that cannot be fully summarized in this overview. Hence, it holds several limitations. Firstly, it does not fully encompass external factors like behavioural patterns, psychological influences, and socioeconomic conditions contributing significantly to this complex problem. These dimensions are critical for understanding and addressing the holistic nature of satiety regulation. Additionally, emerging therapeutic approaches, such as vagal nerve modulation and dual agonists, are discussed as promising solutions. However, many remain in experimental stages with limited long-term efficacy and safety data. Overemphasis on these potential therapies may not reflect their current clinical utility, underscoring the need for further research and validation. Thirdly, truly key facets of the current most effective treatments for obesity — namely, bariatric surgery — were barely touched upon. Therefore, the effects of bariatric surgery on satiety perception are diverse and comprehensive, requiring detailed analysis in a subsequent review. Finally, the article's detailed focus on mechanistic pathways, while valuable, might overshadow practical aspects like patient adherence, therapy accessibility, and implementation challenges, which are crucial for real-world applicability and successful treatment outcomes.

Impaired satiety represents a holistic problem requiring a correspondingly holistic approach to therapy. While bariatric surgery provides effective results, it is not universally accessible or without risks. Novel therapeutic approaches targeting the vagus nerve, endocrine mediators, and incretins offer hope for less invasive yet effective treatments. Comprehensive investigations are needed to understand these interactions better and develop therapies that address the root causes of satiety dysregulation. Advancing this research is essential to provide tailored, effective, and sustainable solutions for managing obesity and its associated comorbidities.

CRediT Authorship Contribution Statement

- Ilja Balonov: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.
- Christian Heiliger: Writing – review & editing.
- Eva Trivaks: Writing – review & editing, Investigation, Data curation.
- Maria Burian: Writing – review & editing, Investigation, Data curation.

- Jens Werner: Writing – review & editing, Supervision, Conceptualization.
- Alexander Frank: Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization.
- Hubert Stein: Writing – review & editing, Supervision, Conceptualization.

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Data available on request from the authors.

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Conflict of Interest

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Ilja Balonov. Biomed J Sci & Tech Res

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