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REVIEW ARTICLE

Diverse Routes in the Development of Obesity

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Abstract

Obesity, a prevalent community health concern, is a diseased state characterised by an abundance of adipose tissue. This condition arises from notable transformations resulting from modern civilisation, where overconsumption and sedentary behaviours have become commonplace in contemporary society. Obesity's prevalence and associated health effects present a significant public health challenge affecting both physical and cognitive health and executive function impairments are commonly observed. In obese individuals, suggesting a complex interplay between weight and cognitive well-being, the gut microbiota serves as a bridge between external factors like diet and lifestyle and the body's physiological processes, potentially illuminating the intricate pathways connecting these health issues. Unhealthy dietary patterns characteristic of Western diets contributes to imbalances in the gut microbiota, which can exacerbate obesity-related complications. Research indicates that the gut microbiota linked to obesity may instigate various changes in the body, including disruptions in the hypothalamic-pituitary-adrenal axis. These disruptions can lead to disturbances in hormone regulation, desensitisation of leptin receptors, resistance and neuroinflammation. It is crucial to grasp the interplay between altered the hypothalamic-pituitary-adrenal (HPA) axis activity and long-term consequences of obesity, considering factors like age, gender and racial disparities. Examining the intricate connection between neuro-immunology and immune metabolism, particularly in adipose tissue where immune cells and the sympathetic nervous system (SNS) play crucial roles, can provide insights into the complex mechanisms of obesity-related health issues. This review emphasises the multifaceted mechanisms in the development of obesity, laying the groundwork for understanding various avenues that could be explored for innovative and effective pharmaceutical interventions in obesity management.

Key words: Obesity; Neuroinflammatory diseases; Gastrointestinal microbiome; Hypothalamo-hypophyseal system; Adrenal glands; Immunology; Leptin; Resistance.

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Introduction

The incidence of obesity has witnessed a steady rise over recent decades. In 2016, approximately 39 % of adults aged 18 and above were classified as overweight, with around 13 % falling into the category of obesity.[1] According to the National Family Health Survey (NFHS) (2019–2021), the prevalence of abdominal obesity in India was found to be 40 % in women and 12 % in men.[2] Unhealthy dietary patterns, particularly the consumption of high-fat and high-glycaemic index products, contribute significantly to this trend, particularly in developed nations.[3] It is common-

ly recognised that opting for unhealthy dietary patterns can lead to elevated body weight and obesity, as well as metabolic conditions like insulin resistance, type 2 diabetes mellitus and dyslipidaemia.

The principal purpose of adipose tissue is to uphold the energy balance by orchestrating the reserve and utilisation of energy in accordance with systemic energy requirements and the fed-fasted state. It also plays a crucial role in protecting peripheral tissues from the adverse effects of lipid excess and lipotoxicity. However, in the presence of a consistently positive caloric balance, it undergoes continuous expansion, leading to weight gain and eventual obesity. As it approaches its upper limit of expansion, its capacity for lipid storage diminishes, resulting in lipid leakage, ectopic lipid accumulation in peripheral organs and a systemic deterioration in metabolic health.[4] Further complicating the understanding of obesity, recent findings suggest that the regulation of metabolic health is influenced not just by the quantity but also by the quality, functionality and location of adipose tissue.[5] The surplus fat accumulated in individuals with obesity is predominantly stored in subcutaneous adipose tissue, but it also extends to deep-seated adipose tissue[6, 7] as well as non-adipose tissue organs, including the liver, pancreas, skeletal muscles and blood vessels.[8-10] The fat stored in these non-adipose tissue organs is commonly referred to as atypical fat; moreover, obesity is characterised by a state of low-grade chronic inflammation within the body,[11] which further extends to other tissues. The augmented immune cell infiltration and proinflammatory activation observed in the intramuscular and perimuscular tissues of obese persons are indicative of the inflammatory condition of the skeletal muscles.[12]

An imbalance in the distribution of energy is the primary factor behind obesity. People can effectively control their weight over time, even with daily variations in calorie intake and expenditure, irrespective of adiposity levels. Essentially, factors triggering changes in body weight must disturb the equilibrium between energy intake and expenditure over time, as well as the utilisation of substances like fat, protein and carbohydrates and/or the allocation of nutrients involving the storage of excess calories. Studies on individuals with a normal physiological weight have indicated that total energy expenditure typically decreases by approximately 10 % during acute caloric restriction and rises with a surplus of calories.[13] The management of consumption, disbursement and storage significantly impacts fluctuations within the framework of energy equilibrium.[14] Energy sourced from protein, carbohydrates, fat and alcohol is utilised through resting metabolic rate (RMR). The thermogenic effect of food and physical activity (RMR) linked to body mass, particularly fat-free mass, along with the thermogenic effect of food, plays a role in sustaining energy balance. When consumption and disbursement synchronise, the body stabilises energy, similar to maintaining body weight.

The specific timeframe for overseeing energy equilibrium remains uncertain, leading to diverse responses to interventions. Positive energy balance, where intake surpasses disbursement, results in an augmentation of body mass, predominantly consisting of 60–80 % body fat. Conversely, a negative energy balance fuelled by disbursement exceeding intake culminates in a reduction in body mass accompanied by a decline of 60–80 % in body fat.[15]

This review article aimed to delve into the intricate mechanisms underlying obesity development, shedding light on pivotal pathways that significantly facilitate this complex phenomenon. The microflora-gut pathway, which intricately links the gut microbiota to energy metabolism, was scrutinised for its role in obesity progression.[16] Simultaneously, the arcuate nucleus pathway, a central regulator of appetite and energy balance, were examined to elucidate its contributions to the pathogenesis of obesity.[17, 18] Furthermore, it delved into the leptin resistance pathway, scrutinising the mechanisms that underlie resistance to this critical hormone in relation to appetite control and energy balance.[19] To understand the complex interactions between the immunological and neurological systems and how inflammatory responses lead to obesity, the neuroimmune route was investigated.[20-22]

Through a comprehensive synthesis of the most recent research results on these pathways, this review seeks to offer a thorough knowledge of the complex nature of obesity development. A comprehensive investigation of these pathways will enable the development of targeted therapeutic options and further our theoretical understanding.

Gut microbiota pathway

Gut-brain axis (GBA)

GBA is a complex system of interactive conveyance between the gastrointestinal (GI) system and the brain, which is aided by immune, endocrinological and neurological signals.[23] This intricate network works as a medium through which intestinal flora might impact brain neuro-developmental processes.[24] Mental health issues and related non-psychiatric disorders are linked to disruptions in the discourse equilibrium of the GBA.[25-27] In contrast, these conditions frequently show alterations in the makeup of the intestinal flora, which further disrupts the complex molecular interaction between the brain and the GI tract.[28]

GBA incorporates enteric nervous system (ENS), the HPA axis, intestinal micro flora, exterior fibres of the autonomic nervous system (ANS), GI peripheral innervations provide a neurological bridge between the brain and gut by means of vagal and neural fibres and the brain responds via sending autonomic efferent fibres to GI tract.[29, 30] GI functionality encompassing gut peristalsis, secretory function and fluid fluxes is intricately directed by the collaborative efforts of central nervous system (CNS) and ENS. ENS, composed of millions of neural cells, operates as an autonomous system playing a crucial role in regulating various aspects of GI function despite the physical separation of enteric innervations from luminal content by epithelial barricades. Previous findings suggest communication between the intestinal micro flora and enteric innervations, potentially affecting GI functions.[31] Even GBA, the CNS integrates signals related to energy needs, producing behavioural responses that affect the ingestive behaviour and subsequently impact the gut microbiota composition.[32]

Role of gut microbiota in energy metabolism

A diverse range of intestinal flora is pivotal for sustaining the body's metabolic equilibrium which is associated to the onset of obesity.[33] Additionally, this microbial diversity plays a vital role in metabolising food and foreign substances. Short-chain fatty acids (SCFAs) and other microbial byproducts such as butyric acid actively direct the GI barricade provocative responses and enzymatic management in a variety of tissues.[34] Moreover, they foster to production of vitamin and help in the assimilation of compounds ie oligo and poly-sugars as well as medicines.[35]

Mechanism related to metabolism and appetite regulation influenced by the microbiota

Microbes in the intestines metabolise dietary nutrients into substances like short-chain fatty acids (SCFAs), γ-amino butyric acid (GABA), serotonin (5-HT) and other neurotransmitters (NTs).[36] These metabolites exert peripheral and central effects, impacting host metabolism and appetite regulation through mechanisms like vagal stimulation or immune–neuroendocrine pathways. Activation of enteroendocrine cells (EECs) by microbial-derived metabolites triggers the release of gut hormones such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and cholecystokinin (CCK). These hormones signal from the gut to the brain's nucleus tractus solitarius (NTS) via the vagal nerve and into the circulatory system, influencing appetite and energy balance regulation in the hypothalamus' arcuate nucleus (ARC).[37] Additionally, gut microbes may interact with bile acids, activating receptors like farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5), thereby affecting GLP-1 secretion. Furthermore, microbial-derived metabolites can influence peripheral effects such as leptin and ghrelin production, as well as contribute to inflammation through the release of lipopolysaccharide (LPS) and activation of immune cells.[38]

Microbiota-gut-brain axis dynamics: implications for development of obesity

The intricate interplay between intestinal microbiota and GBA is paramount for overall well-being. Dysbiosis stemming from lifestyle factors such as unhealthy diets and stress not only correlates with obesity but also exerts adverse effects on mood and cognition.[39] Western dietary patterns characterised by an excess of simple sugars and saturated fat contribute to a diminished microbe heterogeneity and heightened activation of Toll-like receptors (TLRs), initiating an immune response.[40] This scenario promotes the translocation of components from gram-negative bacteria, instigating leaky gut syndrome and triggering endotoxemia, culminating in an escalated immune response, peripheral inflammation and neuroinflammation.[41, 42] The impact of western-

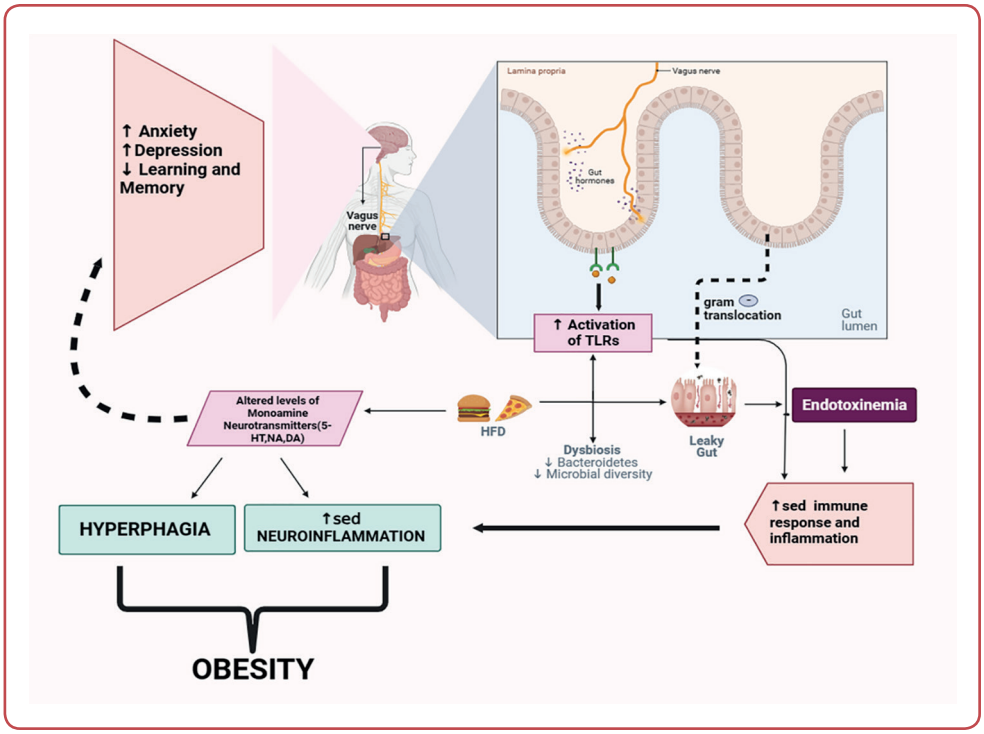

Figure 1: Developmental pathway of obesity through the microbiota-gut-brain axis

ised diet patterns extends to neurotransmitter levels, including 5-hydroxytryptamine, norepinephrine and dopamine.[43] These alterations not only suppress the satiety feeling but also stimulate hyperphagic behaviour, ultimately leading to weight gain. Simultaneously, changes in NT levels are implicated in depressive states and altered neuropsychological functions (Figure 1).[44]

Hypothalamic pathway of obesity

Regulation of energy balance by the hypothalamus

The hypothalamus, a substantial segment positioned at brain's foundation is accountable for directing several biological activities encompassing as energy equilibrium and dietary patterns amidst hypothalamus segment.[45, 46] Distinct subnucleus mainly devoted to coordinating the specified vital activities maintaining energy balance is chiefly dependent on arcuate nucleus (ARC), ventromedial hypothalamic segment (VMH), dorsomedial nuclei (DMH).[47-50] The third cerebral ventricle arc located within central basal hypothalamus segment relate to medial prominence act as a central hub for integrating peripheral metabolic and hormonal functions.[50]

Amongst ARC, there are two divergent physiologically opposed communities of neurons in order to stimulate appropriate dietary consumption. Neurons with orexigenic properties produce neuropeptide Y/Agouti-related peptide (NPY/AgRP). Cocaine- and amphetamine-regulated transcript (CART) neurons and pro-opiomelanocortin (POMC), on the other hand are accountable for fullness and appetency suppression in anorexics.[46, 49] The complex neuronal networks formed by the arc neurons extend to many parts of the brain, comprising the medulla oblongata, which impacts eating behaviour and caloric disbursement. The hypothalamic segment, in particular the arc, is vital to preserving the nuanced equilibrium between calorie intake dissipation and the body's general equilibrium, primarily through the control of hormonal and metabolic signals.[50] The arcuate nucleus's melanocytic neurons analyse synthesise the information to carry out the appropriate behavioural biochemical responses maintaining energy equilibrium and metabolic stability. It is possible for changes in eating behaviour and metabolic conditions like obesity to result from malfunctions in these hypothalamus circuits.[18]

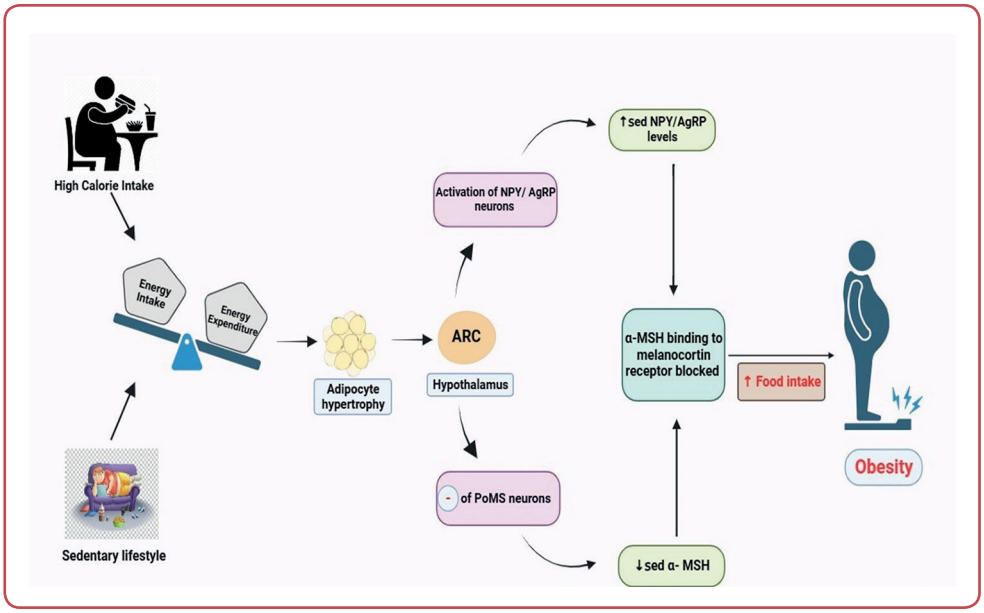

Figure 2: The arcuate nucleus pathway

Disrupted hypothalamic signalling and inflammation: pathway to obesity

Surplus calorie consumption particularly in pertaining to a static lifestyle gives rise to a pronounced energy imbalance. This dissonance occurs when the input of energy into the body surpasses the amount expended causing a disruption in the intricate process of fat metabolism. The consequence is the disproportionate accretion of fat primarily in the central or visceral regions culminating in the enlargement of adipocytes a condition known as hypertrophy.[51] This state of hypertrophy sets off a cascade of effects notably impacting the signalling mechanisms within the hypothalamus a pivotal region responsible for regulating feeding and satiety.[46] The arcuate nucleus situated at the core of feeding control, experiences a disturbance in the equilibrium between anorexigenic (appetite-suppressing) and orexigenic (appetite-stimulating) neurons within the ARC.[52] This disturbance manifests as an excessive activation of NPY/AgRP neurons and a concurrent inhibition of POMC neurons the outcome is an elevation in the levels of NPY/AgRP and a reduction in α- MSH levels this altered balance disrupts the binding of α- MSH to melanocortin receptors impeding the normal functioning of the feeding control system.[53] The subsequent consequence of this impaired signalling is a significant increase in food intake thereby creating a pivotal link in the chain of events that ultimately fosters to the intricate progression of obesity (Figure 2).[54]

Leptin resistance pathway

Leptin - a key controller of human energy balance Leptin, a 16-kDa polypeptide, is mostly originating from white blood cells.[55] It is secreted into the bloodstream and its expression is complexly regulated by various hormones such as glucocorticoids, insulin and growth hormones.[56] Though the amount of leptin dynamically adjusts reciprocally to dietary status, decreasing amid fasting, it also correlates commensurately with body fat reserve, serving as a crucial corpulence signal, although articulated to a lesser extent in diverse tissues, including bone marrow, ovary, placenta, stomach and lymphoid structures. The precise biological role of locally expressed leptin remains largely unknown. It can be because the transcription factor FOS-like antigen 2 (FOSL2) engages in governing leptin production in fat cells.[57] Leptin's biological effects are mediated by binding to stimulation of LRs in their extended form.[58-60] Leptin is principally articulated in distinct subsets of neurons in the brain, encompassing those of the arc of the hypothalamic segment and other hypothalamic brainstem neurons, cerebrocortical neurons.[61] The pleiotropic effects of leptin include the regulation of eating behaviour, energy disbursement, locomotor activity and bone mass development. Thermogenesis, fertility, lifespan thyroid and adrenal functions.[62] Leptin inadequacy, as seen in people and mammals, causes a complicated phenotype that includes extreme weight gain and hyperphagia. This happens as

a result of leptin-responsive neurons altering CNS pathways intended to protect animals from the dangers of famine in response to the lack of leptin.[63, 64]

Leptin receptor

Leptin receptor (LR) belonging to the cytokine receptor family exhibits numerous variants resulting from alternative RNA splicing. Among these variants, LRb stands out as the longest, possessing the only cytoplastic segment capable of communication in the brain LRb finds primary expression in distinct neuronal subsets, notably within the arc of the hypothalamus.[65] While the particular role of peripheral LRb remains elusive, it is established that LRb is present in tissues beyond the brain.[66, 67] The LepR gene generates six variants, namely LepRa, b, c, d, e and f, all sharing the same n-terminal exterior region accountable for binding of leptin.[67, 68] These variants are categorised as curtailed LepRa, c, d and f, elongated LRb and secreted LepRe based on differences in their c-terminal cytoplastic segment.[19] The pivotal mediator of leptin signalling is predominantly LRb, featuring a complete cytoplastic domain comprising approximately 300 amino acid residues.[69-71]

Leptin signalling

LepRb is a cytokine receptor that, although lacking intrinsic enzymatic action, interacts with the same receptor as other IL-6-related proteins.[72] It is composed of an outside segment, one membrane-spanning region and an inner domain. Janus kinase 2 (JAK2) is bound by LepRb.[73] The phosphorylated tyrosine's act as fastening sites for downstream communicating particles with the Src homology 2 (SH2) segment, facilitating their induction into the LepRb-JAK2 complex, which enables JAK2 to phosphorylate these effector proteins.[74-76] The hormone leptin triggers JAK2 stimulation and autophosphorylation on several tyrosines, including Tyr^{1077}, Tyr^{985} and Tyr^{1138} on LepRb.[77] The complexly regulated pathways are essential for controlling metabolic equilibrium and body weight.[78]

Leptin resistance

In addition to its function in the CNS, the hormone leptin also regulates tangential tissues.[79] The processes that result in leptin insensitivity, which is considered a major risk factor for weight gain, involve disrupted neuronal circuits that convey signals.[80] Substances like megalin may have an impact on this disruption. Positive regulators like Src homology 2 (adaptor protein 1) (SH2B1) enhance the leptin communicating pathway, which is crucial for maintaining metabolic equilibrium. Improvements to the melanocortin system and other leptin-targeted neural circuits can lead to conditions like obesity. Deficiency in LepRb signalling components like suppressor of cytokine signalling 3 (SOCS3) and protein- tyrosine phosphatise 1B (PTP1B) are the source of negative repression.[81-83] Understanding all

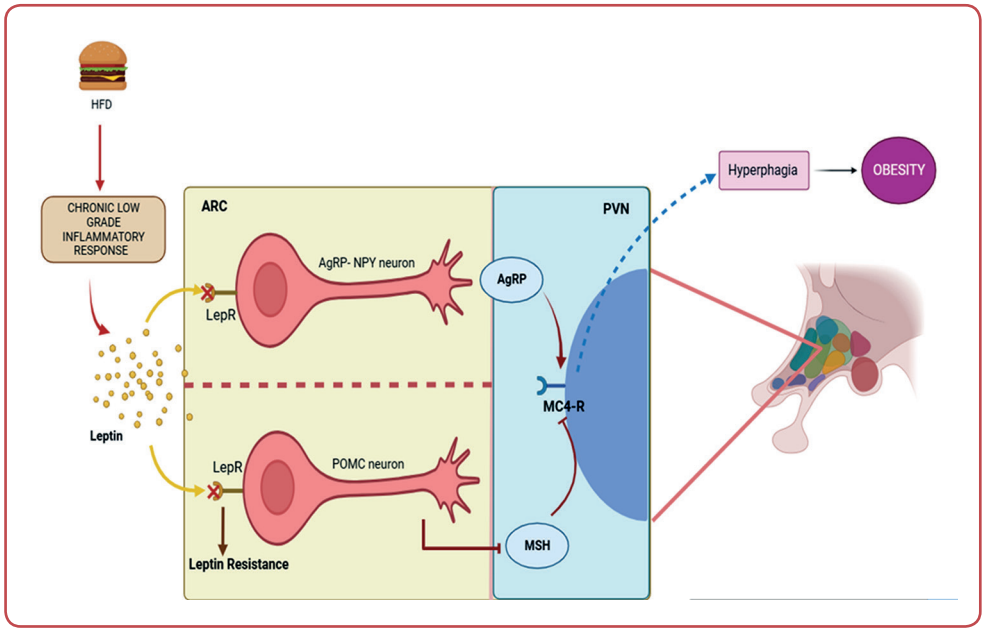

Figure 3: Leptin resistance pathway

these details helps to clarify the complex nature of leptin insensitivity and how metabolic illnesses are caused.[84] The persistently low provocative response in the hypothalamic region induces stress through the TLR4 pathway, leading to the downregulation of LRs.[83] This downregulation diminishes the responsiveness of the hormone leptin to LepRb, prompting uplifted circulating levels of leptin.[85] The brain misinterprets this information, triggering a starvation response that stimulates hyperphagic behaviour characterised by excessive eating. Ultimately, this cascade of events leads to the development of obesity (Figure 3).[86, 87]

Integrated neuroimmunometabolic pathway of obesity

The term immunometabolism, which refers to the complex relationship between immune cell growth and migration and how it affects an organism's metabolism systemically, has gained popularity.[20] This review explores the function of immune cells, in particular macrophages, in relation to obesity.

Macrophages in adipose tissue: key players in metabolic dynamics

Adipocytes contribute to immune responses by expressing monocyte chemoattractant protein 1 (MCP1), which promotes macrophage recruitment and local proliferation.[88, 89] The oversimplified M1, M2 categorisation has faced criticism, particularly concerning metabolically activated macrophages influenced by non-canonical inflammatory factors like glucose, insulin and palmitate.[90] Macrophages polarise into classically activated M1-like and alternatively activated M2-like states, which is a crucial characteristic in lean and obese adipose tissue. Increased free fatty acids affect macrophage toll-like receptor 4 (TLR4) activation due to obesity-related variables.[91-93] Adipose tissue hypoxia exacerbates insulin resistance and macrophage polarisation. Free fatty acids (FFAs) in obesity result in a m1-like phenotype with pro-inflammatory cytokine production. The complex interplay between insulin resistance and FFAS-TLR4 further muddies this feed forward process.[94, 95]

Interplay of neurological, immunological and metabolic factors in obesity development

Through a feed forward mechanism obesity initiates a provocative cascade; an increase in the number of these fat cells plays a key role in this process. As a result, there is an elevated release of MCP1 from adipocytes and this MCP1 is upregulated that acts as a signal for the recruitment of the macrophages to at once in the adipose environment.[93] These macrophages are stimulated in

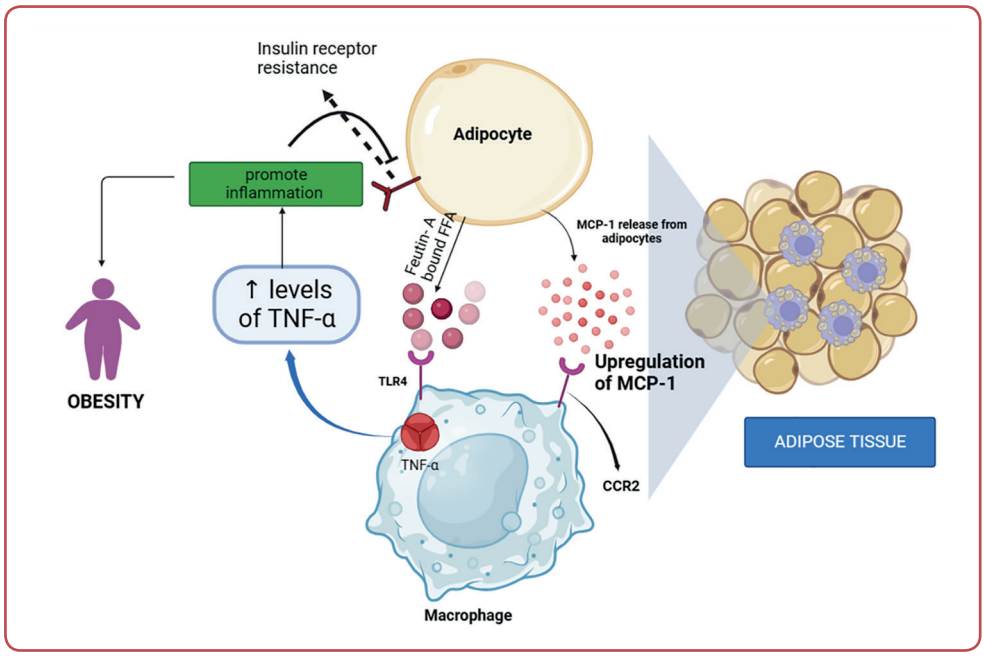

Figure 4: *Neuroimmunometabolic pathway*

response to FFAs bound to fetuin a process mediated by TLR4.[96] This stimulation results in the release of pro- provocative cytokines like TNF which in turn raises the expression of MCP1 in fat cells feeds the cycle of inflammation indefinitely.[97, 98] This convoluted interaction ultimately results in elevated free fatty acids release insulin resistance which are important aspects in the aetiology of obesity (Figure 4).[99]

HPA axis pathway of obesity

Cortisol: stress hormonal regulator

The steroid hormone cortisol, often referred to as the "stress hormone," is secreted by the adrenal glands, which are located above each kidney. Stressful events cause the release of cortisol into the circulation, which raises blood glucose levels and mobilises energy for the "fight or flight" response.[100] Cortisol is a natural circadian rhythm hormone that regulates the sleep-wake cycle and other daily physiological activities. It peaks in the early morning and troughs in the evening.[101] In addition to its stress-related functions, cortisol affects metabolism and encourages gluconeogenesis, which maintains blood sugar levels.[102] By reducing inflammation and controlling immunological responses, it also has a significant impact on immune function. Cortisol helps regulate blood pressure and works with aldosterone to balance sodium and potassium levels, which affects blood volume and pressure.[103] Furthermore, cortisol regulates processes such as bone formation and tissue breakdown, contributing to tissue development and repair.[104] On the other hand, long-term stress-induced rise of cortisol has been connected to detrimental health outcomes, such as compromised immune system performance, disruptions in metabolism and a higher chance of developing diseases like cardiovascular disease. Through a feedback process involving the pituitary gland and the brain, its production is closely controlled.[105]

HPA axis

The hypothalamic-pituitary-adrenal (HPA) axis is a vital regulatory mechanism that controls the release of cortisol, a major stress hormone and is essential for preserving the body's homeostasis.[100] The HPA axis functions by means of a sequence of interrelated stages. Adrenocorticotropic hormone (ACTH) is secreted by the pituitary gland in response to the hypothalamus' release of corticotrophin-releasing hormone (CRH).[106] The adrenal cortex is then prompted by ACTH to release cortisol into the bloodstream. Notably, the hypothalamus and pituitary are negatively impacted by circulating cortisol, which prevents them from secreting more CRH and ACTH.[107] The HPA axis, which is made up of this precisely regulated feedback loop including the adrenal cortex, pituitary and brain, is liable for the body's sensitive and dynamic regulation of cortisol levels.[108] The HPA axis is primarily engaged in the host's reaction to stress, but it also controls a variety of peripheral processes, such as the metabolism of macronutrients, endocrine and immunological activations,[109, 110] as well as central superior processes,

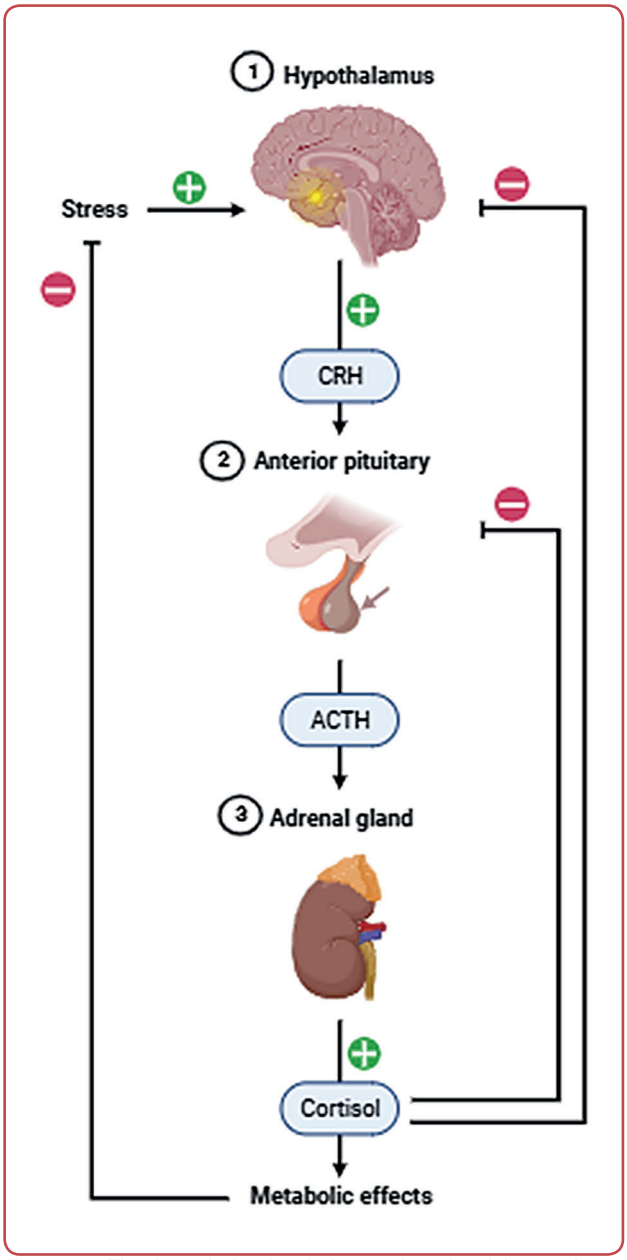

Figure 5: The hypothalamic-pituitary-adrenal axis's regulatory pathway

including mood, anxiety and cognition. This gives the HPA axis a pivotal role at the nexus of stress and disorders associated with stress, like depression, and metabolic/inflammatory illnesses, like obesity (Figure 5).[111]

Dysregulation of the HPA axis: the obesity developmental pathway

One of the main contributing factors to the development of obesity has been identified as the disruption of the HPA axis pathway. The complex neuroendocrine system known as the HPA axis releases chemicals like cortisol, which are essential to the body's reaction to stress.[112] Repeated exposure to stressors or chronic stress can cause this pathway to become dysregulated, which keeps cortisol levels up for an extended period of time.[113] Cortisol, sometimes called the "stress hormone," affects hunger control and metabolism. An imbalance in energy homeostasis can be caused by dysregulated HPA axis activity, which encourages consumption of more food, especially tasty and high-calorie items. Furthermore, cortisol contributes to central obesity by encouraging the deposition of fat, especially in visceral adipose tissue.[114]

Malfunctions in negative feedback mechanisms, such as the inability of glucocorticoids (GC) to effectively regulate HPA axis activity and their own synthesis, seem to be a major contributing factor to HPA axis hyperactivity.[115-117] This hyperactivity is associated with hippocampal atrophy, reduced neurogenesis and disrupted monoamine oxidase (MAO) signalling, leading to the suppression of satiety signals and ultimately triggering hyperphagic behavior.[118] Additionally, elevated cortisol levels are observed. The increased cortisol production in adipose tissue during obesity is believed to result from heightened local activity of 11β-hydroxysteroid dehydrogenase (HSD) type 1.[119] This enzyme converts inactive cortisone/11-dehydrocorticosterone into active cortisol/corticosterone within the local adipose tissue environment.[120-122] Importantly, the escalated activity of 11β-HSD1 is proposed to play a significant role in the onset of obesity, a hypothesis supported by clinical evidence indicating a strong correlation between the expression of 11β-HSD1 in adipose tissue and various parameters related to obesity (Figure 6).[123]

Intricate interplay of divergent pathways in development of obesity

The intricate interplay among the hypothalamic pathway, leptin resistance pathway, gut-brain axis-microbiota pathway, HPA axis pathway and neuroimmunometabolic pathway represents a dynamic and complex network that significantly influences the development and progression

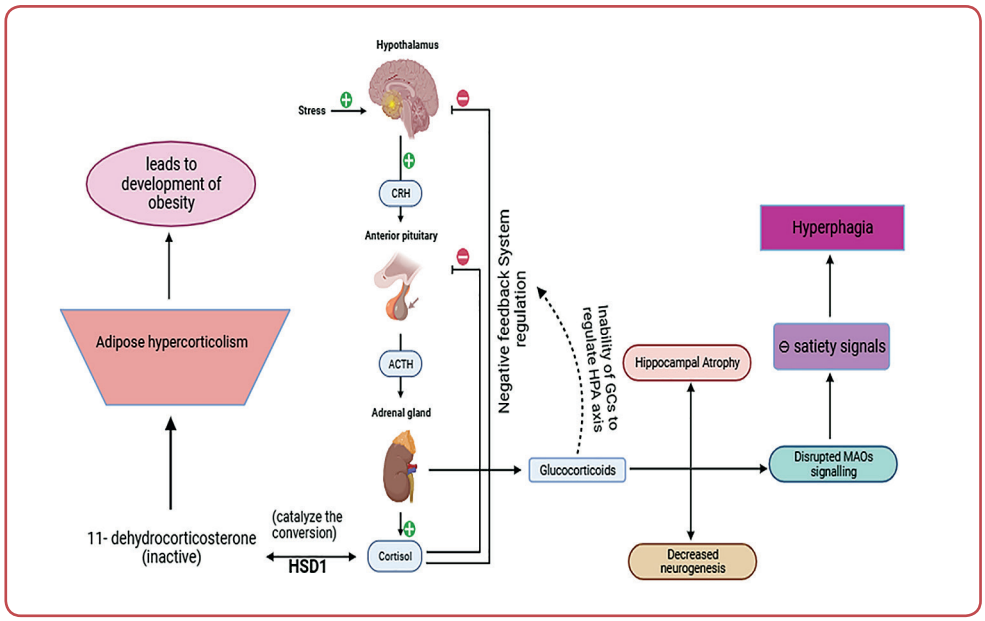

Figure 6: Dysregulation of the HPA axis: the obesity developmental pathway

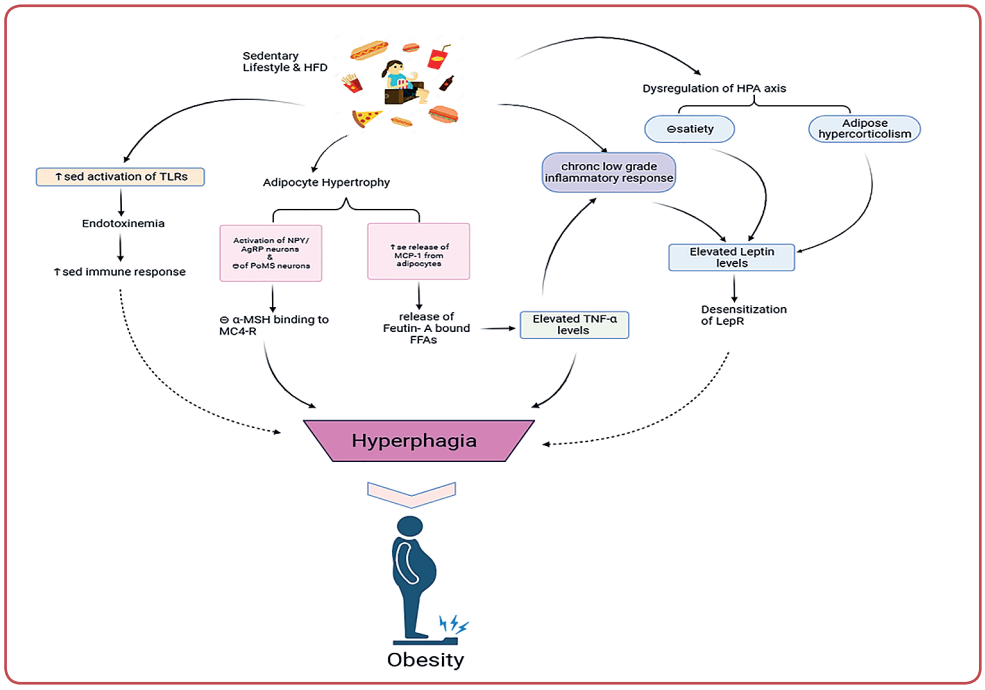

Figure 7: Intricate interplay of divergent pathways in development of obesity

of obesity (Figure 7). The convergence of these pathways underscores the multifactorial nature of obesity, integrating hormonal, neurological, immunological and metabolic factors.[124]

The hypothalamic pathway, as a central regulator of energy balance, plays a pivotal role in coordinating responses to nutrient availability and energy expenditure. Leptin, a key player in this pathway, signals the body's adipose stores to the hypothalamus, orchestrating metabolic responses. However, leptin resistance disrupts this communication, leading to dysregulated appetite, impaired energy homeostasis and ultimately contributing to the development of obesity.[125]

The gut-brain axis and microbiota pathway add another layer of complexity by highlighting the bidirectional communication between the GI system and the CNS. The composition of the gut microbiota influences energy metabolism and inflammation, contributing to the development of obesity. Disruptions in this pathway can lead to metabolic imbalances and exacerbate the progression of obesity.[126]

The HPA axis pathway, closely intertwined with stress responses, connects neuroendocrine signalling with metabolic regulation. Chronic stress can dysregulate the HPA axis, promoting the accumulation of abdominal fat and exacerbating obesity-related metabolic complications. The interplay between stress, cortisol release and metabolic dysfunction underscores the importance of considering psychological factors in understanding obesity development.[127]

The neuroimmunometabolic pathway integrates neural, immune and metabolic signals, emphasising the cross-talk between these systems in obesity. Neuroinflammation, a characteristic feature of obesity, contributes to insulin resistance and disrupts metabolic homeostasis. The immune system's involvement in adipose tissue inflammation further complicates the obesity landscape, linking inflammation with metabolic dysregulation.[20]

In navigating the complexities of obesity development, it is evident that a comprehensive and integrative approach is essential. Targeting one pathway in isolation may prove insufficient, necessitating a holistic understanding of the interconnections between these intricate systems. Personalised interventions that address the specific factors contributing to an individual's obesity profile hold promise in the development of effective therapeutic strategies.

Future directions and implications for managing obesity

Understanding and targeting multiple pathways associated with obesity presents a nuanced approach for effective management and offers promising future directions. The hypothalamic pathway, crucial for energy homeostasis, involves intricate signalling mechanisms that regulate appetite and metabolism. Leptin resistance, a key aspect of this pathway, can be a barrier to weight loss. Addressing this resistance may open avenues for novel therapeutic interventions. The gut-brain axis and microbiota pathway, influencing energy balance and metabolic processes, highlight the importance of a healthy gut microbiome in obesity management. Modulating the gut microbiota through dietary interventions or probiotics may emerge as a viable strategy. The HPA axis pathway, linking stress and obesity, underscores the intricate relationship between mental health and metabolic regulation. Integrating stress management techniques into obesity interventions may yield holistic benefits. Lastly, the neuroimmunometabolic pathway emphasises the intersection of neurological, immune and metabolic functions. Unravelling this complex interplay may lead to innovative therapies that target neuroinflammation and metabolic dysregulation.[128]

Future directions in obesity management should explore personalised interventions, leveraging advances in genomics, precision medicine and digital health technologies to tailor strategies based on individual variations in these pathways. Additionally, emerging technologies, such as artificial intelligence and wearable devices, hold the potential to enhance the precision and effectiveness of obesity interventions by continuously monitoring and adapting treatment plans. The integration of behavioural science and psychology into weight management programs is also gaining prominence, recognising the importance of addressing psychological factors that contribute to overeating and sedentary behaviours. This multifaceted approach holds the potential to revolutionise obesity management, offering more effective and tailored solutions to address the diverse factors contributing to this global health challenge.[129]

Reasoning

Obesity, a complicated and ubiquitous health concern, has far-reaching consequences for numerous organs and greatly impairs everyday living for a large section of the population. With over half of people struggling with obesity in today's society, it has become a critical issue. Beyond its effects on physical health, obesity has a negative impact on mental health, especially in young people dealing with the fallout from contemporary eating patterns and sedentary lives. Obesity has clear social consequences, including a decrease in self-esteem and a tendency for people to doubt their talents and looks.[130-132] The several processes that lead to obesity are carefully examined in this paper, including the disruption of the HPA axis system, the gut microbiota pathway, the hypothalamic/arcuate nucleus pathway, the leptin resistance pathway and the neuroimmunometabolic pathway. Consolidating knowledge on the numerous elements that contribute to obesity's development and expanding our grasp of the complex pathophysiology of the disease are the main objectives.[128]

A full perspective of obesity's evolution comes from combining data from different avenues. Crucially, this conversation establishes the foundation for determining important goals when creating interventions. Obesity must be addressed holistically through varied techniques that take into account the complex interaction of genetic, environmental and lifestyle variables.

The overarching theme emphasises the crucial need for personalised interventions. The awareness of the multitude of pathways that lead to obesity highlights the need for personalised solutions. For instance, the gut microbiota pathway underscores the significance of dietary adjustments and probiotics,[133] while the hypothalamic/arcuate nucleus pathway focuses on brain circuits regulating appetite and identifies specific dietary interventions. At the same time, the leptin resistance pathway suggests potential drug therapies that try to raise leptin sensitivity.[134] The neuroimmunometabolic pathway's involvement in chronic low-grade inflammation renders anti-inflammatory measures necessary to take into account.[135-137] Comprehensive obesity management techniques can benefit from the addition of stress management strategies that are based on a knowledge of the disrupted HPA axis pathway.[138, 139]

Conclusion

In conclusion, this extensive investigation not only clarifies the nuances surrounding obesity but also lays the groundwork for practical solutions. Finding important targets along several paths provides an itinerary for successful interventions. Tailored strategies, grounded on a thorough comprehension of these pathways, have the capacity to revolutionise the treatment of obesity and mitigate the worldwide consequences of this complex health concern. As research progresses, turning these insights into practical treatments gives hope for a better future.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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