**Exfoliating the petals of Obesity Pathology: From Pathogenesis to Emerging Drug Targets**

Nikita Nayak, Shivangi Kumari, Tuhin Mukherjee, Satyajit Mohanty\*

Division of Pharmacology, Department of Pharmaceutical Sciences & Technology, Birla Institute of Technology, Mesra, Ranchi, Jharkhand, India 835215

**Corresponding author Mail-** satyajitmohanty922@gmail.com

**ABSTRACT**

This is a comprehensive book chapter that delves into the multifaceted aspects of obesity, exploring its pathogenesis and emerging drug targets. A brief overview of the prevalence and health consequences of obesity sets the stage for the subsequent discussions. Genetic and environmental factors in obesity are examined in detail, emphasizing the role of genetic predisposition and the influence of environmental factors such as diet, sedentary lifestyle, and socioeconomic influences. The chapter then shifts focus to the adipose tissue, highlighting its role as an endocrine organ and exploring the relationship between adipose tissue inflammation and metabolic dysfunction associated with obesity. The impact of gut microbiota on metabolism is explored, with an overview of gut dysbiosis and its association with obesity. Potential mechanisms linking gut microbiota to weight regulation are examined, shedding light on the interplay between the microbiome and obesity. The chapter delves into the central nervous system's regulation of energy homeostasis, providing an overview of the hypothalamus and its role in appetite regulation, with a specific focus on the leptin-melanocortin pathway and its implications in obesity pathogenesis. Epigenetic modifications associated with obesity and their impact on metabolic processes are explored. The role of neurotransmitters, such as dopamine and serotonin, in appetite regulation and reward pathways are discussed. The latter part of the chapter focuses on emerging drug targets for obesity treatment and it provides an overview of current pharmacological approaches and discusses recent research on novel drug targets and therapeutic strategies.

**Keyword: -** Obesity, Pathology, gut microbiota, Epigenetic modifications

**I. INTRODUCTION TO OBESITY**

Obesity is a critical and escalating global health concern. While it is characterized as the excessive build-up of body fat, there is currently no universally agreed-upon definition directly linked to body fat. Instead, the diagnosis of obesity relies on an anthropometric measure known as body mass index (BMI)1. Depending on the distribution of body fat, obesity is categorized into two types: central, where fat mainly accumulates in the intra-abdominal region, and peripheral, with fatty tissue predominantly gathering in the femorogluteal region. This distribution varies among genders and races, often being mixed during infancy and significantly impacting one's quality of life2. Body mass index is defined as weight in kilograms divided by height in centimetres squared. A body mass index of 18.5 to 24.9 is considered normal, less than 18.5 is considered underweight, and values of 25 and above are considered obese3. Obesity is a highly diverse condition from clinical and physiological perspectives. It typically arises due to an energy imbalance caused by the interplay of individual susceptibility4 and lifestyle choices that promote excessive calorie intake and insufficient physical activity. This complex issue involves various factors, including the influence of environmental, behavioral, and socio-economic elements on individuals with distinct physiological susceptibilities. Research has demonstrated that genetic factors play a significant role in determining 30–80% of the variation in weight5, 6. Obesity rates have tripled since 1975, according to the WHO, and in 2016, 39% of the world's adult population (>1.9 billion) was overweight, with 13% (650 million) obese5. By 2025, the percentages will have risen to 18% and 21%, respectively7. Global obesity rates in men and women were 10.8% and 14.9%, respectively in 2014, and are expected to rise further. Obesity affects nearly four out of every ten US adults, a figure that has steadily increased since 2000 and is significantly higher than the Healthy People 2020 goal of 30.5%8. Obesity is associated with a wide range of health problems and morbidities. The risks of sleep apnea, insulin resistance, dyslipidemia4, gallbladder disease, and non-insulin-dependent diabetes mellitus are significantly increased (relative risk >3)10. There is a moderate increase in the risk (relative risk 2–3) for developing coronary heart disease, hypertension, osteoarthritis, and hyperuricemia11. The risk of breast, colon, and endometrial cancer, as well as the risk of increased anesthetic complications, impaired fertility, and polycystic ovary syndrome, is slightly elevated (relative risk 1–2)12. Numerous research studies indicate that work-related stressors like shift work, long work hours, high work demands, and low job control (job strain), along with effort-reward imbalance and inadequate social support, are linked to chronic illnesses such as depression13, 14 high blood pressure, 15-17 and cardiovascular diseases18-20 among the general working population. The stressors have also been linked to CVD risk factors such as low physical activity stress-related eating and obesity21-23. A model was put forth to explain how occupational factors, including shift work, sedentary work, and job stress, could contribute to the obesity epidemic in the general population, going beyond the influence of aging and the food and health culture in the U.S. This model suggests that work-related factors offer an essential intervention site for prevention24. Obesity is relatively uncommon in African and Asian countries compared to urban populations, and prevalence rates are higher in economically developed regions, even approaching those seen in industrialized countries. Women tend to have higher obesity rates than men, while men may have higher rates of overweight 25. The prevalence of overweight and obesity in the United States and Germany is approximately 60% and is on the rise. The countries of the former Soviet Union report the highest rates at about 75%. Samoa's obesity prevalence is estimated at around 60–80%. In China, roughly 30% of men are overweight, whereas 40% of women are overweight. Europe's lowest obesity rates are found in Sweden (1% in men and 9.1% in women) and The Netherlands (8% in both men and women). The prevalence of obesity in the United Kingdom doubled from 8% to 16% between 1980 and 1995 (WHO Geneva)26.

**2. Genetic and environmental factors in obesity**

Obese people are more likely to have multiple genes that predispose them to gain excess weight. The fat mass and obesity-associated gene (FTO), which is found in up to 43% of the population, is one such gene. Individuals carrying the fat mass and obesity-associated gene may encounter challenges in regulating their caloric intake when faced with easily accessible food. Obesity results from a combination of environmental factors and innate biological elements. Notably, the significant variation between individuals in body weight, which determines their response to the "obesogenic" environment, is strongly influenced by genetics. Twin, family, and adoption studies have estimated obesity heritability to range from 40% to 70%27. Therefore, genetic approaches offer valuable insights into understanding the physiological and genetic mechanisms that govern body weight. Over the last two decades, genetic investigations into both common and rare forms of obesity have provided two important overarching biological findings: firstly, the leptin-melanocortin pathway plays a vital role in controlling appetite, and secondly, genes predominantly or exclusively expressed in the brain and central nervous system (CNS) have a central involvement in obesity28. Numerous healthcare professionals acknowledge the considerable impact of social and environmental factors on obesity, yet they feel uncertain about how to tackle them. Some may view these factors as beyond their control and outside their scope of practice, leading them to avoid discussing the topic with their patients. Conversely, certain medical providers still attribute obesity to factors within an individual's control, such as dietary choices, exercise levels, or willpower29. Globalization and economic shifts in the last decade have resulted in reduced costs and an increased prevalence of fast food, coupled with a decline in physical activity. Moreover, food accessibility plays a crucial role, and there are disparities in access to affordable healthy food based on ethnicity, race, and socioeconomic status, particularly in the United States. Minority and low-income neighbourhoods have approximately 30% fewer supermarkets30. Higher socioeconomic status is associated with a higher likelihood of obesity in developing countries. In developed countries, however, there is an inverse relationship between socioeconomic status and BMI. The ability to afford food, cultural values, and less physical labour may favour a larger body size in developing countries, whereas developed countries can afford more nutritious food and prefer high-energy exercise31. Various factors, including sedentary lifestyles, level of physical activity, quality of sleep, and stress, are all independently linked to weight gain. The US Department of Health and Human Services recommends engaging in at least 150 to 250 minutes of moderate exercise per week to prevent weight gain. Physical inactivity in children has become more prevalent due to increased screen time, leading to more sedentary lifestyles. Implementing early childhood preventative measures, such as promoting sports and outdoor activities, has shown long-term health benefits 32. Excess body weight is associated with a significant increase in morbidity. Obesity is linked to numerous clinical co-morbidities and is considered a modifiable risk factor. The psychological effects of obesity perpetuate a vicious cycle. Obesity is more common in people who suffer from depression and binge eating33. Patients who are obese or overweight may face social discrimination and stigma. This may harm their quality of life. This begins at a young age and can continue into adulthood. According to studies, this has increased by 66% in the last decade. Understanding that obesity is caused not only by an imbalance in calorie intake versus expenditure, but also by environmental, and psychosocial, genetic factors 34.

1. **Adipose tissue and obesity**

**3.1 Adipose tissue as an endocrine organ**

The biological functions of adipose tissue have drawn much more attention recently than they formerly did when it was just seen as an organ for storing triacylglycerol. Over the last decades there has been a significant accumulation of experimental data about the biology and biochemistry of adipose tissue This tissue is no longer been considered to be a fat-storing inert tissue [35]. The primary site for the storage of additional energy is adipose tissue, which also functions as an endocrine organ capable of synthesizing a variety of substance with biological activity that control metabolic balance. In addition to adipocytes, this dynamic tissue also contains additional cell types known as the stroma-vascular fraction, which includes blood cells, endothelial cells, pericytes, and adipose precursor cells 36,37.

Brown and white adipose tissue are the two different forms of adipose tissue found in mammals. In adult humans, brown adipose tissue, which is highly specialized in thermogenesis, is nearly absent, yet it is present at birth. Adipocytes in brown adipose tissue are smaller than those in white adipose tissue. They have many cytoplasmic lipid droplets of various sizes, an enormous amount of cytoplasm, and several mitochondria that oxidize fatty acids to release heat. Similarly, it stores energy in the form of lipids, but it generates heat more frequently by oxidizing fatty acids inside the adipocyte than by distributing free fatty acids to other cell types 38,39.

**Fig 1-The most significant physiological functions of white adipose tissue**

The largest endocrine tissue in humans could represent white adipose tissue. Since fat cells can secrete a wide range of hormones, growth factors, enzymes, cytokines, complement factors, and matrix proteins, it has pleiotropic properties. The majority of these variables, including those involved in the control of food intake, energy expenditure, metabolic homeostasis, immunity, and blood pressure homeostasis, are expressed by adipose tissue also 40,41. Adipose tissue dynamically regulates cell function through a complicated network of endocrine, paracrine, and autocrine signals that affect the response of numerous tissues, including the hypothalamus, skeletal muscle, pancreas, endothelium, liver, kidneys, and the immune system. Endocrine signals travel through the circulatory system to reach all parts of the body. Because of its secretory qualities, white adipose tissue is now thought to be a very active endocrine tissue 42. Leptin is expressed mainly by adipose tissue, but its low levels have been found in the placenta, skeletal muscle, gastric and mammary epithelium and the brain. Various factors such as acute infection, glucocorticoids, and proinflammatory cytokines all boost leptin levels. Leptin, on the other hand, is decreased by smoking, melatonin, adrenergic stimulation, growth hormone (GH), cold exposure, thyroid hormone, and thiazolidinediones 43,44. Its levels are higher in women than in men, because androgens cause inhibition, estrogen leads to stimulation, and there is more subcutaneous fat in women. Subcutaneous adipose tissue produces more leptin than visceral adipose tissue 45. Adipose tissue is the only place where adiponectin is secreted. There is a strong negative connection between plasma adiponectin concentration in humans and fat mass, except for severe undernutrition and in new-borns. Visceral adipose tissue increases the chance of developing some illnesses, including metabolic syndrome. This observed variation in disease risk may result from variations in endocrine activity among adipose tissue depots. Each adipose tissue depot's anatomic location has an impact on endocrine function. While endocrine hormones originating from SC adipose tissue are secreted into the systemic circulation, those from visceral adipose tissue are released into the portal system and have direct access to the liver46. As a result, the former has a more significant impact on hepatic metabolic activity. Additionally, distinct adipokine expression and secretion characteristics can be seen in adipose tissue depots. For instance, visceral adipose tissue expresses and secretes more IL-6 and PAI-1, although leptin and adiponectin are more abundantly secreted by adipose tissue.

Numerous hormones originating from adipose tissue, such as leptin, have been identified and relatively well understood, but further investigation is necessary to precisely determine their physiological roles. Apart from the known genes, there are about 40% of genes expressed in adipose tissue are novel, and a significant portion (20–30%) of these genes may code for secreted proteins47. Continual identification and characterization of these novel genes are expected to provide deeper insights into the endocrine function of adipose tissue and its connection to energy homeostasis and other physiological systems. More research is required to clarify the specific contributions of individual cellular components within adipose tissue.

**3.2 Inflammation in adipose tissue and its role in obesity-related metabolic dysfunction**

Obesity is associated with increased adipose mass and a chronic low-grade inflammatory response, marked by changes in the production of adipokines and elevated levels of inflammatory markers like tumor necrosis factor, interleukin-6, monocyte-chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), colony-stimulating factor (CSF), and inducible nitric oxide synthase (iNOS). Despite this, research indicates that adipocytes are not the primary source of inflammatory cytokine secretion within adipose tissue. Instead, non-adipose cells, such as preadipocytes, endothelial cells, fibroblasts, leukocytes, and macrophages, appear to play a significant role in driving the chronic inflammatory response observed in obesity48,49. Obesity leads to reduced secretion of the anti-inflammatory hormone adiponectin, which normally has beneficial effects on macrophages, while the production of the pro-inflammatory hormone leptin is increased. Another factor contributing to the inflammatory response is the elevated levels of free fatty acids released from enlarged adipose tissue in obesity. Recent findings suggest that saturated fatty acids can activate the NF-B pathway in macrophages through TLR-4, leading to the production of inflammatory cytokines50. Adipose tissue secretes various bioactive substances, including adiponectin, leptin, angiotensin, resistin, visfatin, acylation stimulating protein, sex steroids, glucocorticoids, tumor necrosis factor (TNF), interleukin-6 (IL-6), and free fatty acids (FFA). In obese adipose tissue, there is an imbalance in the production of pro- and anti-inflammatory adipocytokines, which may contribute to the development of metabolic syndrome51. The over-secretion of harmful adipocytokines, such as PAI-1, TNF-α, or visfatin, coupled with the under-secretion of potentially beneficial adipocytokines like adiponectin, are likely significant mechanisms involved in various metabolic syndromes52,53.

Obesity is the state of systemic, chronic low-grade inflammation. Recent studies have revealed that obesity has a strong impact on adipokine secretion and insulin resistance 54. In recent times, there has been growing recognition that macrophages play a crucial role in the secretory function of adipose tissue, serving as the primary source of inflammatory cytokines such as TNF-α and IL-6. Adipose tissue functions as a secretory organ with distinct characteristics, and its secretory activity is influenced by humoral and hormonal regulatory mechanisms. This observation has led to the proposal that leptin and adiponectin, with their central actions, perform reciprocal functions in the body's homeostatic mechanisms, maintaining fat and energy stores by either suppressing or stimulating appetite and energy expenditure 55. TNF- was the first adipose-derived factor to be linked to diabetes, obesity, and inflammation. Because it has been shown that TNF can impede insulin signaling in hepatocytes and adipose tissue, studies reveal that mRNA expression levels of TNF- in adipose tissue in obesity are substantially implicated in the etiology of insulin resistance. Adipose tissue is the source of about 30% of the circulating Interleukin-6 (IL-6) in humans. In comparison to subcutaneous fat, visceral fat has larger concentrations. They are induced by TNF- and interleukin-1, and their levels rise with obesity 56,57. The protein known as PAI-1, which is involved in fibrinolysis, is changed in obesity. Visceral obesity is inversely correlated with plasma levels of PAI-1. Not only do adipocytes secrete resistin, but also secreted by immunocompetent cells. Circulating resistin levels are increased in mouse models of obesity and obese humans and increased in diet-induced and genetic forms of obesity.Increases in fat cell quantity, size, or a combination of the two are indicators of obesity. Adipocytokine synthesis is dysregulated as a result of low-grade inflammation in adipose tissue, according to more recent research. In the obese condition, inflammatory macrophages enter the adipose tissue and release TNF- and IL-6, forming a connection between obesity, inflammation, and insulin resistance58. Understanding the signalling pathways by which adipokines regulate metabolism and looking for innovative treatments for disorders associated with adipose tissue are becoming more and more crucial today.

**4. Gut Microbiota and Obesity**

The initial link between obesity and gut microbiota was established through studies conducted on germ-free mice. In one subgroup, mice were raised in a sterile environment, while another subgroup was raised in a normal environment. Surprisingly, the mice raised in the conventional environment had a 40% higher body fat percentage and a 47% higher fat percentage around their reproductive organs, despite consuming less food compared to the germ-free mice. To further investigate this connection, the researchers transplanted gut microbiota from regular mice into germ-free mice, which resulted in a remarkable sixty percent increase in body fat within just fourteen days, even without any significant changes in their food intake or energy expenditure. The discovery indicates that gut microbiota plays a significant role in influencing the characteristics associated with obesity in the host. When the microbiota was transplanted, it not only increased the availability of energy from dietary plant polysaccharides but also modified specific genes (ChREBP and SREBP-1) in the host, affecting energy storage in adipocytes 59. The human gut houses over 100 trillion microbial cells that play a crucial role in regulating human metabolism through their symbiotic interactions with the host. Recently, gut microbiota has been identified as a key environmental factor contributing to metabolic diseases. It is now considered to function as a distinct endocrine organ, engaging in molecular crosstalk with the host to maintain energy homeostasis and stimulate host immunity60. Changes in the gut microbial composition influenced by external factors can lead to a significant alteration of the symbiotic relationship between gut bacteria and the host, ultimately promoting the development of metabolic diseases. The gut microbiota is thought to contribute to these diseases by stimulating low-grade inflammation. Research indicates that the gut microbiota plays a role in harvesting energy and increasing the host's fat storage 61,62. Germ-free mice have 40% less total body fat than conventionally raised mice, despite consuming 29% more calories than their conventionally raised counterparts 63. Moreover, germ-free mice gain less weight and are protected against diet-induced glucose intolerance and insulin resistance compared to conventionally raised mice 64. When fecal microbiota from conventionally raised mice was transplanted into germ-free mice, it led to a substantial 57% increase in body fat, along with elevated hepatic triglyceride levels and insulin resistance, without any changes in food consumption 65. Differences in gene expression related to energy homeostasis, lipid metabolism, and mitochondrial metabolism were observed in various parts of the gut, liver, and adipose tissues between germ-free mice and conventionally raised mice 66. Both human studies and animal models have been used to demonstrate alterations in the gut microbiota associated with obesity. A comparison of bacterial composition in the gut of lean, wild-type mice, and obese mice (leptin-deficient ob/ob mice, where obesity is induced by a lack of the hormone leptin, responsible for controlling satiety) revealed differences in the abundance of the Bacteroidetes and Firmicutes phyla. Notably, the Firmicutes: Bacteroidetes ratio positively correlated with the obese phenotype, regardless of diet 67. However, these differences were linked to the overgrowth of a specific class within the Firmicutes phylum, the Mollicutes class, in animals with diet-induced obesity 68. Furthermore, these changes in composition were entirely reversed upon returning to a normal diet, indicating that diet plays a primary role in obesity-related alterations in the gut microbiota. This observation was further supported by Murphy and colleagues, who found an increase in the Firmicutes: Bacteroidetes ratio in both ob/ob mice and mice fed a high-fat diet compared to lean mice. Recent research has shown that the increase in the Firmicutes: Bacteroidetes ratio was more significant in mice fed a high-fat diet compared to ob/ob mice 69. Studies are currently exploring the relationship between the nervous system and the gut's microbial composition, focusing on the recovery from dysbiosis and the establishment of eubiosis70. The enteric nervous system, often referred to as the second brain, plays a crucial role in controlling physiological responses to the environment through the structure of enteric neurons 71. Research has demonstrated the regenerative function of the microbiota, which can reduce significant pathology symptoms, particularly those associated with degenerative diseases, through microbiota-targeted therapies that modulate the microbial pattern and influence host homeostasis 72. Restoring the gut microbiota can lead to improved overall functioning and support the functionality of other tissues and organs73. This evidence linking gut microbiota to degenerative pathologies is well-established, and further research is needed to uncover new links in the current epidemiological context. Obesity has been newly identified as a condition influenced by the role of the microbiota. Identifying critical mediators of this process presents an opportunity for novel therapeutic approaches by correcting dysbiosis and reducing the inflammatory response.

**4.1 Effect of diet or dietary components on the gut microbiota**

The diet significantly influences the individual microbiome by serving as a substrate for microbial metabolism. Different diets and dietary components can either positively or negatively modulate the composition of the microbiome74. Western diets, which are characterized by low fiber, vegetable, and fruit intake, but high in saturated fat, sugar, and animal protein, have far-reaching consequences beyond metabolic aspects. They can lead to hyperinsulinemia, insulin resistance, dyslipidaemia, overstimulation of the sympathetic nervous system and renin-angiotensin system, and oxidative stress. Moreover, such diets can cause dysbiosis, impair intestinal barrier function, increase intestinal permeability, and result in the leakage of toxic bacterial metabolites into the bloodstream. These effects collectively contribute significantly to the development of low-grade systemic inflammation 75.

**4.2 Impact of lifestyle and environmental factors on the gut microbiome**

A diet high in both carbohydrates and fats can lead to an imbalance in gut bacteria, known as dysbiosis, which reduces the expression of angiopoietin-like protein 4 (Angptl4). This protein plays a role in regulating lipid metabolism76. The decrease in Angptl4 leads to higher activity of lipoprotein lipase (LPL), resulting in increased uptake of fatty acids and higher fat storage in peripheral tissues 77. Ultimately, this leads to fat accumulation and obesity. High-fat diets also negatively impact beneficial bacteria like Bifidobacterium spp., Lactobacillus spp., and Prevotella spp., while promoting the overactivation of the endocannabinoid system. These changes disrupt the gut microbial composition, increase gut permeability, and allow the translocation of bacterial fragments, contributing to weight gain 78,79. The type of fatty acids consumed also influences gut microbiota, with omega-3 promoting the growth of Lactobacillus, and monounsaturated and omega-6 polyunsaturated fatty acids being inversely related to the growth of bifid bacteria 80. High-fat diets also encourage the overgrowth of Gram-negative pathogens, leading to the passage of bacterial fragments like lipopolysaccharides (LPS) through the intestinal barrier. In the bloodstream, LPS acts as an endotoxin, triggering inflammation and intestinal permeability, which may contribute to obesity-induced chronic inflammation 81.

**5. Central Nervous system Regulation of Energy Homeostasis**

The hypothalamus, located beneath the thalamus at the base of the brain, is part of the limbic system and constitutes the ventral portion of the diencephalon in all vertebrates. It serves as a vital regulator of metabolic processes and acts as an intermediary between the nervous and endocrine systems. The hypothalamus contains receptors for circulating hormones, enabling it to receive signals from organs involved in energy balance 82. Additionally, it produces and releases neurohormones into the portal circulation, regulating the release of hormones from the anterior pituitary gland. The hypothalamus governs various functions, including body temperature, hunger, satiety, parenting behaviors, emotions like rage, short-term memory, thirst, fatigue, blood pressure, heart rate, gastrointestinal peristalsis, arousal, and circadian rhythms. While peripheral hormones need to cross the blood-brain barrier to reach the hypothalamus, it is connected to brain regions like the neurohypophysis and median eminence, where the barrier is not fully intact due to a fenestrated capillary endothelium, allowing large proteins to pass freely 83.

The hypothalamus connects with specific brain regions, known as circumventricular organs (CVO), which sample the blood's composition. These CVOs, including the subfornical organ and organum vasculum of the lamina terminalis, have neurons that interact with both blood and cerebrospinal fluid, with a rich vascular supply 84,85. These neurons have receptors for various circulating peptides and play crucial roles in regulating fluid balance and sodium appetite. Additionally, they project to other hypothalamic areas like the supraoptic nucleus (SON), paraventricular nucleus (PVN), and preoptic nucleus (PON). The hypothalamus, particularly the arcuate nucleus (ARC), is well-studied and essential in controlling feeding and energy expenditure86. The ARC, located near the median eminence, integrates peripheral hormonal and nutrient signals through its neurons, leading to coordinated responses. Within the ARC, there are two types of neurons: orexigenic (appetite-stimulating) neuropeptide Y (NPY) and agouti-related peptide (AgRP)-expressing neurons, and anorexigenic (appetite-suppressing) pro-opiomelanocortin (POMC)-expressing neurons 87,88. The hypothalamus' role in energy homeostasis and its communication with peripheral organs are significant areas of research for bariatric endocrinologists. Upon nutrient ingestion, POMC is cleaved to α-melanocyte-stimulating hormone (α-MSH), which activates melanocortin 3 and 4 receptors (MC3/4R) on downstream neurons, including those in the paraventricular nucleus (PVN) 89. This activation leads to a decrease in food intake and an increase in energy expenditure. The PVN, within the hypothalamus, has the highest expression of MC4R and is considered 90,91 to be the primary site for regulating energy intake within the central nervous system92,93. Studies in mice have demonstrated that disruption of MC4R, specifically in the PVN, results in obesity due to increased food intake, reduced energy expenditure, and impaired glucose homeostasis94.

**5.1 Extrahypothalamic neuronal circuits**

Hypothalamic nuclei interact with brain regions beyond the hypothalamus, such as the nucleus of the solitary tract (NTS), to control food intake and energy expenditure. They are also directly connected to the mesolimbic reward system, including the ventral tegmental area (VTA) and the nucleus accumbens (NAc), which influence the pleasurable aspects of food intake. When glucose levels decrease during fasting, neurons in the lateral hypothalamus (LH) that contain glutamate and orexin are activated and stimulate dopaminergic neurons in the VTA95.

In the melanocortin system, hormones like leptin and insulin released by adipocytes and pancreatic β-cells in the bloodstream cross the blood-brain barrier to bind to receptors on pro-opiomelanocortin (POMC) neurons in the hypothalamus. This promotes the production of α-melanocyte-stimulating hormone (α-MSH), which signals reduced energy intake during the "fed state96,97." Leptin also inhibits the secretion of neuropeptide Y (NPY) and agouti-related neuropeptide (AgRP) from AgRP/NPY neurons. However, in the "starved state," decreased circulating leptin, insulin, and the orexigenic hormone ghrelin increase the activity of AgRP/NPY neurons. Both POMC and AgRP/NPY neurons originate in the arcuate nucleus of the hypothalamus and send axons to the paraventricular nucleus (PVN). Cholinergic neurons from the dorsomedial hypothalamus (DMH) and excitatory glutamatergic signals from steroidogenic factor (SF-1)-expressing neurons in the ventromedial hypothalamus provide inhibitory and excitatory inputs, respectively, to hypothalamic POMC neurons in the melanocortin pathway that regulates feeding98. The discovery of leptin in 1994 provided evidence of a hormonal system that regulates body weight. Mutations in the obese gene (ob) lead to a lack of leptin production, causing severe obesity in ob/ob mice. Leptin-deficient infants also exhibit early-onset obesity after weaning. Leptin deficiency is associated with various endocrine, metabolic, and immunological disorders, including hypogonadotropic hypogonadism, hyperinsulinemia, and reduced T-cell function, highlighting leptin's regulatory role in different physiological processes 99-105. Interestingly, studies on leptin-deficient adults show a gradual improvement in their phenotype over time, suggesting possible compensation by other mechanisms, although the exact reasons for this phenomenon remain unknown106.

**6. Epigenetic modification and obesity**

Cells within an organism, despite having the same DNA, exhibit distinct functions and characteristics due to variations in gene expression. Proper control of gene expression is essential for cellular differentiation and development. The unique gene expression patterns observed in differentiated cells are established during development and are perpetuated through cell division. Besides genetic information, cells also inherit epigenetic information, which is not encoded in the DNA sequence. Epigenetics refers to the study of mitotically heritable changes in gene expression that are not caused by alterations in DNA sequence107 Epigenetic mechanisms, including cytosine methylation, post-translational modification of histone proteins, chromatin remodeling, and RNA-based processes, play a crucial role in permanently altering gene expression patterns and transmitting these changes to subsequent generations 108,109.

DNA methylation is a reversible chemical modification that occurs at the 5'-position of cytosine residues, resulting in the formation of 5-methylcytosine. Approximately 3% of cytosines in human DNA are methylated, and this methylation primarily occurs at sites where cytosine is followed by guanosine, known as CpGs. These methyl groups influence the hydrogen bonding in DNA and project into the major groove, altering the biophysical properties of the DNA molecule. This modification can inhibit the recognition of DNA by certain proteins while facilitating the binding of other proteins to the DNA. In general, DNA methylation is associated with gene repression. One significant feature of DNA methylation is its ability to be maintained through DNA replication and cell division (mitosis), leading to the inheritance of the repressed state in subsequent generations. This epigenetic modification plays a role in regulating gene expression patterns. The core histones, which are basic proteins with globular domains around which the DNA is wrapped in nucleosomes, also play a crucial role in epigenetic regulation. They possess flexible "tails" that protrude from the nucleosome and can undergo various post-translational modifications, including methylation, acetylation, and phosphorylation. These histone modifications further contribute to the regulation of gene expression and chromatin structure. Histone proteins have flexible tails that undergo various post-translational modifications. These modifications, along with nucleosome composition and arrangement, constitute an epigenetic layer of information that can either enhance or inhibit gene expression. Epigenetic mechanisms play a crucial role in regulating gene expression, impacting various stages of gene activity, from gene accessibility in the chromosomal landscape to transcription, RNA processing, and translation. Unlike the stable and uniform genome present in all cells of a vertebrate throughout their life, the epigenome varies between cells. It exhibits plasticity, changing over time and in response to environmental influences. The epigenome is particularly vulnerable during specific developmental stages, such as cleavage, perinatal period, and puberty. Changes in gene expression patterns occurring during these critical periods can persist for an extended duration, shaping the phenotype of the adult individual. These long-term alterations in gene expression offer a potential molecular basis for the hypothesis that exposure to environmental events during an individual's prenatal or postnatal development could contribute to the development of adult diseases110-115.

**6.1 Epigenetic modifications associated with obesity and their impact on the metabolic process**

Obesity is a complex disease involving excessive fat accumulation causing serious health risks. Till now genetics alone cannot explain the pandemic of global obesity. Obesity is caused by a complex interaction of susceptibility genes with multiple environmental factors such as stress, chemicals, pharmacological treatments, physical activity, or diet. At the molecular level, the epigenome is the flexible interface of gene-environment interactions. Epigenetics highlights the potential influence of mitochondrial metabolism on the formation or modification of epigenetic marks which occur at nuclear level116.

Epigenetics refers to heritable alterations in gene activity that do not involve changes. to the DNA sequence. Recent decades have led to the discovery of some important genes for monogenic obesity (including leptin, proopiomelanocortin POMC or melanocortin 4 receptor [MC4R]. The identification of these genes has underscored pathways to various metabolic diseases for the proper understanding of obesity. Although, for most individuals, a genetic predisposition to obesity has a polygenic basis117. In the context of obesity, DNA methylation is a well-studied epigenetic mark, especially in humans. One of the key components of the melanocortin system, which regulates food intake and energy balance, is POMC. DNA hypermethylation at the POMC variably methylated region in intron 2/exon 3 has been associated with weight gain in both children and adults. Additionally, altered DNA methylation in other regions of the POMC gene has been linked to specific metabolic profiles. Another imprinted gene called Insulin-like growth factor 2 (IGF2), responsible for growth and body composition regulation, is hypomethylated and correlated with increased body mass index (BMI). Furthermore, studies have shown that BMI is associated with altered DNA methylation patterns of other genes in the melanocortin pathway and obesity-related genes, such as leptin receptor (LEPR), leptin (LEP), adiponectin (ADIPOQ), and Insulin receptor substrate 1 (IRS1). DNA methylation patterns in circadian clock genes like CLOCK, BMAL1, and PER2 have also been linked to various metabolic syndromes and increased body fat118.

Various studies suggest the impact of gut microbial metabolites on the epigenome. Long-term dietary choices affect various function of the gut microbiota, which ultimately influences the bioavailability of dietary elements and cofactors of epigenetic reactions. Studies have also suggested that miRNAs play a prominent role in adipocyte differentiation which contribute to the pathogenesis of obesity. The first study which suggest a role for miRNA was in Drosophila in the regulation of fat cells, showing that miR-14 inhibits the metabolism of fat by targeting p38 and MAPK. After that, the role of miRNA in adipocyte biology has been explored in various cell lines, rodents, and humans. An array of miRNAs by different molecular mechanisms have been shown to potentially promote adipogenesis miR-143 acting via MAPK signalling5 pathway promotes human adipocyte differentiation, miR-17 promotes adipocyte differentiation by inhibiting Rb2/p130, miR-26b targets the phosphatase PTEN to enhance adipocyte differentiation, andmiR-21 regulates the adipogenesis derived from human adipose tissue through the modulation of TGF-β pathway in mesenchymal stem cells (MSC)119,120. DNA methylation reprogramming in PPARGC1A (the gene encoding PGC1a, a master regulator of mitochondrial biogenesis and function) has been observed in tissues from obese patients, which suggests that epigenetic regulation of mitochondrial function may play a role in the obesity pathophysiology. Also, a high-fat diet affects the mitochondrial pathways that generate acetyl-CoA, which may change the cellular levels of histone acetylation hence affect in gene expression. Epigenetic research has become increasingly important in recent years for gaining a deeper understanding of the sharp rise in obesity prevalence worldwide. According to the available data, environmental exposures cause changes to the epigenome that pass down the risk of obesity from one generation to the next. It is quite unlikely that the recent drastic changes to our genes have made the entire world's population more susceptible to obesity. The fast-rising obesity rates may be explained by the mounting evidence that diet and lifestyle choices influence the epigenetic inheritance of disease risk. Epigenetics of obesity is a growing field of study today121-125.

**7. Neurotransmitters and obesity**

**7.1 Role of neurotransmitters in appetite regulation and reward pathways**

Neurotransmitter disorder is a broad term encompassing neurometabolic disturbances affecting neurotransmitter synthesis, transport, or breakdown. These conditions include rare inherited neurological disorders (e.g., tyrosine hydroxylase deficiency), as well as more common conditions like Parkinson's, Alzheimer's, and depression. Neurotransmitter pathways affected include amino acids (GABA, glycine, glutamate), monoamines (dopamine, serotonin, noradrenaline, adrenaline), purines (adenosine), and cholinergic systems (acetylcholine and nicotine). Neuropeptides and ion channels involved in neurotransmission mechanisms can also contribute to neurological disorders. Obesity is associated with changes in neurotransmitters and neuropeptides that regulate food intake and energy expenditure. It is uncertain whether these alterations are a cause or consequence of weight gain. Iatrogenic medications targeting neurotransmission, such as certain antipsychotics, antidepressants, and antihistamines, can lead to weight gain, suggesting that changes in neurotransmission may precede obesity. Anti-obesity drugs often act on neurotransmitter metabolism, acting as monoamine reuptake inhibitors, nicotinic antagonists, opioid antagonists, 5-HT receptor agonists, TAAR1 agonists, or monoamine-releasing agents, and have shown efficacy in weight loss. Metabolic surgeries, the most effective weight loss treatments, may also impact neurotransmitter metabolism. In this mini-review, we explore the intriguing concept of obesity as a disorder of neurotransmission126-129. Multiple neurotransmitters, including dopamine (DA), cannabinoids, opioids, and serotonin, along with neuropeptides like orexin, leptin, and ghrelin, play crucial roles in the rewarding effects of food and the homeostatic regulation of food intake. Among them, dopamine has been extensively studied and is well-understood. It acts as a key neurotransmitter in modulating natural and drug rewards, primarily through its projections from the ventral tegmental area (VTA) into the nucleus accumbens (NAc)130. Other dopamine pathways in regions like the dorsal striatum, cortical areas (OFC and ACC), limbic regions (hippocampus and amygdala), and the lateral hypothalamus are also involved. Interestingly, in humans, the ingestion of pleasurable food releases dopamine in the dorsal striatum in proportion to the perceived pleasure from eating the food. However, dopamine's role in reward is not simply about encoding pleasure. Initially, upon exposure to a food reward, dopamine neuron firing in the VTA increases, leading to dopamine release in the NAc. But with repeated exposure to the reward, the dopamine response habituates, shifting the focus onto the stimuli associated with the reward (e.g., the smell of food), which becomes a cue conditioned to the reward. The dopamine signal now conveys a 'reward prediction error' in response. Dopamine and serotonin are vital for hedonic and homeostatic signalling, respectively, but other neurotransmitters also play important roles131-135. Research in rodents and humans has shown that manipulating dopaminergic and serotonergic signalling leads to changes in feeding behavior, motivation to eat, reward learning related to food, and energy expenditure114-116. Based on these findings and others, it is hypothesized that disrupted feeding behavior in obesity may result from alterations in central dopamine and serotonin systems136,137.

**7.2 Serotonin signalling in the homeostatic circuitry**

In cases where the body's energy stores are sufficient, the failure to adequately suppress food intake leads to excessive consumption of food beyond nutritional needs, resulting in weight gain. Reduced serotonin signalling in the homeostatic circuit has been proposed to contribute to this pathological condition. Serotonin's role in obesity development has been extensively studied over the years, involving multiple neurotransmitters and brain regions in the functional circuit. The primary brain regions responsible for the homeostatic regulation of food intake are the hypothalamus and brainstem. These regions integrate central and peripheral inputs related to hunger, satiety, and whole-body nutrient availability to appropriately adjust subsequent feeding behavior based on the current nutritional state. Within these regions, several nuclei play crucial roles in regulating food intake, including the raphe nuclei, nucleus tractus solitaries (NTS), parabrachial nucleus (PBN) in the brainstem, and the arcuate nucleus (ARC), paraventricular nucleus (PVN), ventral medial nucleus (VMN), dorsomedial nucleus (DMN), and lateral hypothalamic area (LHA) in the hypothalamus138-144.

**8. Emerging drug targets for obesity treatment**

**8.1 Overview of current pharmacological approaches for obesity management**

Medical weight control is still an effective method for treating obesity, and recent developments have fundamentally changed how we currently treat and, more significantly, how we will treat obesity shortly. All anti-obesity drugs improve weight and metabolic parameters, although the effects and efficacy vary depending on the medication. Obesity treatment guidelines affirm that a multidisciplinary approach to weight management is the ideal strategy for actions, involving medication, behavioral therapy, and/or bariatric surgery 145-146.

**8.2 FDA-approved medications for monogenic syndromes of obesity**

**a. Setmelanotide**

In 2020, the FDA approved the melanocortin-4 (MC4) receptor agonist setmelanotide as a subcutaneous injectable formulation for the treatment of chronic obesity in patients aged 6 and older with a genetically confirmed deficiency in proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR). By reducing calorie intake and raising energy expenditure in animal models, setmelanotide restores the function of the MC4 receptor system, hence reducing hunger and encouraging body weight loss. Injection site reactions and hyperpigmentation problems (100 percent in POMC deficiencies and 45 percent in LEPR deficiency) were the most frequent adverse effects of Setmelanotide. A 7.6% decrease in overall body weight was seen after one year in patients with Bardet-Biedl or Alstrom Syndrome147-149.

**b. Metreleptin**

As a replacement medication for leptin deficiency in individuals with congenital or acquired lipodystrophy and related co-morbidities, metreleptin is a leptin analog that the FDA approved in 2014. For patients with a baseline weight of less than 40 kg, the dose is 0.06 mg/kg/day with a maximum of 0.13 mg/kg/day; for patients with a baseline weight of more than 40 kg, the dose is 2.5 mg (for males) or 5 mg (for females) once daily with a maximum of 10 mg/day. It is administered as a subcutaneous injection once daily. The development of antibodies against metreleptin was reported, but the consequences are not well understood due to the small number.

**8.3 FDA-approved medications for non-syndromic obesity**

**a. (Orlistat (Xenical, Alli)**

Orlistat primarily inhibits pancreatic and gastric lipases, which reduces the absorption of dietary fat. In 1-year research, the waist circumference (WC) was reduced by 9.6 cm with orlistat and by 7.0 cm in the placebo group as compared to baseline (p 0.01). When compared to baseline, the orlistat and placebo groups' WC decreased by 6.4 cm and 4.4 cm, respectively, at 4 years. In the primary orlistat trials, gastrointestinal (GI) symptoms such as abdominal pain, fecal urgency, steatorrhea, and fecal incontinence were seen in more than 10% of the population150..

**b. Phentermine/Topiramate (Qsymia)**

Topiramate and phentermine are both approved for the long-term treatment of obesity. It has been established that topiramate, a gamma-aminobutyric acid agonist, glutamate antagonist, and carbonic anhydrase inhibitor, reduces appetite. At 56 weeks in a trial, mean WC reductions were 5.6 (9.8%) for the low-dosage group, 10.9 (10.3%) for the high-dose group, and 3.1 (10.3%) for the placebo group (p 0.0001). These differences between the high-dose group and placebo, as well as between the two doses, were statistically significant. Increased heart rate, issues with mood and sleep, memory loss, paraesthesia, diarrhea, and dry mouth are a few instances of adverse events151.

**c. Naltrexone/bupropion (Contrave/Mysimba)**

Bupropion, an antidepressant, norepinephrine, and dopamine reuptake inhibitors that directly stimulate POMC cells, and  Naltrexone, an opioid receptor antagonist that blocks the POMC pathway, both act together to stimulate POMC peptide production, which in turn reduces appetite. Additionally, the Naltrexone/Bupropion (NB) combination affects reward circuits, suggesting improved self-control and internal fullness signals. Constipation, dry mouth, and gastrointestinal (GI) symptoms have all been documented as adverse events in the major trials.

**d. Glucagon-like peptide receptor (GLP1-R)** agonists, Liraglutide and Semaglutide, act peripherally on the gastrointestinal tract, boosting insulin secretion and the pancreas, slowing intestinal motility and delaying gastric emptying.

* **Liraglutide (Saxenda)**

At 56 weeks of the Obesity and Pre-Diabetes Trial, the mean WC decrease was 8.2 (7.3) cm in the liraglutide arm and 3.9 (6.6) cm in the placebo arm (p 0.001). At 160 weeks in the Extension research mean WC reductions of 6.9 (8.3) cm and 3.4 (7.5) cm, respectively, were attained compared to baseline in the liraglutide 3 mg and placebo groups (n = 738) (p 0.0001). Increased heart rate, gastrointestinal problems such as constipation and diarrhea, and infections like nasopharyngitis are among some of the adverse effects.

* **Semaglutide (Wegovy)**

At 68 weeks, the STEP 1 trial revealed that the intervention group's mean waist circumference had decreased by 13.5 cm while the control group's had decreased by 4.1 cm (p 0.001). More than 10% of the population in the major studies experienced adverse effects such as GI symptoms, infections such as upper respiratory tract infections, urinary tract infections etc152-156.

**8.4 Medication under consideration for FDA-Approval**

**a. Tirzepatide**

Tirzepatide is a centrally acting gastric inhibitory polypeptide (GIP)/GLP-1 dual agonist that decreases food intake and may also enhance energy expenditure by desensitizing the GIP receptor through persistent GIP agonism. It was approved in 2022 to treat type 2 diabetes. Patients with DM were randomized to receive tirzepatide at dosages of 5, 10, and 15 mg or semaglutide 1 mg in a 40-week phase 3 trial. In terms of lowering HbA1c, tirzepatide was superior to semaglutide at all doses. Weight loss was 6.7% with semaglutide compared to 8.5, 11.0, and 13.0% with each dose of tirzepatide. It is now being studied in a number of phase 3 trials in obese patients (n = 210–900 participants). It may be associated with less gastro-intestinal side effects compared to GLP-1 agonists157.

**8.5 Medications in phase 3 trials**

**a. Methylphenidate**

An approved stimulant for the treatment of attention deficit hyperactivity disorder (ADHD) is methylphenidate. It is a dopamine reuptake inhibitor that is recommended to reduce caloric consumption. The most frequent adverse effects include tachycardia, upper abdomen pain, sleeplessness, and headache.

**b. Exenatide**

Exenatide, a GLP1-RA, was investigated for the treatment of obese patients with diabetes. Exenatide (n = 73) and placebo (n = 79) were compared in a 24-week RCT among patients with a mean baseline weight range of 107-109 kg, along with lifestyle improvement as a cointervention for both arms. With the medicine, a substantial difference in total body weight loss was seen.

**c. Cagrilintide**

An analog of amylin called cagrilintide improves central satiety signals while decreasing peripheral stomach emptying. It is now being researched for phase 3 trial in combination with semaglutide compared to placebo in patients with obesity and DM (n = 1200) for total body weight loss. Various other molecules are being tested for their potential use in reducing overall weight including leptin sensitizer, PPAR gamma modulator AMG,208,209 210 MBL949,211 NO-13065,212 NNC0247-0829,213 LY3841136214 and BMS-986172. The difficulty of predicting a patient's response to medications, along with the broad variation in how each person's weight changes in response to a particular treatment, is one of the biggest obstacles to effective weight management. According to these data, in the next few years, new pharmacotherapies will revolutionize how we manage obesity and its comorbidities, including cardio-renal disease and metabolic disease158-162.

**8.6 Recent research on novel drug targets and therapeutic strategies**

An unprecedented hunt for new anti-obesity medications has been sparked by the growing obesity problem. Recently found targets include both central and periphery. The pharmaceutical business is currently utilizing several mechanisms to decrease body weight like lower food intake, preventing lipid absorption from the stomach, increasing energy expenditure, and mobilize fat stores, and preventing lipogenesis. Sites of action for novel anti-obesity drugs, therefore, include the brain, the gastro intestinal system, adipose tissue, the liver and skeletal muscle.

**a. Hypothalamic mechanisms and targets in research**

1. In obese mice fed a high-fat diet, the cannabinoid (CB 1 receptor antagonist rimonabant lowers body weight, adiposity, and insulin resistance. A 12-month Phase III trial in obese dyslipidaemias demonstrated clinically significant weight loss (>5%) that was maintained for a year, as well as changes in obesity-related risk variables like plasma lipid profiles and glycaemic control. Therefore, preliminary results in humans don't show that this medication will significantly outperform currently available options in terms of efficacy163.
2. **5-HT** is well known for playing a significant part in the brain's control of appetite. Studies demonstrating that food intake is decreased in rats after central administration of antisense to 5-HT6 receptors have also linked 5-HT6 receptors to obesity. Furthermore, 5HT6 knockout mice are resistant to gaining weight on a high-fat diet, and the selective 5-HT6 receptor antagonist BVT 5182C has been reported to reduce body weight in obese mice.
3. **Histamine** and H3 receptors on presynaptic terminals mostly function as auto receptors. Selective H3 receptor antagonists, such as A-331440, have potential use in the treatment of obesity since they lower body weight and body fat in diet-induced obese mice. Interestingly, results from H3 receptor deletion mice demonstrate an obese phenotype characterized by hyperinsulinemia and hyperleptinemia, in contrast to those obtained with selective ligands164-168.
4. **Melanin-concentrating hormone** (MCH) given centrally to animals causes obesity. Conversely, mice that overexpress MCH are moderately fat with increased food intake, whereas MCH knockout mice are lean, hyperphagic, and hypermetabolic. Pre-clinical investigations have demonstrated that MCH-1 receptor antagonists are effective anti-obesity medications because they cause long-lasting reductions in food intake and body weight.
5. **Melanocortins, including adrenocorticotrophin** and alpha, beta, and gamma-melanocyte-stimulating hormones (MSH), originate from the common precursor pro-opiomelanocortin (POMC) and interact with a group of receptors, MC1–5. Research using genetic mouse models, knockout mice, and feeding studies with MC3/ agonists and antagonists has provided evidence that MC4 receptor agonists not only have the potential to decrease weight but also show beneficial effects on hyperinsulinemia. A recent discovery is PGE-657022, a high-affinity MC4 receptor agonist, which has shown promising results in reducing food intake, body weight, and fat mass in obese rodents.
6. **Adipose tissue** secretes the peptide hormone **leptin.** It generally travels to the hypothalamus, where it starts lipolysis and decreases appetite. Two groups of substances have recently been found to be able to bypass the leptin transporter system and easily diffuse into the brain.  One of these compounds has been reported to produce a significant 10% reduction in body weight in dietary-induced obese rats within three weeks, as well as a 20% reduction in their food intake. Leptin transport into the brain becomes saturated when present at high levels in plasma, blunting its effects169-173.
7. **Fatty acid synthase** (FAS) inhibition is another effective strategy for the management of obesity. C75, a FAS inhibitor, was identified which reduces body weight in rodents by a central action that reduces appetite and increases energy expenditure.
8. The anti-obesity potential of drugs that decrease gastric peptide **ghrelin** or inhibit its function is a matter of debate. In laboratory animals’ exogenous ghrelin has been reported to increase food intake, adiposity and fat utilization, which is present in the hypothalamus. The potential use of ghrelin inhibitors for weight-loss is, under study174.

**b. Peripheral mechanisms and targets in research**

1. It is well known that thyroid hormones cause weight reduction by increasing metabolic rate, however, implementing them is linked to cardio-stimulation and protein loss. A specific b-subtype agonist, KB-141, has been developed recently and has been shown to significantly lower plasma cholesterol in a variety of species and body weight in cynomolgus monkeys by up to 7% in just one week.
2. Key regulators of adaptive thermogenesis in brown fat and skeletal muscle include the peroxisome proliferators-activated receptor gamma-coactivator 1-alpha (PGC-1-alpha) and its related peroxisome proliferator-activated receptor. Investigating and using this regulatory pathway in search of brand-new anti-obesity medications is of great interest due to the activation of its components175.
3. Studies have shown that when Acetyl-coenzymeA carboxylase (ACC) is knocked out in mice (ACC2 knockout mice), it leads to reduced body weight and less fat accumulation, rather than increased food intake. Additionally, administering a proteolytic cleavage product of the adipocyte complement-related protein (Acrp30) called Famoxin to mice resulted in increased fatty-acid oxidation and induced weight loss.
4. Inhibition of triglyceride synthesis is a significant focus for peripheral anti-obesity drugs. Diacylglycerol acyltransferase (DGAT) plays a crucial role in the final step of triglyceride synthesis. Knocking out this gene in mice leads to resistance to diet-induced obesity. To compensate for the reduced ability to store fat, these mice increase their energy expenditure.
5. Protein tyrosine phosphatase-1B (PTP-1B) knockout mice have improved insulin sensitivity and they are resistant to becoming obese on high-fat diets. Consequently, inhibitors of this enzyme have beneficial effects in the treatment of obesity. An antisense nucleotide (ISIS 113715) is claimed to selectively block PTP-1B gene expression and shows relevant activity in rodents and monkeys. But currently, at this point, none of the novel strategies examined in Phase II or Phase III clinical trials has demonstrated indications of providing much more efficacy than orlistat, phentermine, or sibutramine. There is always a chance that these new medications, particularly the CB1 receptor antagonist rimonabant, will be less harmful or tolerated better than current medications. As a result, the experimental data being produced for some of the newer molecular targets, such as MCH1 antagonists and MC4 agonists, suggests that they may cause significantly more weight loss in the clinic than current medications and be effective against co-morbid conditions related to obesity. Additionally, some of the newly discovered peripheral targets may open up the possibility of combining therapies to treat obesity176.

**c. Discussion of promising preclinical and clinical studies**

An in-depth comprehension of the mechanisms underlying this complicated condition is required to develop a multifaceted strategy to combat the worldwide obesity epidemic. These experimental models mimic certain aspects of the human condition and its root causes, particularly the over-consumption of calories and unbalanced diets. Obesity in rats is caused by intricate gene-environment interactions, much like it is in humans. The fight against obesity, which is likely to last for decades to come, relies heavily on preclinical animal models as a research tool. The models that are currently accessible are either genetic, such as spontaneous mutants or transgenic lines, or dietary, with the latter being the result of the same gene-environment interactions that are at the root of the majority of cases of human obesity. Progress has been made with the development of polygenic diet-induced obesity (DIO) models, but more work is required to better mimic human behaviors177-182

* **Traditional genetic models of obesity**

The entire energy balance is influenced by several genes and metabolic pathways, making human obesity a complicated genetic trait. Monogenic mouse model research has led to the greatest improvements in our mechanistic understanding of appetite and energy balance. Over 200 mouse models of monogenic obesity are available. Some of these developed naturally (for instance, the ob/ob mouse), whereas others were created through genetic engineering, including the tyrosine receptor kinase B (TrkB, also known as tropomyosin receptor kinase B) knock-in mouse, the FTO (fat mass and obesity-associated protein) overexpression mouse, and the melanocortin receptor 4 (MC4R) knock out mouse. The ob/ob mouse is the most significant obesity model. The identification of leptin and the subsequent identification of the mutant leptin receptors in the db/db mouse emphasized hypothalamic regions that are involved in integrating and controlling energy balance signals. The melanocortin receptor 4 (MC4R) gene is mainly expressed in the PVN and, unlike in Npy- or Agrp-null mice, transgenic knockout of this gene results in an obese phenotype in mice. In obese individuals in support of a role for this gene in human obesity, MC4R mutations are relatively common 183.

* **Models of DIO**

The time frames for the development of DIO more closely resemble the gradual weight gain that occurs in the majority of the human population as a result of a marginally positive energy balance over several years when compared to monogenic models. In rodent models of DIO, animals are switched from a diet with a relatively low energy density that is high in complex carbohydrates and fiber and low in fat to one with a higher energy density that is high in fat and sugar. A significant disadvantage of data obtained from DIO models can be inconsistent. Additionally, although many diets resemble (Western) diets in terms of composition, animals are typically fed ad libitum throughout the cycle of day and night, frequently for periods of many weeks, and monotonously.

* **Cafeteria diets**

Cafeteria diets serve as relevant models of modern human obesogenic diets, providing rodents with a mix of sweet and savory high-fat and/or high-sugar solid foods similar to what humans consume. These diets lead to an increase in body fat mass in all tested groups. Exposure to high-fat or high-sugar diets during the perinatal period causes the offspring to have higher fat intake after weaning, even in choice conditions. The manipulation of these diets also impacts the expression of genes in the mesolimbic reward system, as demonstrated in a study on male Wistar rats. In this study, rats were fed a cafeteria diet consisting of sweet and savory human foods for an extended period (18-23) hours daily over 40 days) developed obesity, accompanied by compulsive-like feeding behavior and a decrease in striatal D2 dopamine receptors.

* **Fat or sugar choice diets**

Given the significant resource input and diversity of the foods consumed, cafeteria diets are only seldom useful for routine high- or semi-high-throughput screening of potential therapeutics. Compared to animals fed a no-choice pre-mix of fat, sugar, and chow, which merely temporarily increased binging, animals were consistently hyperphagic and developed obesity. The free-choice group's increased calorie intake was the result of eating more meals because they drank sugary drinks rather than changing the quantity of their meals. This obesity paradigm has the appeal of encouraging excessive calorie consumption while satisfying appetite on a healthy diet184-185.

* **Meal feeding**

For the generic approach of screening pharmacological compounds or bioactive, ad libitum, free access to a single HF diet would be useful but it does not easily relate to human diet and behavior, any more than it does to that of rodents in their natural environment. The study applied variants of a feeding-plus-exercise regime and reported that a feeding time of 2 h before 2 h of exercise for each meal gave the greatest attenuation of HF-diet-induced weight gain.

* **Binge-type feeding**

It is effectively an extreme for the majority of meal feeding in preclinical animal models. Rats that had access for 2 h to the 60% HF diet consumed 60% of their daily calories from this source, leading to increased fat mass. The ability of mice (C57BL/6) to engage in binge-like eating on HF pellet diets was considerably more prominent than it was in rats. These mice consumed 86%of their daily calories during the 2 h scheduled access period, but in this case without increased body fat.

* **Modulation of genetic models- new approaches**

As was previously mentioned, transgenic knockout animals have helped identify some of the genes involved in the brain control of energy balance (for example, MC4R). Recent advances in optogenetic and chemo genetic mouse models, coupled with imaging methods, are creating the prospect of understanding and deciphering the complex wiring of the brain and relating this to behavior.

* **Optogenetics and chemo genetics**

The significant advancement brought about by optogenetics is its ability to activate or inhibit a small group of neurons using light in mouse models. This method offers precise and targeted cell activation with millisecond timescales, even in freely moving animals without satiety. This breakthrough allows researchers to investigate the specific role of neurons or neuronal subsets in feeding behavior, revolutionizing the use of animal models in obesity research. Chemo genetics, on the other hand, involves introducing an engineered gene into specific cell types in mice to achieve targeted expression. This engineered gene can be a modified G-protein-coupled receptor or an ion channel. Both optogenetic and chemo genetic activation induces strong food-seeking behavior and prompt food consumption within minutes. Consequently, these studies can uncover the intricate functional aspects within a single neuronal cell type186.

* **Activating feeding circuits with electromagnetic wave**

The use of electromagnetic radiation (radio waves or magnetic fields) to either activate or inhibit ion channels to regulate eating and glucose sensing in the mouse hypothalamus is an intriguing new finding. The identification of therapeutic targets and effective pharmacological agents, as well as the creation and characterization of nutritional therapies, could all be influenced by preclinical research into obesity. Preclinical research in obesity should focus on developing more accurate models of feeding and obesity, analyzing feeding behavior more thoroughly, and using molecular and genetic tools to better understand these intricate mechanisms, how they are connected, and how they can be used therapeutically187-189.

**9. Conclusion**

This comprehensive book chapter delves into the multifaceted nature of obesity, providing a detailed exploration of its pathogenesis and emerging drug targets. The chapter begins by offering a brief overview of obesity's prevalence and its consequential health implications. It then meticulously examines the intricate interplay between genetic and environmental factors, emphasizing the role of genetic predisposition and the influence of environmental elements such as diet, sedentary lifestyle, and socioeconomic factors. Moving forward, the chapter sheds light on the remarkable characteristics of adipose tissue, highlighting its role as an endocrine organ and investigating the intricate relationship between adipose tissue inflammation and metabolic dysfunction commonly associated with obesity. The impact of gut microbiota on metabolism is thoroughly investigated, presenting an insightful overview of gut dysbiosis and its association with obesity. The chapter delves into potential mechanisms that link gut microbiota to weight regulation, shedding light on the intriguing interplay between the microbiome and obesity. Shifting the focus to the central nervous system, an overview of the hypothalamus and its pivotal role in appetite regulation is provided, with a specific emphasis on the leptin-melanocortin pathway and its implications in obesity pathogenesis. Moreover, the chapter explores the significant influence of epigenetic modifications associated with obesity on metabolic processes. It also delves into the role of neurotransmitters, such as dopamine and serotonin, in appetite regulation and reward pathways. In its final section, the chapter centers on emerging drug targets for obesity treatment. It offers an extensive overview of current pharmacological approaches, while also discussing recent research on novel drug targets and therapeutic strategies, thereby providing valuable insights for future advancements in the field.

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