

# EXFOLIATING THE PETALS OF OBESITY PATHOLOGY: FROM PATHOGENESIS TO EMERGING DRUG TARGETS

## Abstract

This is a comprehensive book chapter that delves into the multifaceted aspects of obesity, exploring its pathogenesis and emerging drug targets. A detail outline of the prevalence and health ramifications of obesity sets a stage for the subsequent discussions. Genetic and other factors in obesity are examined in detail, emphasizing the role of genetic predisposition and the impact of environmental factors such as diet, immobile lifestyle, and socioeconomic influences. The chapter then shifts focus to the fat 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 gives an overview of current pharmacological approaches and

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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)<sup>1</sup>. Depending on body fat distribution, 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 femoro gluteal region. This distribution varies among genders and races, often being mixed during infancy and significantly impacting one's quality of life<sup>2</sup>. Body mass index is calculated by weight (kilograms) divided by the square of height (centimetres). A BMI of 18.5 to 24.9 is considered normal, less than 18.5 is considered underweight, and with 25 and above are categorized as obese<sup>3</sup>. 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 susceptibility<sup>4</sup> and lifestyle choices that promote excessive calorie intake and insufficient physical activity. This complex issue involves various factors, such as the environmental, behavioural, and socioeconomic factors of a person with distinct physiological vulnerability. Research has demonstrated that genetic factors play a significant role in determining 30–80% of the variation in weight<sup>5, 6</sup>. Since 1975 overall rate of obesity has increased by three folds, according to the WHO, and, 39% of the adult population was overweight in 2016, with 13% obese<sup>5</sup>. By 2025, the percentages will have risen to 18% and 21%, respectively<sup>7</sup>. In 2014 the worldwide rate of obesity was 10.8% and 14.9% in men and women respectively, and may rise further. Obesity affects nearly four out of every ten US adults, a figure that has remarkably increased since 2000 and is significantly higher than the Healthy People 2020 with 30.5%<sup>8</sup>. It leads to a wide range of health problems and morbidities. Obesity increases the risks of sleep apnea, insulin resistance, dyslipidemia, gallbladder disease, and non-insulin-dependent diabetes mellitus (relative risk >3)<sup>10</sup>. There is a moderate increase in the risk for coronary heart disease, hypertension, osteoarthritis, and hyperuricemia<sup>11</sup>. There is a slightly elevated risk of breast, colon, and endometrial cancer, as well as the risk of increased anaesthetic complications, impaired fertility, and polycystic ovary syndrome, is slightly elevated (relative risk 1–2)<sup>12</sup>.

Numerous studies indicate that various work-related stress such long duration of work hours, high work demands, and low job control, along with effort-reward imbalance and less social support, are related to chronic disease such as depression<sup>13, 14</sup> high blood pressure<sup>15-17</sup> and heart diseases<sup>18-20</sup> among the general working population. Thee stress have also been related to heart disease risk factors like less physical activity, stress eating, and obesity<sup>21-23</sup>. A model was put forth to explain how occupational factors, like shift work, sedentary lifestyle, and stress in a job, could increase the epidemic of obesity in the individual, going beyond the influence of age, food, and health culture in the U.S. It suggests that work-related factors offer an essential intervention factor for prevention<sup>24</sup>. Obesity is comparatively less common 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. Higher obesity rates are observed in women than men, but men may have higher overweight rates<sup>25</sup>. In the United States and Germany, the rate of obesity is approximately 60% and is increasing. The highest rate is reported in the countries of the former Soviet Union at about 75%. Samoa's obesity prevalence is around 60–80%. In China, roughly 30% of men are obese, whereas 40% of women are of more weight. The lowest obesity rates in

Europe are found in Sweden (9.1% in women and 1% in men) and The Netherlands (8% in men and women). The occurrence of obesity in the United Kingdom doubled from 8% to 16% between 1980 and 1995 (WHO Geneva)<sup>26</sup>.

## II. GENETIC AND ENVIRONMENTAL FACTORS IN OBESITY

People with obesity are more likely to have multiple genes which predispose them to become overweight. The fat mass and obesity associated gene (FTO), that is found in up to 43% of the whole population, is one such gene. Individuals carrying this FTO gene may face challenges in regulating their intake of calorie when faced with easily accessible food. Obesity results from a number of environmental factors and innate biological elements. Notably, the significant variation between individuals in weight of the body, which measures their response to the "obesogenic" condition, is strongly influenced by genetics. Twin, family, and adoption research studies have estimated obesity heritability to range from 40% to 70%<sup>27</sup>. Therefore, genetic approaches offer valuable insights into understanding the physiological and genetic mechanisms which measure 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 more expressed in the brain and central nervous system have a central involvement in obesity<sup>28</sup>. 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 content with their patients. Conversely, certain medical providers also attribute obesity to factors within an individual's control, like willpower, dietary choices<sup>29</sup>. Globalization and economic shifts in the last decade have resulted in reduced costs and increased fast food consumption and a decrease 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 neighborhoods have approximately 30% fewer supermarkets<sup>30</sup>. Higher socio-economic status is related with a higher likelihood of obesity in developing countries. In developed countries, however, there is an inverse relationship between body mass index and socioeconomic status. The capability to afford food, cultural values, and less physical labour may favour overweight in developing countries, whereas developed countries can afford more calorie rich food and prefer high energy exercise<sup>31</sup>.

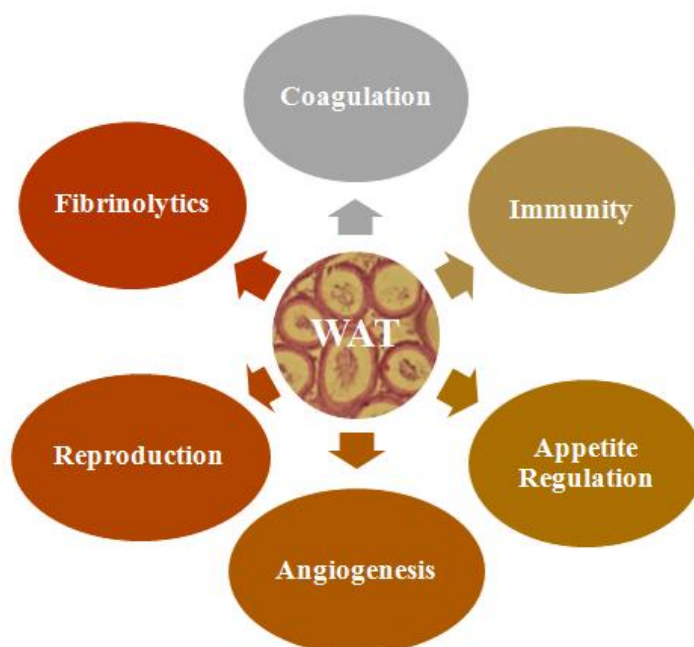
Various factors, including sedentary lifestyles, level of physical activity, sleep, and stress, are all indirectly linked to obesity. The US Department of Health and Human Services suggests engaging in at least 150 to 250 minutes of exercise to prevent overweight. Less physical activity in children has 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<sup>32</sup>. Obesity is linked with a significant increase in morbidity. It is linked to numerous co-morbidities and is considered a risk factor. The psychological effects of overweight perpetuate a vicious cycle. Obesity is more common in people who suffer from depression and binge eating<sup>33</sup>. Patients who are obese may face social stigma which may harm their quality of life. This begins at a very young age and can continue into adulthood. According to report, this has hiked by 66%

in the last decade. Therefore, obesity is caused not only by an imbalance in calorie intake and expenditure, but also by various other environmental, psychosocial and genetic factors<sup>34</sup>

### III. ADIPOSE TISSUE AND OBESITY

**1. Adipose Tissue as an Endocrine Organ:** The biological functions of adipose tissue have drawn much attention recently than they formerly did when it was just seen as an organ for storing triacylglycerol. Over the several last decades there has been a significant collection of experimental data about the biology and biochemistry of adipose tissue that it is no longer regarded to be a fat-storing inert tissue<sup>[35]</sup>. The primary site for additional energy storage is adipose tissue, which also functions as an endocrine organ capable of synthesizing a variety of substance with biological activity that control metabolic balance. Along with adipocytes, this dynamic tissue also has various cell types known as the stroma vascular fraction, comprises of blood cells, endothelial cells, pericytes, and adipose precursor cells<sup>36,37</sup>.

Brown and white adipose tissue are the two forms of adipose tissue in mammals. In adults, brown adipose tissue, which is highly specialized in thermo genesis, is nearly absent, yet it is present at birth. Adipocytes in the brown adipose tissue are smaller than those in white one. They comprise of numerous cytoplasmic lipid droplets of different sizes, an enormous cytoplasm, and several mitochondria which oxidize fatty acids to release heat. Similarly, it reserves energy in the lipid form, but it generates heat more frequently by oxidation of fatty acids inside the adipocyte than by distributing free fatty acids to other types of cell<sup>38,39</sup>.



**Figure 1:** The most important 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 factor, enzymes, cytokines, complement factors, and matrix proteins, it has pleiotropic properties. The majority of these variables, including those regulating food intake, energy expenditure, metabolic homeostasis, and immunity are expressed by adipose tissue also<sup>40,41</sup>. Adipose tissue dynamically regulates the function of cells by a complicated series of endocrine, paracrine, and autocrine signals which affects numerous tissues, like hypothalamus, skeletal muscle, pancreas, endothelium, liver, kidneys, and the immune system. Signals of endocrine travel by the circulatory system which travel to all parts of the body. Because of its secretory qualities, white adipose tissue is now considered to be a very active endocrine tissue<sup>42</sup>. Leptin is expressed mainly by the adipose tissue, but its low levels are found in the gastric, mammary epithelium skeletal muscle 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, cold exposure, thyroid hormone and thiazolidinediones<sup>43,44</sup>. Leptin levels are more in women than in men, because androgens cause inhibition, oestrogen leads to stimulation, and there is more subcutaneous fat in women<sup>45</sup>. Adipose tissue is the only place where adiponectin is secreted. There is a strong negative connection between plasma adiponectin quantity in humans and fat content, except for severe undernutrition and in newborns. Visceral adipose tissue increases the chance of developing some illnesses, including various metabolic syndromes. The variation in risk of disease may result from variations in endocrine activity among adipose tissue depots. Each adipose tissue depot's anatomic location has an impact on function of endocrine system. While endocrine hormones originating from SC adipose tissue are secreted into systemic circulation, those from visceral adipose tissue are released into the portal system which have direct access to the liver<sup>46</sup>. 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. 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 which are expressed in adipose tissue are novel, and a significant portion (20–30%) of these genes may code for secreted proteins<sup>47</sup>. Continual identification and characterization of these genes are expected to provide deeper insights into the endocrine function of adipose tissue and its connection to energy homeostasis and physiological systems. More research is needed to confirm the specific contributions of individual cellular components within adipose tissue.

- 2. Inflammation in Adipose Tissue and its role in Obesity Related Metabolic Dysfunction:** Obesity is related with increased adipose mass and a chronic 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, plasminogen activator inhibitor-1, colony-stimulating factor, and inducible nitric oxide synthase. 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 obesity<sup>48,49</sup>. Obesity leads to reduced secretion of the anti-inflammatory hormone adiponectin, which normally has beneficial effects on macrophages, while the production leptin is increased. Other factor which contributes to the inflammatory response is the elevated levels of free fatty acids which are released from large adipose tissue. Recent findings suggest that saturated fatty acids can activate the NF- $\kappa$ B pathway in macrophages through TLR-4, leading to the production of inflammatory cytokines<sup>50</sup>. Adipose tissue produces many bioactive substances, including resistin, glucocorticoids, adiponectin, leptin, angiotensin, visfatin, sex steroids, tumor necrosis factor, interleukin-6, acylation stimulating protein and free fatty acids. In obese adipose tissue, there is an imbalance in the production of pro as well as anti-inflammatory adipocytokines, which can cause development of metabolic syndrome<sup>51</sup>. The over-secretion of harmful adipocytokines, such as PAI-1, TNF- $\alpha$ , or visfatin, coupled with the under-secretion of potentially beneficial adipocytokines like adiponectin, are likely significant mechanisms involved in various metabolic syndromes<sup>52,53</sup>.

Obesity is the state of systemic, chronic inflammation. Recent studies have revealed that obesity affects adipokine secretion as well as resistance to insulin<sup>54</sup>. In recent times, there has been growing recognition that macrophages play a crucial role in the adipose tissue secretory function serving as main inflammatory cytokines like TNF alpha and Interleukin 6. Adipose tissue performs endocrine functions with distinct characteristics, greatly influenced by hormonal and humoral regulatory functions. This can conclude that adiponectin and leptin, 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<sup>55</sup>. The first adipose derived factor is TNF alpha to be linked to diabetes, obesity, and inflammation. As TNF can impede in adipose tissue and hepatocytes, research reveal that expression of mRNA levels of TNF alpha in adipocytes in obesity are substantially involved in the etiology of resistance of insulin. In humans this tissue constitutes of about 30% of the Interleukin-6. In comparison to subcutaneous fat, visceral fat has larger concentrations. They are induced by TNF alpha and interleukin-1, which is increased in obesity<sup>56,57</sup>. 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. Levels of resistin are upsurged in obesity mice model and humans with obesity and also in diet and genetic obesity. Increases in adipocytes cell quantity and size are indicators of overweight. 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 resistance<sup>58</sup>. Knowing the pathways of signalling by which adipokines regulates the metabolism and further innovative cure for disorders associated with obesity are becoming more and more crucial today.

#### **IV. GUT MICROBIOTA AND OBESITY**

The initial link between gut microbiota and obesity was linked through studies conducted on mice free from germs. In one group, mice were raised in a sterile condition,

while another subgroup was raised in a normal environment. Surprisingly, the mice developed in the conventional condition had a 40 percent more 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 microbiota from gut from normal mice into mice which is germ free, which caused a remarkable 60% increase in adipocytes in just 14 days, even without any remarkable swap in their intake of food or expenditure of energy. The discovery indicates that gut microbiota plays a significant role in influencing the characteristics associated with overweight in the host. When the microbiota was transplanted, it not only upsurges the energy availability from dietary polysaccharides from plant but also specific genes (ChREBP and SREBP1) in the cells of host, which affect storage of energy in adipocytes<sup>59</sup>.

Over 100 trillion microbial cells in human gut houses that play major role in the human metabolism through their symbiotic interactions with the host. Recently, microbiota from gut has been called as a major factor contributing to metabolic disorders. Basically, it is now involved as a distinct endocrine organ, engaging in molecular crosstalk with the host to maintain energy homeostasis and stimulate host immunity<sup>60</sup>. Changes in the microbial composition of gut influenced by various condition which can lead to a significant change in host and gut bacteria symbiotic relationship, ultimately promoting metabolic disorder. This microbe is thought to involve in these disorders by stimulating inflammation. Research indicates that they play a role in harvesting energy and host's fat storage upsurge<sup>61,62</sup>. There is 40% less total body fat in mice free from germs than conventionally raised ones, despite consuming 29% more food than their normally mice<sup>63</sup>. Moreover, less weight is gained in these mice and are secured from glucose intolerance and resistance of insulin than normal animal<sup>64</sup>. When fecal microbiota from normal animal was transplanted into mice which was germ free, it led to a substantial 57% upsurge in fat cells, along with elevated triglyceride levels of liver and resistance of insulin, although no alteration in without any changes in taking food<sup>65</sup>.

Alterations in gene expression related to homeostasis of energy, metabolism of lipids and mitochondria were observed in liver, gut and adipose tissues between normal and germ free mice<sup>66</sup>. Both clinical and preclinical studies are considered to represent changes in microbiota of gut associated with overweight. Composition in the lean gut, wild type mice, and obese mice were compared, where induction of obesity is caused by a lack of the leptin, responsible for controlling satiety) revealed alterations in both Firmicutes and Bacteroidetes phyla. Notably, the ratio of both is related with the phenotype of obesity, regardless of food taken<sup>67</sup>. In the animals with diet induced obesity these alterations were linked to overgrowth of a particular class of Firmicutes phylum and the Mollicutes class<sup>68</sup>.

Furthermore, these alterations in composition came back to normal upon returning to a normal food consumption, indicating that food consumed is important in overweight changes in the microbiota of gut. Murphy and colleagues further supported these findings, which was upsurge in Firmicutes: Bacteroidetes ratio in both mice fed with a high-fat diet and ob/ob mice than lean one. Recent research has shown that the upsurge in this ratio was highly significant in high-fat diet mice compared to ob/ob animal<sup>69</sup>. Studies are currently exploring the relation between the gut's microbial composition and nervous system, focusing on the recovery from dysbiosis and the establishment of eubiosis<sup>70</sup>. The enteric nervous system, often referred to as the second brain, is important in controlling responses to the



environment through the structure of enteric neurons<sup>71</sup>. Research has demonstrated the regenerative function of the microbiota, which can reduce significant pathology symptoms, particularly those associated with degenerative diseases, through microbiota targeted therapy which ameliorate patterns of microbes that modulate the microbial pattern which affect host homeostasis<sup>72</sup>. Gut microbiota restoration cause improvement in function of other organs<sup>73</sup>.

The findings which links degenerative pathologies to gut microbiota is well-established, and further exploration to uncover new links in current epidemiological relationship. Obesity has been newly identified as a condition influenced by the role of the microbiota. Critical mediator identification presents an opportunity for novel curative strategies by and decreasing the inflammatory response improving dysbiosis.

- 1. Effect of Dietary Components on the Gut Microbiota:** The diet significantly influences the individual microbiome by serving as substrate for metabolism of microorganism. Different diets and dietary components can either positively or negatively modulate the composition of the microbiome<sup>74</sup>. Western diets, which are characterized by low fiber, vegetable, and fruit intake, but higher in fat which is saturated, sugar, and protein of animal, have far-reaching results. They can lead to increase in insulin, resistance of insulin, dyslipidaemia, more stimulation of the renin-angiotensin system, sympathetic nervous system and oxidative stress. Moreover, such diets can cause dysbiosis, hampers function of intestine, upsurge permeability of intestine, and result in toxic bacterial metabolites leakage into the bloodstream. The effects collectively can lead to significantly to systemic inflammation development<sup>75</sup>.
- 2. Impact of Lifestyle and Environmental Factors on the Gut Microbiome:** A high fat diet in both fats and carbohydrates results in gut bacteria imbalance, known as dysbiosis, reduces angiotensin-like protein 4 expression. This protein plays a role in regulating lipid metabolism<sup>76</sup>. The decrease in Angptl4 leads to higher activity of lipoprotein lipase, which results in upsurge of fatty acids and more storage of fat in peripheral tissues<sup>77</sup>. Ultimately, this leads to fat accumulation and obesity. High-fat diets also negatively impact beneficial bacteria like *Lactobacillus* spp and *Bifidobacterium* spp., and *Prevotella* spp., while causing the endocannabinoid system overactivation. This causes the gut microbial composition alterations, which upsurge permeability of gut, and allow the movement of bacterial fragments, contributing to weight gain<sup>78,79</sup>. The type of fatty acids consumed also influences gut microbiota, with omega-3 promotes *Lactobacillus*, and monounsaturated and omega-6 polyunsaturated fatty acids growth which is indirectly related bifid bacteria growth<sup>80</sup>. Fat rich diets also encourage more growth of Gram-negative bacteria, leading to the passage of fragments of bacteria like lipopolysaccharides through the barrier of intestine. In bloodstream, it acts as an endotoxin, triggering inflammation and intestinal permeability, which may contribute to obesity-induced chronic inflammation<sup>81</sup>.

## V. CENTRAL NERVOUS SYSTEM REGULATION OF ENERGY HOMEOSTASIS

The hypothalamus, located at the base of brain, is a limbic system part and constitutes ventral portion of diencephalon in all vertebrates. It serves as a vital regulator of metabolic processes and acts as an intermediary between the nervous and endocrine systems. It has various circulating hormones receptors to get signals from organs related to energy balance

<sup>82</sup>. Additionally, it produces and releases neurohormones into the portal circulation, regulating the release anterior pituitary gland hormones. The hypothalamus governs various functions, including, hunger, body temperature satiety, behaviors, emotions like, short-term memory rage, thirst, heart rate, blood pressure, gastrointestinal peristalsis and circadian rhythms. While hormones from peripheral need to reach hypothalamus by crossing the blood-brain barrier, which is coordinated to regions of brain like neurohypophysis and median eminence, where the barrier is not fully intact due to a fenestrated capillary endothelium, allowing large proteins to pass freely <sup>83</sup>.

The hypothalamus connects with specific brain regions, known as circumventricular organs (CVO), which sample the blood's composition. These CVOs, including the organum vasculum of the lamina terminalis and subfornical organ, have neurons that interact with both blood and cerebrospinal fluid with a rich vascular supply <sup>84,85</sup>. 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 paraventricular nucleus, supraoptic nucleus and preoptic nucleus. The hypothalamus, particularly the arcuate nucleus (ARC), is well-studied and essential in controlling feeding and energy expenditure <sup>86</sup>.

Near the median eminence ARC is located, integrates peripheral hormonal as well as nutrient signals through its neurons, leading to coordinated responses. Within the ARC, there are agouti-related peptide expressing neurons, orexigenic neuropeptide Y and anorexigenic (appetite-suppressing) pro-opiomelanocortin POMC expressing neurons <sup>87,88</sup>. Energy homeostasis as well as its communication to peripheral organs hypothalamuses are significant areas of research for bariatric endocrinologists. Upon nutrient ingestion, POMC is cleaved to alpha melanocyte stimulating hormone, by which melanocortin 3 and 4 receptors are activated on downstream neurons, including paraventricular nucleus <sup>89</sup>. It causes an increase in energy expenditure and decrease in intake of food. The paraventricular nucleus in the hypothalamus, has the highest MC4R expression and is considered <sup>90,91</sup> to be main region for energy intake regulation within central nervous system <sup>92,93</sup>. Studies in mice have demonstrated that MC4R disruption, in the paraventricular nucleus, causes overweight due to, reduction in energy expenditure, enhancement of food intake and glucose homeostasis impairment <sup>94</sup>.

### **Extrahypothalamic Neuronal Circuits**

Hypothalamic nuclei interact with brain regions beyond the hypothalamus, like nucleus of the solitary tract, to control intake of food and expenditure of energy. They are also related to mesolimbic reward system, including the nucleus accumbens and ventral tegmental area and influences the pleasurable food intake properties. When level of glucose is reduced decrease during fasting, lateral hypothalamus neurons that contain glutamate and orexin are activated and stimulate dopaminergic neurons in the VTA <sup>95</sup>.

Hormones like leptin and insulin released by pancreatic  $\beta$ -cells and adipocytes in the blood stream in melanocortin system cross blood brain barrier and bind on pro opiomelanocortin neurons receptor in the hypothalamus. It causes production of alpha melanocyte stimulating hormone, whose signals reduces energy intake during the "fed state" <sup>96,97</sup>. The secretion of agouti-related neuropeptide and neuropeptide Y from neurons of AgRP/NPY. However, in "starved state," reduced level of leptin, insulin and orexigenic

hormone ghrelin increase the AgRP/NPY neurons activity. Both AgRP/NPY and POMC neurons originate in the hypothalamus from arcuate nucleus and send axons to the paraventricular nucleus. Cholinergic neurons from the dorsomedial hypothalamus (DMH) and glutamatergic excitatory signals from steroidogenic factor which expresses neurons in ventromedial hypothalamus provide excitatory and inhibitory inputs respectively to POMC neurons of hypothalamic in the melanocortin pathway that regulates feeding<sup>98</sup>.

The leptin discovery in 1994 gives a proof of a hormonal system which regulates weight. Severe obesity in ob/ob mice caused by mutations in the obese gene leading to a lack of production of leptin. Infants deficient in leptin also exhibit early-onset obesity after weaning. Leptin deficiency is associated with various, metabolic, endocrine and immunological problems, like, hyperinsulinemia, hypogonadotropic hypogonadism and reduced T-cell function, highlighting leptin's regulatory role in different physiological processes<sup>99-105</sup>. Although, findings on adults deficient in leptin shows slow improvement in their phenotype, suggesting possible compensation by other mechanisms, although the exact reasons for this phenomenon remain unknown<sup>106</sup>.

## VI. 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 gene expression control is required for development and cellular differentiation. The unique gene expression patterns observed in cells which are differentiated takes place in development which is perpetuated through cell division. Cells also acquire epigenetic information, normally not encoded in the sequence of DNA besides genetic information. The study of acquired mitotically alterations in expression of gene which is not caused by changes in DNA sequence is known as Epigenetics<sup>107</sup>. Epigenetic mechanisms, including, post-translational modification of histone proteins cytosine methylation, chromatin remodelling, and RNA-based processes, are important in permanently altering expression of gene patterns as well as transmitting these changes to subsequent generations<sup>108,109</sup>.

**Methylation of DNA** is a chemical modification which is reversible and occurs in cytosine residues at the 5' position, resulting in 5-methylcytosine formation. Although 3 percent cytosines DNA are methylated in human, which primarily occurs at sites where cytosine is followed by guanosine, known as CpGs. They are influenced by the bonding of hydrogen in DNA and major groove projection, altering the DNA biophysical properties. This modification cause inhibition of DNA recognition by certain proteins also linking of DNA to other proteins. Methylation of DNA is linked with the gene repression. One significant feature of DNA methylation is its ability to maintain by replication of DNA and division of cell (mitosis), leading to the inheritance of the repressed state in subsequent generations. This epigenetic modification plays a role in gene expression patterns. Basic proteins which is core histones around which the DNA is wrapped in nucleosomes (globular domains), also play a crucial role in regulation of epigenesis. Flexible "tails" which arise from nucleosome and can undergo many post-translational modifications. These histone modifications further contribute to the gene expression regulation and chromatin structure. Histone proteins have flexible tails that undergo various post-translational modifications. These modifications, along with composition and arrangement of nucleosome, constitute an epigenetic description that can either enhance or inhibit expression of gene.

For regulation of expression of gene, impacting various stages of gene activity, from gene accessibility in the chromosomal properties to transcription, RNA processing as well as translation. Unlike the stable and uniform genome present in vertebrate cell, 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 patterns of gene regulation occurring during these critical periods can persist for an extended duration, shaping the phenotype of the adult individual. These alterations in expression of gene offer a hypothesis that exposure to environmental events in an individual's prenatal or postnatal progression could lead to adult diseases<sup>110-115</sup>.

### **Epigenetic Modifications Associated with Obesity and yheir Impact on the Metabolic Process**

Obesity is a chronic disorder involving numerous depositions of fat causing serious health risks. Till now only genetics could not solve the pandemic of global disease. Obesity is caused by a various gene's interaction with numerous environmental factors such as chemicals, stress pharmacological treatments, exercise or diet. The epigenome is flexible interaction of gene-environment interactions at the molecular level. Epigenetics highlights various potential influence of the mitochondrial metabolism on formation or modification of the epigenetic marks which occur at nuclear level<sup>116</sup>.

Epigenetics refers to alterations in the activity of genes which passes to generations which do not cause any changes to sequence of DNA. Recently various genes have been discovered for obesity like, proopiomelanocortin POMC, leptin or melanocortin 4 receptor. Pathways of these genes is understood for various metabolic diseases for the proper understanding of obesity. Although, obesity has a polygenic basis for various genetic predisposition<sup>117</sup>. In the context of obesity, DNA methylation is a well reported epigenetic mark. POMC is one of the major melanocortin system components that regulates the intake of food and balance of energy. Additionally, altered methylation of DNA in areas of the POMC gene is linked to specific metabolic profiles. Insulin-like growth factor 2 is a imprinted gene responsible for growth and body composition regulation, is hypomethylated and correlated with higher body mass index. Furthermore, it is reported about association of BMI with methylation of DNA patterns of genes in the obesity related genes, like leptin adiponectin, leptin receptor and Insulin receptor substrate 1. Circadian clock genes BMAL1, CLOCK, and PER2 have been reported to be linked with various metabolic syndromes and increased body fat<sup>118</sup>.

Various studies suggest the effect of metabolites of gut microbes on epigenome. Long-term dietary choices affect various gut microbiota function, that affect bioavailability of cofactors of epigenetic reactions and diet. It is also reported about the role of miRNAs influences differentiation of adipocytes which leads to obesity pathogenesis. The first report that provides miRNA effect was in *Drosophila* for the fat cell which demonstrated that miR-14 causes inhibition of fat metabolism by MAPK and p38 targeting. After that, effect of the miRNA was extensively explored in various, rodents, cell lines and humans' beings. By different molecular mechanisms miRNAs promotes adipogenesis miR-143 acting via MAPK signalling5 pathway promotes human adipocyte differentiation and miR-21 regulates the

adipogenesis derived from human adipose tissue in the mesenchymal stem cells by modulating TGF- $\beta$  pathway<sup>119,120</sup>.

Methylation of DNA in PPARGC1A observed obese patients tissue, suggesting the epigenetic regulation of mitochondria function is involved in disease pathophysiology. Also, a high-fat diet affects pathways of mitochondria generating acetyl-CoA, that may change the acetylation of histone influencing expression of gene. Epigenetic research is important for gaining a deeper understanding of the sharp rise in obesity prevalence worldwide. Based on the available data, exposures of environment can lead to epigenome that increase risk of obesity. 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 today<sup>121-125</sup>.

## VII. NEUROTRANSMITTERS AND OBESITY

**1. Role of Neurotransmitters in Appetite Regulation and Reward Pathways:** A neurotransmitter disorder is a broad term that includes neurometabolic disturbances that affect neurotransmitter synthesis, transport, or breakdown. These conditions include both rare inherited neurological disorders (such as tyrosine hydroxylase deficiency) and more common diseases such as Parkinson's, Alzheimer's, and depression. Amino acids (GABA, glycine, and glutamate), monoamines (dopamine, serotonin, noradrenaline and adrenaline), purines (adenosine), and cholinergic systems (acetylcholine and nicotine) are among the neurotransmitter pathways that are affected. Neuropeptides and ion channels that are involved in neurotransmission mechanisms can also play a role in neurological disorders. Changes in neurotransmitters and neuropeptides that regulate food intake and energy expenditure are linked to obesity. It is unclear whether these changes are a result of or a result of weight gain. Certain antipsychotics, antidepressants, and antihistamines, as well as other iatrogenic medications that target neurotransmission, can cause weight gain, implying that changes in neurotransmission may precede obesity. Anti-obesity drugs that act as monoamine reuptake inhibitors, nicotinic antagonists, opioid antagonists, 5-HT receptor agonists, TAAR1 agonists, or monoamine-releasing agents have shown efficacy in weight loss. The most effective weight loss treatments, metabolic surgeries, may also have an effect on neurotransmitter metabolism. In this mini-review, we look at the intriguing concept of obesity as a neurotransmission disorder<sup>126-129</sup>. Dopamine (DA), cannabinoids, opioids, and serotonin, as well as neuropeptides like orexin, leptin, and ghrelin, all play important roles in the rewarding effects of food and the homeostatic regulation of food intake. Dopamine, for example, has been extensively studied and is well understood. It modulates natural and drug rewards primarily through its ventral tegmental area (VTA) projections into the nucleus accumbens (NAc)<sup>130</sup>. Other dopamine pathways are active in the dorsal striatum, cortical areas (OFC and ACC), limbic areas (hippocampus and amygdala), and the lateral hypothalamus. In humans, eating pleasurable food releases dopamine in the dorsal striatum in proportion to the perceived pleasure from the food. Dopamine's role in reward, however, is more than just encoding pleasure. Dopamine neuron firing in the VTA increases initially in response to a food reward, leading to dopamine release in the NAc. However, repeated exposure to the reward habituates the dopamine response, shifting the focus to the stimuli associated with the reward (e.g., the smell of food), which becomes a cue conditioned to the reward. In

response, a "reward prediction error" is now displayed by the dopamine signal. Dopamine and serotonin are vital for hedonic and homeostatic signalling, respectively, but other neurotransmitters also play important roles<sup>131-135</sup>. Studies in rats and people show that stimulation of dopaminergic and serotonergic signals causes changes in appetite, motivation to feed, reward for education relating to food energy expenditure<sup>114-116</sup>. Based on these and other findings, it is hypothesised that disrupted feeding behaviour in obesity is caused by changes in the central dopamine and serotonin systems<sup>136, 137</sup>.

- 2. Serotonin Signalling in the Homeostatic Circuitry:** In cases where the body's energy stores are adequate, failure to adequately suppress food intake leads to overeating beyond nutritional needs, resulting in weight gain. It has been proposed that reduced serotonin signalling in the homeostatic circuit contributes to this pathological condition. Serotonin's role in obesity development has been extensively researched over the years, with a method involving various neurotransmitters and few areas of brain. The main regions are the hypothalamus and brainstem in charge of food intake homeostasis function. These regions integrate about hunger, satiety, and whole-body nutrient availability in order to adjust frequent eating habits based on the current healthy state. The, nucleus tractus solitaries, raphe nuclei and parabrachial nucleus in the brain, and the arcuate nucleus, ventral medial nucleus, paraventricular nucleus, lateral hypothalamic and dorsomedial nucleus area in the hypothalamus, all play important roles<sup>138-144</sup>.

## VIII. EMERGING DRUG TARGETS FOR OBESITY TREATMENT

- 1. Overview of Current Pharmacological Approaches for Obesity Management:** Medical weight control is still an effective treatment for obesity, and recent developments have fundamentally changed how we treat. Weight as well as metabolic parameters is improved by all anti-obesity medications, though the effects and efficacy vary by medication. Obesity treatment guidelines recommend a multidisciplinary approach to weight management that includes medication, behavioural therapy, and/or bariatric surgery<sup>145-146</sup>.
- 2. FDA-Approved Medications for Monogenic Syndromes of Obesity**
  - **Setmelanotide:** In 2020, the FDA approved setmelanotide, a melanocortin-4 receptor agonist, as a subcutaneous injectable formulation for the treatment of chronic obesity in patients aged 6 and older with a genetically confirmed deficiency in proopiomelanocortin, leptin receptor. Setmelanotide's most common side effects were injection site reactions and hyperpigmentation problems (100 percent in POMC deficiencies and 45 percent in LEPR deficiencies). After one year, patients with Bardet-Biedl or Alstrom Syndrome had a 7.6% decrease in overall body weight<sup>147-149</sup>.
  - **Metreleptin:** Meterleptin is a leptin analogue that the was approved by FDA in 2014 as an alternate medication for leptin deficiency in people with acquired lipodystrophy and congenital related co-morbidities. The dose is 0.06 mg/kg/day with a maximum of 0.13 mg/kg/day for patients weighing less than 40kg; for patients weighing more than 40 kg, the dose is 2.5 mg for males and 5 mg for females once daily with minimum 10 mg/day. It is given as a subcutaneous injection once a day. The growth of antibodies

against metreleptin has been established, but the consequences are unknown because of the small number of cases.

### 3. FDA-Approved Medications for Non-Syndromic Obesity

- **(Orlistat (Xenical, Alli):** Orlistat works primarily by inhibiting pancreatic and gastric lipases, thereby decreasing dietary fat absorption. In a one-year study, orlistat reduced waist circumference (WC) by 9.6 cm while placebo reduced it by 7.0 cm (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. More than 10% of the population experienced gastrointestinal (GI) symptoms such as abdominal pain, faecal urgency, steatorrhea, and faecal incontinence in the primary orlistat trials<sup>150</sup>.
- **Phentermine/Topiramate (Qsymia):** Both topiramate and phentermine have long-term approval for the treatment of obesity. Topiramate, a carbonic anhydrase inhibitor and gamma-aminobutyric acid agonist, has been shown to suppress appetite. At 56 weeks, the low-dose group had a mean WC reduction of 5.6 (9.8%), the high-dose group had a mean WC depletion of 10.9 (10.3%), and the group having a mean WC reduction of 3.1 (10.3%) (p 0.0001). These differences between the high-dose and placebo groups, as well as between the two doses, were statistically significant. A few examples of adverse events include increased heart rate, mood and sleep problems, memory loss, paraesthesia, diarrhoea, and dry mouth<sup>151</sup>.
- **Naltrexone/bupropion (Contrave / Mysimba):** Bupropion, an antidepressant with norepinephrine and dopamine reuptake inhibitors that directly stimulate POMC cells, and Naltrexone, an opioid receptor antagonist that blocks the POMC pathway, both act in concert to stimulate POMC peptide production, which reduces appetite. Furthermore, the combination of Naltrexone and Bupropion (NB) affects reward circuits, implying improved self-control and internal fullness signals. Constipation, dry mouth, and gastrointestinal (GI) symptoms have all been reported as adverse events in major clinical trials.
- **Glucagon-peptide receptor** Semaglutide and Liraglutide act peripherally on the gastrointestinal tract, increasing insulin secretion and pancreatic activity while slowing intestinal motility and delaying gastric emptying.
  - **Liraglutide (Saxenda):** In the Obesity and Pre-Diabetes Trial, the mean Waist circumference decrease at 56 weeks was 8.2 (7.3) cm in the liraglutide arm and 3.9 (6.6) cm in the placebo arm (p 0.001). The liraglutide 3 mg and placebo groups (n = 738) had mean Waist circumference reductions of 6.9 (8.3) cm and 3.4 (7.5) cm, respectively, at 160 weeks (p 0.0001). Increased heart rate, gastrointestinal problems such as constipation and diarrhoea, and infections such as nasopharyngitis are among the side effects.
  - **Semaglutide (Wegovy):** The STEP 1 trial found that at 68 weeks, the intervention group's mean waist circumference had decreased by 13.5 cm, while the control groups had decreased by 4.1 cm (p 0.001). In the major studies, more than 10% of the population experienced adverse effects such as GI symptoms, infections such as upper respiratory tract infections, urinary tract infections, and so on<sup>152-156</sup>.

#### 4. Medication under Consideration for FDA-Approval

- **Tirzepatide:** Tirzepatide is a centrally acting GIP/GLP-1 dual agonist that decreases food intake while potentially increasing use of energy by desensitising the receptor (GIP) through persistent GIP agonism. It was approved to treat type 2 diabetes in 2022. Patients with diabetes were randomly assigned to receive tirzepatide at doses of 5, 10, and 15 mg or semaglutide 1 mg in a 40-week phase 3 trial. Tirzepatide outperformed semaglutide in terms of lowering HbA1c at all doses. It is currently being studied in a number of phase 3 trials in obese patients (n = 210-900). When compared to GLP-1 agonists, it may be associated with fewer gastro-intestinal side effects<sup>157</sup>.

#### 5. Medications in Phase 3 Trials

- **Methylphenidate:** It is a stimulant that is accepted for the cure of attention deficit hyperactivity disorder. It is a dopamine reuptake inhibitor used to control caloric intake. Tachycardia, upper abdominal pain, insomnia, and headache are the most common side effects.
- **Exenatide:** Exenatide, a GLP1-RA, was studied for the treatment of obese diabetic patients. In a 24-week randomised controlled trial, exenatide (n = 73) and placebo (n = 79) were compared in patients with a mean baseline weight range of 107-109 kg, with lifestyle modification as a cointervention for both arms. The medication caused a significant difference in total body weight loss.
- **Cagrilintide:** The amylin analogue cagrilintide improves central satiety signals while decreasing peripheral stomach emptying for a phase 3 trial in patients with obesity and diabetes (n = 1200) versus placebo for total body weight loss. Other molecules being studied for their potential use in weight loss including PPAR gamma modulator AMG, leptin sensitizer AMG, 208, 209 210 MBL949, 212 NNC0247-0829, 213 LY3841136214, 211 NO-13065 and BMS-986172. One of the most significant barriers to effective weight management is the difficulty in predicting a patient's response to medications, as well as the wide variation in how each person's weight changes in response to a particular treatment. According to these findings, new pharmacotherapies will revolutionise how we manage obesity and its comorbidities, such as cardio-renal disease and metabolic disease, in the coming years<sup>158-162</sup>.

**6. Recent Research on Novel Drug Targets and Therapeutic Strategies:** The growing obesity problem has sparked an unprecedented search for new anti-obesity medications. Recently discovered targets include both the centre and the periphery. Several mechanisms are currently being used by the pharmaceutical industry to reduce body weight, including lowering food intake, preventing lipid absorption from the stomach, increasing energy expenditure, mobilising fat stores, and preventing lipogenesis. Novel anti-obesity drugs' sites of action thus include the brain, the gastro intestinal system, adipose tissue, the liver, and skeletal muscle.



## Hypothalamic Mechanisms and Targets in Research

- **Rimonabant** a cannabinoid (CB 1 receptor antagonist), reduces body weight, adiposity, and insulin resistance in obese mice fed a high-fat diet. A 12-month Phase III trial in obese dyslipidaemias showed clinically significant weight loss (>5%) that was sustained for a year, as well as changes in obesity-related risk variables such as plasma lipid profiles and glycaemic control. As a result, preliminary human results do not indicate that this medication will significantly outperform currently available options in terms of efficacy<sup>163</sup>.
- **5-HT** is well known for its importance in the brain's control of appetite. Food intake is reduced in rats after central administration of antisense to 5-HT6 receptors, implying that 5-HT6 receptors are linked to obesity. Furthermore, on a high-fat diet, 5HT6 knockout mice are resistant to gaining weight, and the selective 5-HT6 receptor antagonist BVT 5182C has been shown to reduce body weight in obese mice.
- **Presynaptic Histamine** and H3 receptors primarily function as auto receptors. Because they reduce body weight and body fat in diet-induced obese mice, selective H3 receptor antagonists like A-331440 have the potential to be used in the treatment of obesity. In contrast to results obtained with selective ligands<sup>164</sup>, H3 receptor deletion mice exhibit an obese phenotype characterised by hyperinsulinemia and hyperleptinemia<sup>164-168</sup>.
- **Melanin-Concentrating Hormone (MCH)** administered centrally to animals results in obesity. Overexpressed MCH mice are moderately obese with increased food intake, whereas MCH knockout mice are lean, hyperphagic, and hypermetabolic. MCH-1 receptor antagonists have been shown in pre-clinical studies to be effective anti-obesity medications because they cause long-term reductions in food intake and body weight.
- **Melanocortin's, including adrenocorticotropin** These hormones, as well as alpha, beta, and gamma-melanocyte-stimulating hormones (MSH), are derived from the common precursor pro-opiomelanocortin (POMC) and interact with a group of receptors known as MC1-5. MC4 receptor agonists not only have the potential to reduce weight but also have beneficial effects on hyperinsulinemia, according to research using genetic mouse models, knockout mice, and feeding studies with MC3 agonists and antagonists. PGE-657022, a high-affinity MC4 receptor agonist, was recently discovered and has shown promising results in reducing food intake, body weight, and fat mass in obese rodents.

The peptide hormone **leptin** is secreted by adipose tissue. It usually makes its way to the hypothalamus, where it initiates lipolysis and suppresses appetite. Recently, two groups of substances were discovered to be able to bypass the leptin transporter system and easily diffuse into the brain. One of these compounds has been shown to produce a significant 10% reduction in body weight and a 20% reduction in food intake in dietary-induced obese rats within three weeks. When leptin levels in plasma are high, its transport into the brain becomes saturated, blunting its effects<sup>169-173</sup>.

- **Fatty acid synthase (FAS)** inhibition is another effective strategy for obesity management. C75, a FAS inhibitor, was discovered to reduce body weight in rodents via a central action that decreases appetite while increasing energy expenditure.

The anti-obesity potential of drugs that reduce or inhibit the function of the gastric peptide **ghrelin** is debatable. Exogenous ghrelin, which is found in the hypothalamus, has been shown in laboratory animals to increase food intake, adiposity, and fat utilisation. The potential use of ghrelin inhibitors for weight loss is being investigated<sup>174</sup>.

### Peripheral Mechanisms and Targets in Research

- Although it is well known that thyroid hormones cause weight loss by increasing metabolic rate, their use is associated with cardio-stimulation and protein loss. Recently, KB-141, a specific b-subtype agonist, was developed and 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.
- PGC-1-alpha and its related peroxisome proliferator-activated receptor (PPAR) are important regulators of adaptive thermogenesis in brown fat and skeletal muscle. Because of the activation of its components, this regulatory pathway is of great interest in the search for new anti-obesity medications<sup>175</sup>.
- Studies have shown that knocking out Acetyl-coenzymeA carboxylase (ACC) in mice (ACC2 knockout mice) results in lower body weight and less fat accumulation, rather than increased food intake. Furthermore, giving mice Famoxin, a proteolytic cleavage product of the adipocyte complement-related protein (Acrp30), increased fatty acid oxidation and induced weight loss.
- Triglyceride synthesis inhibition is a major focus for peripheral anti-obesity drugs. The enzyme diacylglycerol acyltransferase (DGAT) is essential in the final step of triglyceride synthesis. In mice, knocking out this gene results in resistance to diet-induced obesity. These mice increase their energy expenditure to compensate for their reduced ability to store fat.
- Protein tyrosine phosphatase-1B (PTP-1B) knockout mice have improved insulin sensitivity and are less likely to become obese when fed high-fat diets. As a result, inhibitors of this enzyme are effective in the treatment of obesity. An antisense nucleotide (ISIS 113715) is claimed to selectively inhibit PTP-1B gene expression in rodents and monkeys. However, at this time, none of the novel strategies studied in Phase II or Phase III clinical trials have shown signs of being significantly more effective than orlistat, phentermine, or sibutramine. There is always the possibility that these new medications, particularly the CB1 receptor antagonist rimonabant, will be less harmful or better tolerated than existing medications. As a result, preliminary data for some of the newer molecular targets, such as MCH1 antagonists and MC4 agonists, suggest that they may cause significantly more weight loss in the clinic than current medications and be effective against obesity-related co-morbid conditions. Furthermore, some of the newly discovered peripheral targets may pave the way for the combination of therapies to treat obesity<sup>176</sup>.

### Discussion of Promising Preclinical and Clinical Studies

To develop a multifaceted strategy to combat the global obesity epidemic, an in-depth understanding of the mechanisms underlying this complex condition is required. These experimental models mimic certain aspects of the human condition and its

underlying causes, most notably calorie overconsumption and unbalanced diets. Obesity in rats, like in humans, is caused by complex gene-environment interactions. Animal models are used as a research method in the battle against obesity, which was expected to last till ages. Recent models include either genetic such as rapid mutants or transgenic lines or dietary with the latter which results from the same gene-environment correlated with the cause of majority of obesity cases. Although betterment has been done in the development of polygenic diet-induced obesity models and future work is to be done for better human behaviours 177<sup>-182</sup>.

- **Traditional genetic models of obesity:** Because several genes and metabolic pathways influence the entire energy balance, human obesity is a complex genetic trait. Monogenic mouse model research has contributed the most to our mechanistic understanding of appetite and energy balance. There are over 200 mouse models of monogenic obesity available. The ob/ob mouse is the most widely used obesity model. The identification of leptin and mutant leptin receptors in the db/db mouse highlighted hypothalamic regions involved in the integration and control of energy balance signals. The melanocortin receptor 4 (MC4R) gene is primarily expressed in the PVN, and mice with a transgenic knockout of this gene have an obese phenotype, as opposed to Npy- or Agrp-null mice. Obese people are more likely to have MC4R mutations <sup>183</sup>.
- **Models of DIO:** In contrast to monogenic models, the time frames for DIO enlargement closely resembled with the gradual weight gain experienced by the majority of the human population as a result of a marginally positive energy balance over several years. Animals in DIO rodent models are switched from a diet low in energy density, high in complex carbohydrates and fibre, and low in fat to one high in fat and sugar. The inconsistency of data obtained from DIO models is a disadvantage. While many diets resemble (Western) diets in terms of composition, animals are typically fed throughout the day and night cycle, frequently for extended periods of time.
- **Cafeteria diets:** Cafeteria diets, which feed rodents a variety of savoury high-fat and/or high-sugar foods similar to those consumed by humans, serve as relevant models of modern human obesogenic diets. These diets cause an increase in body fat mass in all tested groups. Even under ideal conditions, exposure to high-fat or high-sugar diets during pregnancy causes offspring to consume more fat after weaning. In this study, rats fed a cafeteria diet of sweet and savoury human foods for an extended period of time (18-23) hours daily over 40 days) developed obesity, compulsive-like feeding behaviour, and a decrease in striatal D2 dopamine receptors.
- **Fat or sugar choice diets:** Due to the significant resource input and diversity of the foods consumed, cafeteria diets are rarely in use for routine high- or semi-high-throughput screening of potential therapeutics. When compared to animals with no high fat diet which only temporarily increased bingeing, the animals were consistently hyperphagic and developed obesity. The free-choice group's increased calorie intake was due to eating more meals because they drank sugary drinks rather than changing the quantity of their meals. The appeal of this obesity paradigm is that it encourages excessive calorie consumption while satisfying appetite on a healthy diet <sup>184.-185</sup>.
- **Meal feeding:** The generic approach of screening pharmacological compounds or bio actives with free access to a single high fat diet can be useful, but it does not have a

direct link to human diet and behaviour moreover what it does rodents in their natural environment also the study is used for feeding-plus-exercise variations and was discovered that feeding 2 hours before and exercise for each meal resulted in the greatest reduction of HF-diet-induced weight gain.

- **Binge-type eating:** It is effectively an extreme for the vast majority of meal feeding in preclinical animal models. Rats fed a 60% HF diet for two hours used 60% of their daily calories from this source, leading to increased mass. On HF pellet diets, mice (C57BL/6) had significantly greater binge-like eating ability than rats. During the two-hour access period, these mice consumed 86% of their daily calories without gaining weight.

### Modulation of Genetic Models- New Approaches

Transgenic knockout mice, as previously stated, aided in the identification of fewer of the genes involved in the brain's control of energy balance. Recent advances in optogenetic and chemo genetic mouse models, combined with imaging methods, are allowing for a better understanding of the brain's complex wiring and its relationship to behaviour.

- **Optogenetics and chemo genetics:** The ability of optogenetics to use light to activate or inhibit a small group of neurons in mouse models is a significant step forward. This method provides precise and targeted cell mobilization on millisecond even in freely moving animals without satiety. This discovery allows researchers to investigate the specific role of neurons or neuronal subsets in feeding behaviour, potentially revolutionising the use of animal models in obesity research. Chemo genetics, on the other hand, is the process of inserting a genetically engineered gene into specific mouse cell types to achieve targeted expression. This altered gene could function as a G-protein-coupled receptor or an ion channel. Optogenetic and chemo genetic activation both induce food-seeking behaviour and prompt food consumption. As a result, these investigations can shed light on the intricate functional aspects of a single neuronal cell type<sup>186</sup>.
- **Activating feeding circuits with electromagnetic wave:** The use of electromagnetic radiation (radio waves or magnetic fields) to either activate or inhibit ion channels in the mouse hypothalamus to regulate eating and glucose sensing is an intriguing new discovery. Preclinical obesity research can aid in the identification of therapeutic targets and effective pharmacological agents, as well as the development and characterisation of nutritional therapies. Preclinical obesity research should prioritise the development of more accurate feeding and obesity models, the thorough analysis of feeding behaviour, and the use of molecular and genetic tools to better understand these intricate mechanisms, how they are linked, and how they can be used<sup>187-189</sup>.

## IX. 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 other

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 endocrine role 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 centres 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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