# 5-HT and Neurotransmitter Modulation in obesity: A potential Therapeutic Target.

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## Abstract:

Today, obesity has become a global pandemic affecting billions of people worldwide. It is associated with increased risks of various diseases, including cardiovascular and musculoskeletal diseases, psychiatric disorders, cancer, and diabetes, making it a significant public health issue. The escalating prevalence of obesity has led to a substantial number of deaths globally, with obesity rates rising significantly over the past forty years. In 2016, over 1.9 billion adults were overweight, and more than 650 million were obese, indicating that 39% of adults were overweight and 13% were obese. Obesity has also been linked to an elevated risk of metabolic diseases and changes in brain structure and function.

The body mass index (BMI) is widely used to determine excessive weight in relation to height and age, with the World Health Organization classifying obesity into four categories based on BMI. However, BMI may not be accurate for everyone, and BMI z-scores are employed when analyzing data on children and adolescents. The accumulation of excess body fat, which contributes to obesity, is attributed to an imbalance between energy intake and expenditure, controlled by the brain's central nervous system. Disturbances in the brain circuits that regulate energy balance can impact body weight and adiposity, often involving changes in neurotransmission, which may be addressed with CNS-targeting drugs.

The pathogenesis of obesity is characterized by a chronic energy imbalance between excessive calorie intake and inadequate calorie expenditure, primarily driven by decreased physical activity. The sympathetic nervous system (SNS) and the vagus nerve play crucial roles in the regulation of homeostasis and have implications for the metabolic status of adipose tissue. Hormones and peptides produced by the enteric nervous system, such as cholecystokinin, ghrelin, and leptin, influence hunger and fullness, while leptin, an adipocyte-produced hormone, regulates energy expenditure and food intake.

In conclusion, obesity is a complex multifactorial disease with significant public health implications, involving dysregulation of energy balance, neurotransmitter pathways, and neuroimmune interactions. Understanding the pathogenesis and physiological mechanisms underlying obesity is crucial for developing effective prevention and intervention strategies.

## KEYWORDS

Obesity, gut microbiota, pathogenesis of obesity, obesity and neuroinflammation, brain pathways to obesity, neurotransmission.

# INTRODUCTION

Today, obesity has been a universal pandemic after affecting billions of people all over the world [1].Obesity is linked with escalated risks of many diseasessuch as cardiovascular and musculoskeletal diseases, psychiatric disorders, cancer and diabetes that is a significant public health issue [2].Excessive number of deaths all over the world are due to obesity and overweight having obesity ratesincomparable in many countries [3]. The widespread presence of obesity is now three times from last forty years [4].Over 1.9 billion individuals aged 18 and older were overweight in 2016, with over 650 million of them being obese. These figures indicate that 39% of people over the age of 18 (39% men and 40% women) were overweight, while 13% of the adult population worldwide (11% men and 15% women) had obesity [5].Obesity has been linked to an increased risk of metabolic diseases as well as changes in brain structure and function, according to research [6].

One of the most used methods for determining excessive weight in relation to height and age is the body mass index (BMI). The World Health Organisation divides obesity into four categories based on BMI: underweight (BMI less than 18.5 kg/m2), normal weight (18.5 to 25 kg/m2), overweight (26 to 30 kg/m2), and obese (more than 30 kg/m2) [7-10].BMI has traditionally been utilised in adults; however it is now also being used in children and the elderly. Nevertheless, using BMI as an indicator of overweight or obesity is not accurate for everyone. Because BMI changes with age and sex in this group, BMI z-scores are employed when analysing data on children and adolescents [11].

Although obesity is a complex multifactorial disease, the accumulation of excess body fat is mathematically explained by an imbalance between energy intake and energy expenditure [12]. The brain's central nervous system (CNS) controls these two energy balance equation factors [13]. Abnormalities in the brain circuits that control energy balance have a significant impact on body weight and adiposity [14]. These changes are as complex as fat. However, most, if not all, of these disturbances cause changes in neurotransmission, which can be addressed or improved with CNS-targeting drugs. Obesity's aetiology and pharmacology point to a neurotransmitter problem [15].The brain's capacity to integrate behavioural, endocrine, and autonomic responses via afferent and efferent channels from and to the brainstem and peripheral organs underlies the control of body weight. The hypothalamus, in particular, is responsible for this ability [16].

# PATHOGENESIS OF OBESITY

A loss of equilibrium between food intake and energy utilisation leads to obesity [17].A chronic energy imbalance between excessive calorie intake and inadequate calorie expenditure is the primary factor causing obesity [18]. Energy used up during physical exercise, maintaining essential bodily functions, and diet-induced thermogenesis are all included in energy expenditure. The idea that obesity is brought on by irregularities in metabolic energy expenditure and/or diet-induced

thermogenesis has not been substantiated by published studies; instead, data shows that decreased physical activity may significantly contribute to body weight increase [19].

The sympathetic nervous system (SNS) is involved in maintaining homeostasis. Eating, particularly eating excessively carbohydrate boosts SNS activity whereas fasting decreases it. Lipolysis in adipose tissue is innervated by and modulated by the SNS [20].By directly affecting the metabolic status of adipose tissue, parasympathetic input has the potential to modulate the aetiology of obesity. The SNS and macrophages must interact in neuroimmune ways for the homeostasis of many tissues, including adipose tissue [21].The vagus nerve link the brain and digestive system.More than 30 neurotransmitters are produced by the enteric nervous system; these peptides and hormones are released into the circulation, pass across the blood-brain barrier, and stimulate the central nervous system (CNS). Intestinal hormones, including as the peptides cholecystokinin, ghrelin, and leptin, which control the feelings of hunger and fullness, are produced upon ingestion as a result of the stomach's dilation. By blocking vagal signals and repressing the release of insulin, ghrelin increases appetite [20].

The effects on SNS activity are mediated by leptin and insulin. An adipocyte-produced hormone called leptin is increased in obesity [22].It is an adipokine that controls a variety of physiological processes including immunity, energy expenditure, and food intake [23].Circulating leptin concentrations serve as a direct indicator of the amount of energy stored in adipose tissue, and they typically promote energy expenditure while lowering appetite [24].Leptin binds to its receptor in the brain and exerts its effects via the neuroendocrine axis. Additionally, it lessens the hyperglycemia brought on by inadequate insulin [25].Leptin signalling is compromised when obesity progresses, resulting in leptin resistance. Despite having high blood leptin levels in these situations, the hormone is unable to connect to its receptor and regulate physiological activity [26].Leptin resistance, which inhibits leptin signalling and its subsequent physiological consequences, is also linked to obesity. Despite having high amounts of adipokine in the blood, leptin treatment is unsuccessful in obese individuals because they acquire leptin resistance. As there are currently no recognised medications for this function, reducing leptin resistance is an attractive research field with promise for weight-loss treatment [27].

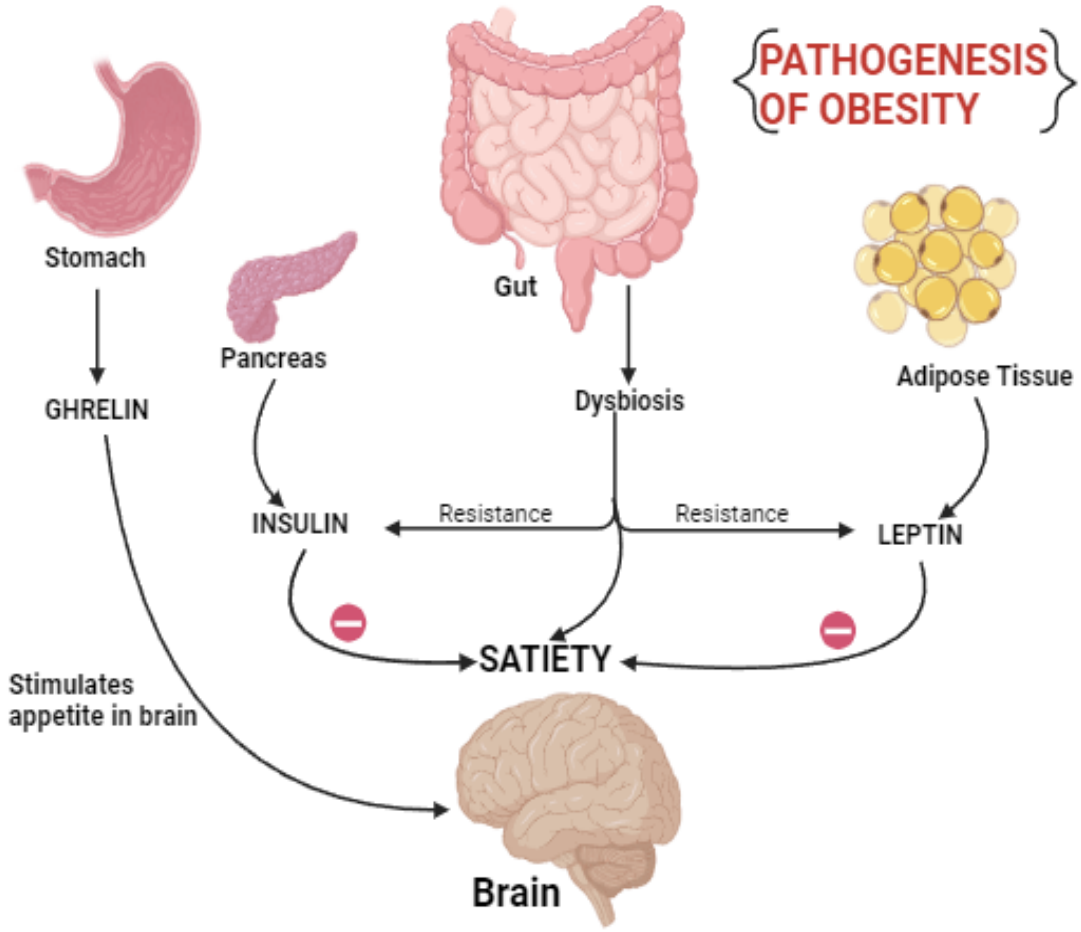



**Figure 1 – Pathogenesis of Obesity**

## GUT MICROBIOTA

The neurobiological control of eating behaviour is incredibly intricate and involves both motivational and energy homeostasis mechanisms [28-33]. Accordingly, controls that are homeostatic and non-homeostatic have been identified in the neural networks that govern eating behaviour [28, 33]. Homeostatic controls, which traditionally include the hypothalamus and brainstem nuclei, are a response to energy and other metabolic shortages [28, 29]. Hedonic and cognitive components of eating are handled by higher-order brain structures such as frontal cortical areas, mesolimbic circuits, and the hippocampus in non-homeostatic regulation [28, 33].Additionally, the vagus nerve connects homeostatic and non-homeostatic feeding regulation by transmitting gastrointestinal hunger and satiety signals and modulating higher-order brain regions. The vagus nerve carries information in both directions between the brain and viscera, including the gastrointestinal tract [34-37]

The non-digestible dietary fibres are fermented by the gut microorganisms into short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, which are important for metabolism [38].There was a correlation between obesity and an increase in the Firmicutes/Bacteroidetes ratio [39].The microbiome's metabolites, which are produced when food is fermented, are crucial in controlling the

metabolism of the host. In the colon, the gut bacteria transform bile acid into deoxycholic acid and lithocholic acid, which promote the release of the incretin hormones GLP-1 and insulin, hence increasing energy expenditure [40].The chemical composition of the microbiome is also related to dietary choline metabolism. Microbiome-mediated trimethylamine-N-oxide (TMAO) synthesis from choline has been linked to metabolic and atherosclerotic diseases [41].Several intestinal-resident bacteria facilitate the conversion of choline to the intermediate trimethylamine [42]. The SCFAs generated by gut bacteria influence GLP-1 release, inhibit the inflammatory immune response in the gut, and are implicated in insulin signalling linked to fat formation [43-45].Additional signs of obesity include indicators for inflammation and intestinal permeability [46].These two issues are related because increased permeability makes it possible for bacterial by products to leak into the bloodstream and cause low-grade inflammation, which is a defining hallmark of obesity and insulin resistance [47].

## BRAIN PATHWAYS TO OBESITY

A forebrain corticolimbic appetitive network is coupled to autonomic hypothalamus and brainstem neural circuits via the brain regions responsible for the control of energy balance.The so-called anorexigenic pro-opiomelanocortin (POMC) neurons and the orexigenic agouti-related peptide (AgRP) neurons, which co-express neuropeptide Y (NPY), make up the melanocortin system in the arcuate nucleus of the hypothalamus [48].With the third ventricle and median eminence nearby, these neurons are in a prime location for receiving a number of signals indicative of metabolic status. In fact, these neurons are able to recognise and react to a wide range of circulating hormonal and nutritional signals including fatty acids, insulin, glucagon-like peptide 1, leptin, glucose, and ghrelin [49].As a result, fasting and other negative energy balance conditions activate AgRP/NPY neurons, whereas positive energy balance states activate POMC neurons [50].Through their combined actions on the downstream cognate central melanocortin receptors melanocortin receptor 3 and melanocortin receptor 4 (MC4R)], these neurons differently control energy balance. The fact that POMC and MC4R mutations are the most prevalent types of monogenic obesitys confirms the significance of these circuits in controlling body weight [51].

The AgRP/NPY neurons, which are a part of the melanocortin system's opposing arm, control feeding through a variety of methods. These neurons coexpress the rapid inhibitory neurotransmitter GABA as well as AgRP, NPY, and NP [52].AgRP's effects at MC4R are primarily what cause a rise in body weight and food intake after central injection of the substance [53].

### Leptin

White adipose tissue is principally responsible for producing leptin, which is then released into the bloodstream. Higher plasma leptin levels are found in those who have more body fat, and these two

variables are positively associated. However, as leptin levels drop by over two thirds following a week of caloric restriction, leptin production is closely linked to energy status [54].Early research using obese animal models showed that leptin reduces food intake while increasing energy expenditure. Leptin deficiency causes animals to consume more food, expend less calories, and experience severe obesity [55].However, only a tiny percentage of people are leptin deficient; the majority of people are leptin resistant, raising doubts about the effectiveness of leptin in treating obesity in people [56].Leptin resistance in humans is evidence indicating people who are more likely to put on weight again after losing it had greater leptin levels, which is associated with poorer leptin sensitivity, than people who successfully maintain their weight [57].

### Insulin

The integration of several peripheral metabolic signals depends on insulin. Insulin's ability to suppress NPY and activate POMC neurons makes this possible. Insulin is more readily present in the CNS because to insulin receptors in the blood-brain barrier. The entryway for insulin's entry into the central nervous system is the hypothalamus, particularly the arcuate nucleus, which is abundant in insulin receptors [58].Mice missing insulin receptors in the CNS are insulin resistant, resulting in increased food intake and the development of diet-induced obesity. Insulin has a role in eating behaviours and consequent body weight maintenance [59].Circulating insulin levels are more strongly connected with visceral fat than subcutaneous fat, in contrast to leptin [60].

### Ghrelin

The hunger hormone, ghrelin, decreases POMC neurons while activating NPY and AgRP neurons in the arcuate to increase appetite.Ghrelin counteracts leptin's suppression of NPY and AgRP neurons, while leptin counteracts ghrelin's stimulation of food intake, demonstrating how the two hormones interact [61].Ghrelin therapy enhances hunger, food intake, and weight gain by acting on both the central and peripheral nervous systems [62].Axons of POMC, NPY, and AgRP neurons that extend to the dorsomedial nucleus, lateral nucleus, paraventricular nucleus, and ventromedial nucleus distribute the orexigenic signal to various areas of the hypothalamus and nonhypothalamic regions. Through its interaction with visceral vagal afferent neurons, ghrelin also affects hunger. Leptin and insulin both reduce the activation of NPY neurons caused by ghrelin [63].Ghrelin levels are lower in obese people than in people of normal weight194 and are lower in people with greater body fat, insulin, and leptin levels [64].

## OBESTY AND NEUROINFLAMMATION

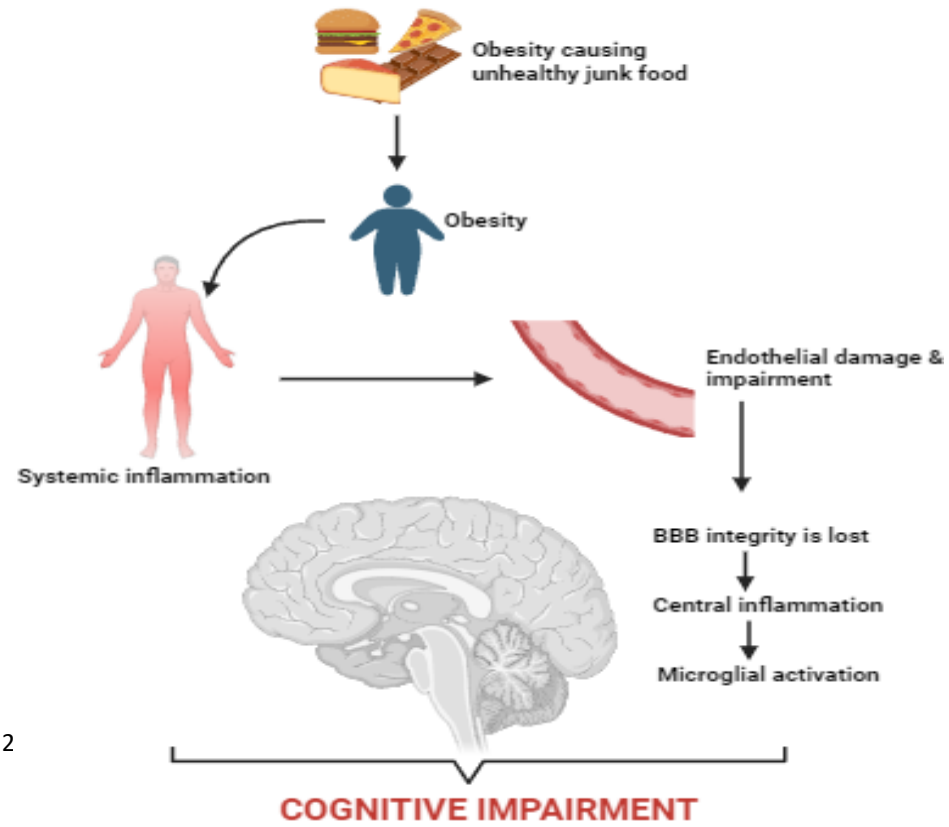
The buildup of glial cells in the brain and spinal cord(CNS) as a reaction to inflammation is known as neuroinflammation.This happens when proinflammatory cytokines (including IL-1 and TNF),

cytotoxic substances, and reactive oxygen species (ROS) are secreted by activated astrocytes and microglia as soon as there is damage, which results in neuronal death [65].

Anatomical anomalies occurs in the amount of grey matter in obese people.When obesity is present, there is a continuous decrease in grey matter in the control areas of the inferior frontal gyri, right insula, left and right precentral gyri, left middle frontal gyrus, left middle temporal gyrus, left amygdala, and left cerebellar hemisphere.Nonetheless, an increase in the amount of grey matter was seen in the left inferior occipital gyrus, left middle frontal gyrus, and left cuneus in the examined studies [66].

A greater body mass index is linked to a reduction in several white matter areas, such as the superior and inferior longitudinal fascicles, corpus callosum, uncinate fascicle, internal capsule, corticospinal tract, inferior front-occipital fascicle, corpus callosum, and cingulum (cingulate gyrus and hippocampus).Local alterations in the white matter fibre tracts linked to elevated body mass index (BMI) provide a connection between the prefrontal and limbic areas, perhaps elucidating the heightened likelihood of cognitive decline and dementia in older adults with obesity [67].

When comparing the diameters of the bilateral caudate with the bilateral thalamus, putamen, and globus pallidus, people who are obese have larger sizes than those who are normal weight [68].The brain area known as the hippocampus, which controls memory and cognition, is frequently linked to obesity-related cognitive decline. Higher BMI (>30 kg/m2) has been linked in human studies to decreases in white matter integrity and grey matter volume in the hippocampus and other brain regions, underscoring the harmful consequences of obesity on brain structure [69].Mechanisms via which obesity and a bad diet affect cognitive performance -



Obesity and/or poor nutrition leads to low-grade systemic inflammation that compromises the blood-brain barrier, causes central inflammation, activates microglia, and expresses pro-inflammatory proteins. These events cause synaptic remodelling, neuronal death, and decreased neurogenesis. Cognitive impairment is also associated with metabolic dysfunction, insulin resistance, development of white adipose tissue, and changes in the gut flora brought on by obesity. When neurotransmitter systems, including the glutamatergic, cholinergic, and dopaminergic systems, are disrupted, acetylcholine and dopamine levels drop and glutamate signalling becomes dysfunctional. These factors further impair memory, learning, and cognition, ultimately resulting in cognitive impairments [70].

More than 100 identified neurotransmitters are members of a large family of chemical messengers that are involved in synaptic transmission and that control physiological processes in the central and peripheral nervous systems [71].The most researched neurotransmitters include glutamate, acetylcholine, norepinephrine, serotonin, gamma-aminobutyric acid (GABA), dopamine, and serotonin because they have therapeutic significance.

## Serotonin

The primary mechanisms controlling feeding action are hedonic and homeostatic systems. The brainstem and hypothalamus are the main areas of the homeostatic system[72].Other neurotransmitters are also involved in hedonic signalling, but dopamine and serotonin play major roles in it [73-74].Serotonin, also known as hydroxy tryptamine, or 5-HT, is mostly found in the GI tract, platelets, and the serotoninergic neuronal network of the central nervous system. Serotonin functions as a peripheral hormone in addition to a neurotransmitter. Nonetheless, the intestinal mucosa's enterochromaffin (EC) cells produce the majority of the 5-HT. The human gut is the biggest endocrine organ, producing over 95% of all serotonin [75].

The reward pathway sometimes refers to the mesolimbic system, which includes the VTA, the nucleus accumbens (NAc) of the ventral striatum, and the CeA. It has also been suggested that these areas participate in the interplay between hedonic and homeostatic control of food intake [76].An excess of energy intake over energy expenditure leads to obesity.As a result, it has been hypothesised that eating above one's needs for energy may be facilitated by reduced homeostatic inhibition and/or greater hedonic desire.Those who are chronically overweight or obese may have disrupted eating behaviour as a result of disruptions in serotonergic signalling, as this signalling plays a crucial role in regulating food intake. Indeed, evidence from several researches suggests that obesity-related disruptions in serotonergic signalling occur in both humans and animals [77-78].

The human central serotonin system cannot be directly studied in vivo. Serotonin and its metabolites in cerebrospinal fluid (CSF), postmortem immunohistochemistry of brain tissue, and molecular neuroimaging methods like positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have all been used to evaluate alterations in serotonergic signalling linked to obesity in humans [79].The infundibular nucleus, which is comparable to the ARC in rats, showed lower levels of SERT protein in the postmortem hypothalamus tissue of overweight/obesity-affected humans [80].

Serotonin (5-HT) has been linked to abnormal signalling in animal models of obesity and is implicated in the control of hunger [81-82].The findings that, over a 4-week hypocaloric diet, thalamic SERT rose when the majority of daily calories were consumed during breakfast and fell when the majority of daily calories were received during supper suggest that meal time plays a role [83].According to these research, serotonergic signalling alterations may arise early in the overindulgence in food that occurs in humans, potentially playing a role in the development and/or maintenance of obesity.

In order to manage food intake, the central 5-HT system is essential.Research from the 1970s was actually the first to demonstrate that in rodents, loss of brain 5-HT due to central infusion of 5,7-dihydroxytryptamine, a neurotoxin that specifically kills serotonergic neurons, or p-chlorophenyl alanine, an inhibitor of tryptophan hydroxylase, the rate-limiting enzyme in the biosynthesis of 5-HT, causes hyperphagia and obesity. Medication that affects the central 5-HT system, such as locaserin, is effective in encouraging weight reduction [84-86].

The activation of central serotonergic transmission emerged as a treatment target for obesity well over ten years ago, based on the clear involvement of serotonergic transmission in eating habits and translational studies showing diminished serotonergic transmission in human obesity. Fenfluramine, sibutramine, and subsequently dexfenfluramine were all effectively marketed as therapies for obesity [87].

## Dopamine

Molecular imaging studies have shown structural dopamine abnormalities in human obesity, namely in the area of dopamine release and availability of the D2/D3 receptor. However, dopamine synthesis capacity and dopamine reuptake transporters have also been studied [88].The production and release of DA are regulated by steroid hormones, insulin, leptin, and other peripheral peptides [89].It seems that DA is connected to the control of food intake on both a short-term (individual meals) and long-term (hunger) time scale [90].

There are five distinct subtypes of DA receptors, which may be divided into D1- (D1, D3) and D2- (D2, D4 and D5) similar subtypes. The regulation of eating behaviour is significantly influenced by

both D1- and D2-like receptors. Reduced meal size through shorter eating sessions is the primary outcome of satiety signals, which are facilitated by DA's actions on D1 receptors.The key relationship between DA and D2 receptors is feeding rate.By shortening the length and pace of eating, a combination of DA agonists, such apomorphine, lowers appetite [91].

The gene that codes for the D2 receptors has received the majority of attention in human genetic research on the role of the DA system in obesity. Research conducted on laboratory animals has demonstrated that DA agonists normalised body weight in genetically obese mice (ob/ob) [92].Human studies have shown a higher prevalence ofthe Taq I A allele for the D2 receptors in obese individuals [93].Variants of the D2 receptor gene and the human obesity (ob) gene have been investigated in connection to obesity. When combined, these two polymorphisms explain around 20% of the variation in body mass index (BMI, which is calculated by dividing weight in kilogrammes by height in metres), especially in younger women [94].The Taq I A allele's correlation with less D2 receptors implies that fat people carrying the A1 allele could use food to raise their DA stimulation to a more tolerable level. This is in line with research showing decreased DA metabolite concentrations in cerebral fluid in bulimic individuals who have frequent binge episodes [95].

According to brain imaging studies on obese patients, there was less binding of the tracer [11C]raclopride, which is selective for D2 and D3 receptors, in the striatum of obese subjects compared to controls. This suggests that the availability of D2/D3 receptors is downregulated in obesity. Comparing overweight and obese individuals (BMI > 27 kg/m2) to controls, similar results were found [96-97].Results on differences in sex and gender in DA release are likewise conflicting. Female controls in a [123I] iodobenzamide SPECT scan responded to amphetamine with considerable DA release, while extreme obese women did not exhibit any meaningful change from baseline [98].

## CONCLUSION

Obesity is a global health issue that affects billions of people worldwide, with obesity rates three times higher than in the last forty years.Obesity accumulation is mathematically explained by an imbalance between energy intake and energy expenditure, which is controlled by the brain's central nervous system (CNS).The pathogenesis of obesity involves a loss of equilibrium between food intake and energy utilization. A chronic energy imbalance between excessive calorie intake and inadequate calorie expenditure is the primary factor causing obesity. The sympathetic nervous system (SNS) is involved in maintaining homeostasis, and parasympathetic input has the potential to modulate the aetiology of obesity. The vagus nerve links the brain and digestive system, producing over 30 neurotransmitters that stimulate the CNS.

The gut microbiome ferments non-digestible dietary fibers into short-chain fatty acids (SCFAs), which are important for metabolism. The chemical composition of the microbiome is also related to

dietary choline metabolism, and the SCFAs generated by gut bacteria influence GLP-1 release, inhibit the inflammatory immune response in the gut, and are implicated in insulin signaling linked to fat formation.Inflammation and intestinal permeability are indicators of obesity, as increased permeability allows bacterial byproducts to leak into the bloodstream and cause low-grade inflammation, a hallmark of obesity and insulin resistance.

Obesity is a complex condition influenced by various factors in the brain. The melanocortin system, composed of anorexigenic pro-opiomelanocortin (POMC) neurons and orexigenic agouti-related peptide (AgRP) neurons, plays a crucial role in controlling energy balance. These neurons are located near the third ventricle and median eminence, and can recognize and react to various hormonal and nutritional signals. Fasting and other negative energy balance conditions activate AgRP/NPY neurons, while positive energy balance states activate POMC neurons. AgRP/NPY neurons control feeding through GABA, NPY, and NP. Leptin, a hormone produced by white adipose tissue, is closely linked to energy status and can reduce food intake while increasing energy expenditure. Insulin, a hormone that regulates peripheral metabolic signals, is more readily present in the central nervous system due to its blood-brain barrier receptors. Ghrelin, a hunger hormone, decreases POMC neurons and activates NPY and AgRP neurons in the arcuate to increase appetite. Ghrelin therapy enhances hunger, food intake, and weight gain by acting on both the central and peripheral nervous systems.

Obesity and neuroinflammation are linked to the buildup of glial cells in the brain and spinal cord, which results in neuronal death. Obesity leads to a decrease in grey matter in control areas such as the inferior frontal gyri, right insula, left and right precentral gyri, left middle frontal gyrus, left middle temporal gyrus, left amygdala, and left cerebellar hemisphere, while an increase in grey matter is seen in the left inferior occipital gyrus, left middle frontal gyrus, and left cuneus. Obesity also leads to alterations in white matter areas, such as the superior and inferior longitudinal fascicles, corpus callosum, uncinate fascicle, internal capsule, corticospinal tract, inferior front-occipital fascicle, corpus callosum, and cingulum.

More than 100 identified neurotransmitters are involved in synaptic transmission and control physiological processes in the central and peripheral nervous systems. The reward pathway, which includes the VTA, the nucleus accumbens (NAc) of the ventral striatum, and the CeA, participates in the interplay between hedonic and homeostatic control of food intake. Obesity-related disruptions in serotonergic signalling occur in both humans and animals.

The activation of central serotonergic transmission emerged as a treatment target for obesity over ten years ago, based on the clear involvement of serotonergic transmission in eating habits and translational studies showing diminished serotonergic transmission in human obesity.Molecular imaging studies have shown structural dopamine abnormalities in human obesity, specifically in the area of dopamine release and availability of the D2/D3 receptor. Dopamine is connected to the control

of food intake on both short-term and long-term time scales. There are five distinct subtypes of DA receptors, with the regulation of eating behavior significantly influenced by both D1- and D2-like receptors. The key relationship between DA and D2 receptors is feeding rate, with a combination of DA agonists like apomorphine lowers appetite. The Taq I A allele, which codes for the D2 receptors, has been linked to obesity, with variations explaining around 20% of the variation in body mass index. Brain imaging studies on obese patients show less binding of the tracer [11C]raclopride, suggesting downregulation of D2/D3 receptors in obesity.

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