Indo Global Journal of Pharmaceutical Sciences, 2024; 14: 1-10

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

Pathophysiology of Obesity: An Extensive Review

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Received: 11.05.2020
Accepted: 20.08.2022
Published: 13.06.2024
Keywords
Obesity, Pathophysiology, Neural, Genetic Epigenetic.

ABSTRACT: Obesity refers to a medical condition where excess adipose tissue accumulates in the body to such an amount that it leads to more than 20 percent of the ideal body weight. Obesity develops due to a chronic energy imbalance between calorie consumption and expenditure. Obesity enhances the chance of different types of diseases such as cardiovascular diseases, Type 2 diabetes, gall stones, obstructive sleep apnea, specific types of cancer, osteoarthritis, depression, obstetrical risks, gout and so on. Excess body fat causes breathlessness on mild to moderate exertion. A combination of different factors such as excessive food intake, especially fast food, sedentary life style, and genetic factors increases obesity risk. To control obesity, it is imperative to create efficient therapy plans and proactive initiatives, both of which will depend on a thorough knowledge of the pathophysiology of obesity. This review paper summarizes the pathophysiology behind obesity, which mainly includes endocrinal, genetic, epigenetic, neural, metabolic, lifestyle factors, micro-environmental factors. Understanding the pathophysiology of the rising trend of obesity epidemic requires a thorough understanding of the systems which can control energy balance in our body. Scientists are working to gain deep knowledge on the pathophysiology of obesity in order to develop effective therapy strategies for this condition, as well as to better influence the development of public policy in favour of public welfare and obesity awareness in ways that can minimise the detrimental effects of obesity on community health and economy.

INTRODUCTION

Obesity is a serious public health issue where excessive fat is deposited in the body, which may develop adverse consequences for health. A subject will be considered obese when the Body Mass Index exceeds 30 kg (kilogram)/m^2 (meter^2) [1]. Although the Body Mass Index is regarded as a helpful tool for classifying individuals into the categories of Underweight, Overweight, or Obese and measuring the population's susceptibility to obesity-related complications, it is not a dependable anthropometric method for determining the fatness of the body because there are large fluctuations in total body mass. It is due to differences in skeletal muscle and other lean mass constituents among people. For instance, persons who have more muscle mass and whose body weight is more in relation to height will have a high Body Mass Index that may misclassify them as overweight or even obese [2]. Obesity opens the door to diseases, impairment, and early death. The chances of developing degenerative diseases like atherosclerosis, high blood pressure, stroke, diabetes, gall bladder diseases, gout, obstetrical risk, osteoarthritis of weight-bearing joints, and varicose veins are enhanced when a person has excess body fat [3]. Obesity is a primary cause of premature death that is becoming more and more prevalent in both adults and children around the world [4]. Recent data reveals that across the world, obese people are about 650 million, and overweight people are about 1.9 billion.

According to the estimate, 2.8 million fatalities are attributable to obesity [5]. Treating these illnesses can put additional strain on the healthcare system. Overall, medical costs are doubling every ten years, and the treatment of obesity complications and consequences poses a great problem for patients [6]. Numerous weight-loss methods have been tried to treat obesity, many of which have drawbacks. Therefore, emphasis should be placed on the development of correct preventive strategies and actions, which is possible only when we have a clear and thorough knowledge of the pathophysiology of obesity. The study of physiological dysfunctions that result from, cause, or are somehow associated with obesity is known as pathophysiology. To understand the pathophysiology of obesity, we have to

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DOI: http://doi.org/10.35652/IGJPS.2024.14001

understand the neural and endocrinal factors regulating energy balance [2, 7, 8]. The main objective of this review article is to increase our knowledge regarding the pathophysiology of obesity.

REGULATION OF FOOD INTAKE BY NEURAL CENTERS

Long-term stability of whole body mass and composition is feasible when a person's energy intake matches his or her energy expenditure. A sufficient supply of energy to the body must be maintained. Many short-term and long-term regulatory systems operate in our bodies to manage energy use, storage, and consumption. Several nerve centers within the hypothalamus play significant roles in controlling the amount of food we take. The lateral nucleus of the hypothalamus acts as a feeding center. When this area or center is stimulated, that leads to hyperphagia. When the lateral nucleus of the hypothalamus is damaged, cravings and hunger are lost. The lateral hypothalamic feeding center stimulates a drive to look for food. The ventromedial nucleus of the hypothalamus functions as the center of satiety. This area or center provides nutritional satisfaction and interferes with the feeding centers. The animal refuses to eat if this center works. The destruction of the ventromedial nucleus makes the subject obese, and the subject exhibits excessive and continuous feeding behavior [9, 10].

The paraventricular, dorsomedial, and arcuate nuclei of the hypothalamus additionally play a vital role in regulating the amount of food we take. Damage or lesions of paraventricular nuclei regularly induce excess food intake. When there is damage or a lesion in the dorsomedial nuclei, that usually reduces the urge for food consumption. The arcuate nuclei of the hypothalamus usually control food intake and energy expenditure. Numerous gastrointestinal hormones and hormones produced by adipose tissue are thought to function at this site [9, 11].

The hypothalamus receives neural signals from the gastrointestinal tract. These neural signals give sensory information that the stomach is full. Additionally, the blood's glucose, amino acids, and fatty acids carry molecular messages indicating satiety to the brain. Feeding behavior is influenced by the signals the hypothalamus receives from the cerebral cortex (sight, taste and smell). Feeding and satiety centers in the hypothalamus contain many receptors for various neurotransmitters and hormones, which significantly impact feeding behavior [9].

ROLE OF NEURONS AND NEUROTRANSMITTERS IN THE HYPOTHALAMUS IN FEEDING BEHAVIOR

The **arcuate nuclei of the hypothalamus** possess two categories of neurons. These two neurons play a significant role in controlling both hunger and energy expenditure.

1. **Pro-opiomelanocortin (POMC) neurons**: These produce an α-melanocyte-stimulating hormone (α-MSH) along with Cocaine and amphetamine-regulated transcript (CART). They have stimulatory signals to the ventromedial hypothalamus (VMH); the lateral hypothalamus (LH) gets inhibitory signals from these neurons.
2. **Neurons that generate orexigenic chemicals**: The second neuron category generates Agouti-related protein (AGRP) and neuropeptide Y (NPY). These chemicals provide stimulatory signals to the lateral hypothalamus (LH). These orexigenic chemicals provide inhibitory inputs to the ventromedial hypothalamus (VMH) [9, 10].

Activation of the Pro-opiomelanocortin (POMC) neurons leads to reduced consumption of foods and enhanced energy expenditure. On the other hand, activation of the Agouti-related protein (AGRP) and neuropeptide Y (NPY) neurons induces food intake and decreases energy expenditure. Our appetite is controlled by many hormones, which mainly include **Leptin, Insulin, Cholecystokinin (CCK),** and **Ghrelin**. These hormones appear to have significant effects on these two types of neurons. Many of the neurological signals and signals seem to come from the periphery that control energy reserves and converge in neurons in arcuate nuclei.

α-Melanocyte stimulating hormone (α-MSH) is released by Pro-opiomelanocortin (POMC) neurons. This hormone then acts on melanocortin receptors. These receptors are present mainly in the neurons belonging to paraventricular nuclei. Five Melanocortin receptor (MCR) subcategories were found. MCR-3 and MCR-4 control our consumption of food and energy balance. When these receptors are activated, food consumption decreases.

On the other hand, when MCR3 and MCR4 are inhibited, this hugely enhances food consumption and reduces energy expenditure. Melanocortin receptors (MCR) primarily activate the neural pathways that emerge from the paraventricular nuclei to the nucleus tractus solitarius. It ultimately stimulates sympathetic nervous system activity. Obesity develops when there is dysfunction in the melanocortin signaling pathway. One of the leading causes of obesity is the mutation of Melanocortin receptor-4 (MCR4). Activation of the melanocortin system leads to anorexia [9, 12].

Orexigenic neurons of the hypothalamus release Agouti Related Protein (AGRP), which is considered a natural antagonist of MCR3 and MCR4. It probably increases food intake by inhibiting the actions of α-Melanocyte stimulating hormone (α-MSH). Orexigenic neurons of the arcuate nuclei release neuropeptide Y (NPY). It is secreted when the body's energy reserves are poor. It mainly arouses our appetite. Simultaneously, the activation of pro-opiomelanocortin (POMC) neurons decreases, reducing the function of the melanocortin pathway and further triggering appetite. Our feeding, mainly appetite, is also controlled by other neural centers such as the amygdala and the prefrontal cortex. These centers are correlated with the hypothalamus. When the

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amygdala is destroyed, some areas enhance food intake, whereas others hinder food intake [9].

FACTORS THAT REGULATE THE QUANTITY OF FOOD TAKEN BY US

A. **Short-term regulation of feeding:** After taking a meal, when the stomach and duodenum are distended, stretch inhibitory signals initiate, primarily passed on through the vagi. Its function hinders the feeding center, so the person does not want to take food.

B. Cholecystokinin (CCK) is secreted primarily when fat enters the duodenum and directly affects the feeding centers to reduce further eating. Studies conducted on experimental animals reveal that Cholecystokinin (CCK) usually activates the melanocortin pathway in the hypothalamus, decreasing feeding behavior.

C. Peptide YY (PYY) is released from the gastrointestinal tract, particularly the ileum and colon. Food consumption stimulates the release of PYY. 1 to 2 hours after taking a meal, the level of PYY in the blood rises to peak levels. These maximum PYY levels are affected by the amount of calorie intake and food composition. The PYY level usually elevates after high-fat meals. PYY, when injected into experimental animals, they show reduced food intake for 12 hours or more.

D. After meals, when foods enter the intestine, they stimulate the release of Glucagon-like peptides. Glucagon-like peptide promotes the production and release of insulin from the pancreas, which again depends on the glucose level. Glucagon-like peptides and insulin are both involved in suppressing appetite. Epithelial cells present in the fundus part of the stomach produce ghrelin. The hypothalamus, pituitary, kidney, and placenta also produce smaller amounts of ghrelin. Ghrelin production rises while fasting and falls when the stomach is full. This hormone acts through the feeding region in the hypothalamus to increase appetite and food intake. It encourages emptying of the stomach. Ghrelin levels in the blood rise during a fast. Its level goes to a peak level just before food consumption and then falls rapidly after a meal. This phenomenon implies that ghrelin stimulates hunger. Experimental animals' food intake is increased when ghrelin is administered [9, 13].

E. **Long-term regulation of feeding:** Ventromedial and paraventricular nuclei of the hypothalamus possess glucoreceptor neurons. After a meal, when the blood sugar level elevates, these neurons start to fire. The hunger center of the lateral hypothalamus has glucosensitive neurons. Simultaneously, the activity of these neurons decreases after a meal.

When exposed to cold, the subject usually eats more. On the other hand, when exposed to heat, the participants prefer to consume fewer calories. Increased food intake in a cold animal has two significant beneficial effects: it speeds up its metabolism and helps it store fat, which is an insulator. The hypothalamus senses energy storage in our body through the actions of leptin. Production of leptin increases when adipose tissue volume increases. After crossing the blood-brain barrier, Leptin binds to its receptor at various sites of the hypothalamus. In the hypothalamus, the feeding center is inhibited by Leptin. As the feeding center is inhibited, the person's appetite is lost, and refuses to take food [9, 13].

LEPTIN AND OBESITY

Leptin is a peptide secreted by adipocytes (adipose tissue cells). It exerts its function by controlling the food intake and adipose tissue volume. This hormone also helps to maintain energy balance. Adipocytes secrete and release a large volume of leptin into the blood when the volume of adipose tissue increases. Leptin crosses the blood-brain barrier while circulating through the brain and enters the hypothalamus. In the hypothalamus, the feeding center is inhibited by leptin, which results in appetite loss (**Figure 1**). People stop food consumption. Usually, the cells present in the blood-brain barrier have many receptors like proteins. These receptors are essential in the transport of leptin across the barrier. Leptin regulates appetite, energy balance, and metabolism; therefore, understanding the cellular and brain mechanisms by which it works may potentially designate targets for therapeutic intervention in various disorders.

Mode of action of Leptin: Leptin exerts its role through some specific neuropeptides in the Hypothalamus.

1. **NeuropeptideY**: It is secreted in the small intestine, medulla, and hypothalamus. This peptide stimulates food consumption. Leptin usually inhibits the action of neuropeptide Y, which leads to cessation of food intake.
2. **Pro-opiomelanocortin (POMC)**: It is secreted from the hypothalamus, anterior pituitary, lungs, gastrointestinal tract, and placenta. Leptin stimulates the secretion of POMC because it reduces food intake [14].

Obese individuals usually have higher levels of leptin. A person with high body fat exhibits a high amount of leptin. It implies that leptin plays a significant role in correlating obesity and energy homeostasis. In obesity, sensitivity to leptin decreases. When sensitivity to leptin falls, that results in a loss of ability to detect satiety. Despite that, the subject shows high energy stores and a high quantity of leptin. Studies on both humans and animals have revealed that lack of leptin leads to severe hyperphagia. Hyperphagia promotes adipose tissue deposition in our body and thus enhances the chance of obesity [15]. Leptin replacement alleviates hyperphagia and obesity in leptin-deficient people [16]. Prolonged calorie restriction leads to a decrease in fat stores along with leptin secretion [17].

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Human obesity develops due to genetic deficiencies of leptin or its receptor known as the **Leptin receptor**. [2]. On the other hand, it has been found that obese individuals have elevated leptin levels in their plasma. This phenomenon enhances the chance of **Leptin resistance** [18]. Within the hypothalamus, different circuits present their role in integrating appetite; the Melanocortin pathway plays a significant role in this case [8]. Disruption of the leptin-melanocortin pathway can result in early onset of obesity phenomena [19].

Leptin regulates neuropeptide Y (NPY)/Agouti-related protein neurons (AgRP) and Pro-opiomelanocortin (POMC)/ Cocaine and amphetamine-regulated transcript neurons (CART) in the arcuate nucleus of the Hypothalamus. Leptin has an inhibitory effect on the NPY/AgRP group, while it has a stimulatory effect on the POMC/CART group. When the Pro-opiomelanocortin (POMC) neurons are activated, the person's food consumption decreases and expenditure of energy increases. When the Agouti-related protein (AGRP) and neuropeptide Y (NPY) neurons are inhibited, the food intake of the subject is reduced, and energy expenditure is increased [6, 7, 8].

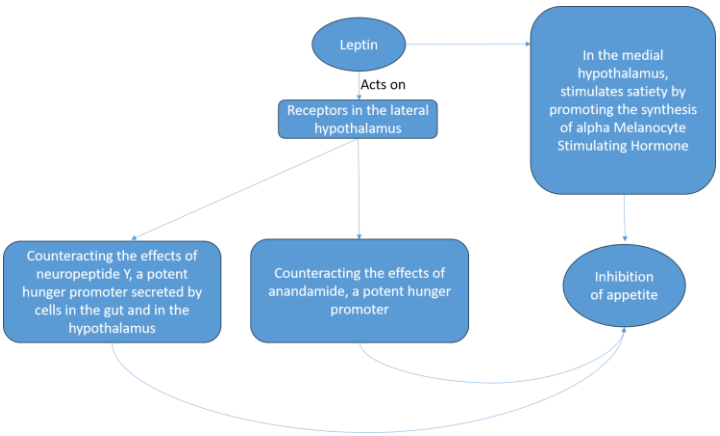

Figure 1. Effects of Leptin

Besides, Leptin promotes the production of Corticotropin, a releasing hormone that reduces food intake. Leptin also increases metabolic rate and energy expenditure by increasing sympathetic nerves' activity. It seems to work via neural projections from the hypothalamus to vasomotor centers. Leptin plays a role in reducing energy storage by decreasing insulin secretion from the pancreas [9].

When leptin activity falls, glucose production in the liver also increases. There is no glucose uptake by muscles. Low leptin levels disrupt many brain processes that affect mood and behavior and promote looking for or consuming food. These physiological and behavioral responses do not occur in a person who is in a negative energy balance [17].

Leptin works through the Leptin receptor (LepRb). Antagonizing the Leptin receptor (LepRb) causes lean and diet-induced obese mice to gain weight and eat more. The two conditions linked to a lack of leptin signaling are leptin resistance and leptin deficiency. This disorder causes hyperphagia and is considered critical in the emergence of obesity [8, 14, 17].

Leptin receptor (LepRb) is a type I cytokine receptor that belongs to the IL-6 receptor family. When Leptin binds to its receptor, it activates Janus kinase-2 (JAK2) tyrosine kinase, which encourages the tyrosine phosphorylation of the Leptin receptor (LepRb) and related proteins. Various downstream signaling molecules are activated by various Leptin receptor (LepRb) tyrosine phosphorylation sites. Leptin receptor (LepRb) begins the activity of latent transcription factors of the Signal transducer and activator of the transcription (STATs) family, which causes them to become phosphorylated and activated [17, 20, 21].

The signal transducer and activator of transcription-5 (STAT5) is not mandatory but helps other cytokines to regulate energy balance. In Pro-opiomelanocortin (POMC) and Agouti-related protein (AgRP) neurons, loss of Signal transducer and activator of transcription-3 (STAT3, which is required for LepRb signaling and leptin activity) has very modest effects on body weight and food consumption. The tyrosine phosphatase of Protein Tyrosine Phosphatase Non-Receptor Type 11 (PTPN11), which is implicated in Extracellular signal-regulated kinase (ERK) signaling, is likewise activated by Leptin receptor (LepRb). Protein Tyrosine Phosphatase 1B (PTP1B) and T-cell phosphatase (TCPTP) are two tyrosine phosphatases, dephosphorylate Janus kinase-2 (Jak2) and Leptin receptor (LepRb), inhibiting their activity, reducing the action of leptin [17].

Leptin receptor (LepRb) neurons are located in the dorsomedial portion of the ventromedial nucleus (VMN) of the Hypothalamus which expresses the transcription factor, Steroidogenic factor-1 (SF1) Nuclear Receptor Subfamily 5 Group A Member 1 (Nr5a1) and the neuropeptide pituitary adenylyl cyclase-activating protein (PACAP) (Adcyap). LepRb excision in SF1/PACAP neurons does not significantly alter energy balance. Given a pleasant high-fat meal, a subject is less able to raise their energy expenditure, which encourages obesity [17, 22, 23].

Our food intake is regulated by two variables working together. One system is the brain's motivational circuits, which mediate the desire for food and the beginning of eating, and the other system induces satiety to stop eating. Food deprivation enhances subjects' motivation, increasing their locomotor activity and behavior in their food quest. The mesolimbic dopaminergic (DA) system controls this type of behavior. This system plays a crucial role in increasing the amount of work an animal is prone to do to reap food. A group of dopaminergic (DA) neurons that are part of this system are found in the midbrain's ventral tegmental region (VTA).

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The enzyme involved in the committed step of dopamine production is Tyrosine hydroxylase in the ventral tegmental area (VTA tyrosine hydroxylase). Leptin controls this enzyme and thus modulates the mesolimbic dopaminergic (DA) system. Leptin also controls Dopamine (DA) reuptake and extracellular dopamine (DA) concentration in the nucleus accumbens (NAc) [17, 24].

GHRELIN AND OBESITY

Ghrelin is well-known as the hunger hormone (**Figure 2**). It is produced by enteroendocrine cells in the gastrointestinal tract, particularly the stomach, where it causes an increase in food intake [25]. Besides controlling hunger, ghrelin is crucial in controlling energy balance [26]. Ghrelin is secreted when the stomach is empty (before meals). Ghrelin production stops after eating when the stomach is expanded. Ghrelin enhances stomach motility and acid release by encouraging eating. The neuropeptide Y neurons that start appetite are activated by ghrelin, which activates adenohypophysis cells and the hypothalamic arcuate nucleus [25]. Ghrelin binds to the hypothalamus's Growth hormone secretagogue receptor (GHS-R). It is also known as the ghrelin receptor [27, 28]. The growth hormone secretagogue receptor works along with G protein, so it is a G protein-coupled receptor. Ghrelin receptors are expressed in particular neurons coexpressing NPY and AgRP, mainly found in the ventromedial and arcuate nuclei [29]. Ghrelin has been associated with triggering appetite and feeding habits. Stomach vagal afferents' reactivity is decreased by ghrelin, making them less sensitive to gastric distension, which typically happens after eating [30]. Lack of sleep raises ghrelin levels and lowers leptin levels, leading to increased hunger and obesity. Although leptin and ghrelin share many of the common central nervous system (CNS) nuclei, leptin and ghrelin receptors have different effects. These hormones usually work on the same population of neurons, which causes changes in food consumption and energy investment [31].

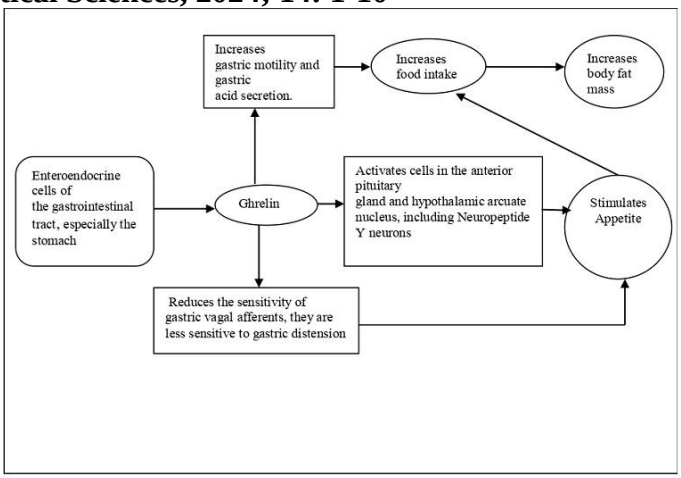

Figure 2. Effects of Ghrelin

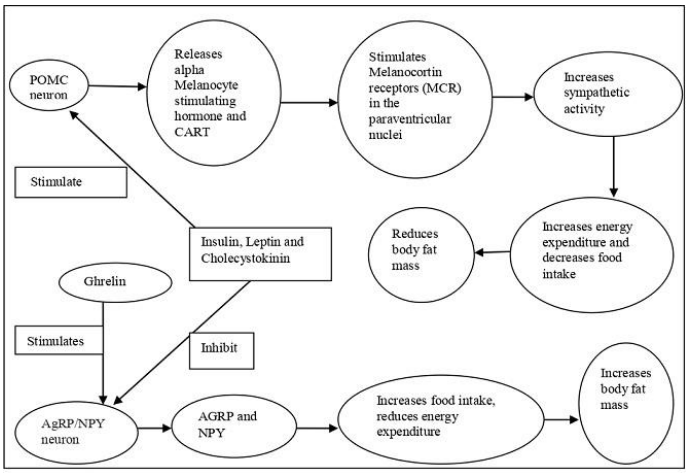

Figure 3. Control of Energy Balance. POMC: Pro-opiomelanocortin; AgRP: Agouti-related protein; NPY: neuropeptide Y; CART: Cocaine and amphetamine-regulated transcript

INSULIN AND OBESITY

On the surface of many cells, mainly adipocytes and myocytes, the enzyme lipoprotein lipase is present, hydrolyzing acylglycerides still attached to circulating apolipoprotein. Additionally, it influences how fatty acids are separated, affecting both the absolute and relative fat amounts [32]. Lipoprotein lipase (LPL) deficiency leads to hypertriglyceridemia (increased triglyceride levels in the circulation) [33]. Overexpression of Lipoprotein lipase (LPL) causes insulin resistance in mice, which results in obesity [34, 35].

Insulin resistance appears in obese people, and the term implies that obesity may impede insulin-mediated nutritional feedback [36]. Refined and simple sugars, in particular, are capable of promoting hyperinsulinemia. As a result, glucose and fatty acids are directed to adipose tissue. Fat deposition is accelerated by glucose and fatty acid entry into adipocytes. In addition, hyperinsulinemia lowers the levels of circulating metabolic substrates, which prompts the need for food. These dietary components usually lower energy expenditure, enhancing fat deposition in our body [2]. Peripheral insulin may indirectly trigger food consumption by lowering plasma glucose and free fatty acid levels [36].

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MEAL-INDUCED SECRETION OF GUT-DERIVED PEPTIDES, SUCH AS GLUCAGON-LIKE PEPTIDES AND CHOLECYSTOKININ, AND ITS ROLE

Gut-derived peptides such as Glucagon-like peptides and Cholecystokinin are usually released from the gastrointestinal tract after a meal. These are released explicitly from the enteroendocrine cells in the gastrointestinal tract. These hormones bring about satiety by triggering the activity of an ascending visceral sensory circuit. This particular circuit starts to work with vagal afferent neurons that transfer gastrointestinal signals to the hindbrain, including the nucleus of the solitary tract (NTS). The nucleus of the solitary tract (NTS) neuron then excites the lateral parabrachial nucleus. Of particular significance are:

1. Parabrachial nucleus (PBN) neurons that express calcitonin gene-related peptide (CGRPPBN) play a fundamental role in regulating appetite.
2. Neurons which are found within the external lateral subnucleus of the parabrachial nucleus.

Food consumption leads to gastric distension and the release of cholecystokinin and glucagon-like peptides. As calcitonin gene-related peptide (CGRPPBN) neurons are activated, physiological satiety develops, and the person cannot take more food. Prolonged activation causes anorexia. By suppressing CGRPPBN neurons, hypothalamic AgRP neurons appear to stimulate feeding. CGRPPBN neurons, when inactivated, increase meal size and shut off the meal-induced satiety effects of cholecystokinin and glucagon-like peptides [2].

Fat cell enlargement occurs when subjects intake excess energy. Altered amounts of many peptides and nutritional signals cause the clinical manifestation of obesity. These are caused by fat cell enlargement [37].

Genetic influence: Common categories of genetic factors for obesity include:

1. **Single gene mutations called monogenic:** These are usually found in the Leptin-Melanocortin pathway. Many of the genes associated with monogenic obesity, including Agouti-related peptide, PeptideYY, and Melanocortin 4 receptor, usually interfere with the system that regulates our appetite and weight.
2. **Syndromic obesity**: It is a severe form of obesity. Neurodevelopmental abnormalities usually lead to this type of obesity. This type of obesity also develops from other organ/system malformations. Alteration in a single gene or a larger chromosomal part covering many genes also leads to obesity.
3. **Polygenic obesity**: The effects of many genes contribute to this type of obesity. These genes allow people to favor food, and that increases the chance of their calorie intake. The problems usually seen in this type of obesity are increased hunger levels and reduced satiety. In this type of obesity, people tend to store body fat.

Mutation in ob and db genes (ob encodes leptin and db encodes leptin receptor) leads to obesity. These, in turn, guide identifying molecular/ cellular signaling pathways (**Figure 3**):
Leptin (LEP) → Leptin Receptor (LEPR) → Pro-opiomelanocortin (POMC),
Agouti-related peptide (AgRP) → Proconvertase Enzyme (PC1) → Melanocortin Receptor 4 (MC4R)

Interactions between many risk alleles or between these risk alleles and different environmental factors raise the chance of obesity. The obesity risk, mostly connected with low levels of physical activity, is greatly influenced by the interaction between genetic predisposition and lifestyle traits.
Diet composition and levels of physical activity greatly influence the effect of obesity risk alleles. These specific alleles belong to the Fat mass and obesity-associated protein (FTO) gene. Besides, variations in the single base pair sequence in non-coding portions of the first intron of the FTO gene have an intimate relation with human obesity. The risk of obesity is primarily influenced by sequence variation in non-coding genome regions [2].

Prader-Willi syndrome (PWS) is the most prevalent genetic cause [37]. Imprinting, an epigenetic phenomenon, is one of the causes of PWS. It is brought on by the deletion of the paternal copies of the SNRPN and NDN necdin genes along with groups of snoRNAs: SNORD64, SNORD107, SNORD108, and two copies of SNORD109, 29 copies of SNORD116 (HBII-85) and 48 copies of SNORD115 (HBII-52). These are found on chromosome 15, located in the region 15q11-13 [38]. A random mutation often results in the deletion of the PWS/AS area (Angelman syndrome). The copies of these genes inherited from the mother are essentially silenced by imprinting. Only the paternal copies of the genes are revealed. PWS results if there is a loss of paternal copies of this specific region [39].

Tumour Necrosis Factor (TNF) is a cytokine communicating information from fat to brain cells. Insulin-resistant obese individuals have higher levels of TNF in their adipose tissue [40]. Uncoupling Protein (UCP-2), a protein that uncouples oxidative phosphorylation in the fat cells of white adipose tissue, has been suggested not to function in obese people [41]. Obesity may result from alteration in Peroxisome Proliferator-Activated Receptors (PPAR) transcription factors. These transcription factors promote fat accumulation (lipogenesis). These transcription factors control the genetic expression of some specific enzymes that maintain lipid and glucose homeostasis. Peroxisome Proliferator-Activated Receptors (PPAR) gamma are mainly present in adipose tissue and have

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coadjuvant effects with CCAAT-enhancer-binding protein (C/EBP) alpha, another transcription factor. All of this works to transform pre-adipocytes into adipocytes. The gene coding for Uncoupling Protein (UCP) in white adipose tissue has regulatory sites for Peroxisome Proliferator-Activated Receptors (PPAR) gamma and CCAAT-enhancer-binding proteins (C/EBP) alpha [42].

Obesity also develops when serotonin signaling in the hypothalamus does not work correctly. Generally, negative feedback results from ingested energy from food [43]. When serotonin signaling does not work, this negative feedback does not result, which promotes excessive calorie consumption. Serotonin can turn on the anorexigenic α-melanocyte-stimulating hormone (α-MSH), a product of pro-opiomelanocortin (POMC) neurons, and turn off the orexigenic neuropeptide Y (NPY) and Agouti-related peptide (AgRP) neurons that are present in the arcuate nucleus of the hypothalamus [44].

The presence of the A1 allele of the Dopamine receptor D2 (DRD2)/ Ankyrin repeat and kinase domain containing 1 (ANKK1) Taq1A polymorphism in humans is associated with lower dopamine D2 receptor (D2/3R) available for function [45], thus increasing the chance for the development of obesity [46].

Endocrinal Disorders lead to obesity: Some endocrine disorders are associated with increased body fat, such as Cushing's syndrome, polycystic ovary disease, and growth hormone deficiency. In addition, when a sedentary subject is exposed to a high-fat diet, it enhances the chance of obesity development [37].

ROLE OF EPIGENETIC MODIFICATION IN OBESITY

Epigenetics is the study of heritable changes that affect the function of genes without modifying the DNA sequence [47]. Tissue-specific epigenetic markers are present. Epigenetic marks include DNA methylation and modification of histones, which turn on biological phenomena such as imprinting. Many of these imprinted genes include growth factors or regulators of gene expression controlling growth. Imprinting disorders are associated with increasing the risk of obesity [48].

Genomic imprinting controls the expression of alleles following their maternal or paternal ancestry [48]. Genomic imprinting balances the expressions of the parental alleles that influence growth [49]. It impairs the growth effects of paternal and maternal genomes [50]. Genetic phenomena such as translocation, inversion, duplication, paternal disomy, and hyper/hypo-methylation can cause imprinting failures that lead to obesity. This imprinting failure results from altering the expression of growth and cellular differentiation factors [51]. In Albright hereditary osteodystrophy (AHO), moderate obesity appears due to upsetting of imprinting on the Guanine Nucleotide binding protein, Alpha Stimulating activity polypeptide (GNAS) gene [49].

In the first trimester of pregnancy, early epigenetic modifications may contribute to an increased risk of obesity in undernourished expectant mothers. The detrimental metabolic effects of undernutrition during the gestational period of mice can be mitigated by methyl donor supplementation. During the periconceptional stage, methylation status is susceptible to undernutrition. Due to a folate shortage, homocysteine levels typically stay high. High homocysteine levels prevent DNA methylase1 from being expressed (a vital enzyme for maintaining methylation during mitosis). During pregnancy, folic acid supplementation can counteract these effects. Human studies have demonstrated that imprinted genes and metastable alleles Pro-opiomelanocortin (POMC) are hypomethylated in a person who is severely undernourished early in gestation; however, this does not occur when the pregnant lady is undernourished just in late gestation.
Epigenetic alterations in pro-opiomelanocortin (POMC) promoters affect the hypothalamic feeding circuits that destroy the response to leptin, which leads to both weight increases and biological defenses against elevated body weight. In the infants of underweight mothers, thousands of hypomethylated loci have been discovered in genome-wide epigenomic research. Additionally, some Endocrine-disrupting chemicals (EDCs) can cause hypomethylation, which can be reversed by adding maternal methyl donor supplementation. Obesity originates from defective genomic imprinting caused by hypomethylation [2].

The risk of obesity increases in offspring if their mothers remain obese during pregnancy. Newborns from obese mothers usually show decreased methylation of a developmental gene (Znf483) that encourages the differentiation of adipocytes. Consequently, it enhances the adipogenic potentiality of white adipose tissue, which ultimately increases the risk of obesity [2].

Slow metabolic rate and Obesity: Energy expenditure (EE) is made up of three components: resting metabolic rate (RMR), activity-related energy expenditure (AEE), and diet-induced thermogenesis (DIT). A slow metabolic rate is associated with reduced resting metabolic rate (RMR), activity-related energy expenditure (AEE), and/or diet-induced thermogenesis (DIT). A slow metabolic rate causes a positive energy balance, resulting in weight rise. Obesity causes an increase not only in fat mass but also an increase in lean body mass. Additionally, obesity is connected with a more prolonged absorptive state and higher absolute activity-related energy expenditure (AEE), complicating the duration of DIT measurement. People with low resting metabolic rate (RMR) for their current body size acquire weight [36].

Cite this article as: Das, B.; Khaled, K.L. Pathophysiology of obesity: An extensive review. Indo Global J. Pharm. Sci., 2024; 14: 1-31.
DOI: http://doi.org/10.35652/IGJPS.2024.14001

Sympathetic Nervous System Activity and Obesity: The sympathetic nervous system (SNS) controls body weight homeostasis. When SNS activity is altered, obesity develops. Increased SNS activity is associated with carbohydrate overfeeding. The activity of the SNS is influenced by leptin and insulin. These results imply that the SNS is involved in maintaining energy homeostasis. The sympathetic nervous system has some specific impacts on metabolism. It stimulates the release of insulin from the pancreas, lipolysis of adipose tissue, glucose uptake by skeletal muscle, and mobilization of liver glucose. When SNS-mediated adipose tissue lipolysis declines, it signals increased lipid storage and, as a result, weight gain [36].

Energy Intake and Obesity: Homeostatic and hedonic pathways are two systems that control food intake. The homeostatic pathway triggers feeding behavior when energy reserves are poor. The centers of this pathway are the hypothalamus and brainstem. Different central and peripheral signals—such as concentrations of various circulating nutrients, gastrointestinal hormones, insulin, leptin, and signals from vagal afferents—are integrated to initiate feelings of hunger vs satiety and to modify feeding behavior. The hedonic or reward-based pathway might override the homeostatic system. Obesity develops when the balance between the hedonic and homeostatic regulatory systems is not maintained [36].

Circadian Rhythms and Obesity: All biological processes, including gene expression and apoptosis, are coordinated by circadian clocks in a rhythmic 24-hour periodicity. The central circadian clock is located in the Central Nervous System, specifically in the hypothalamus's suprachiasmatic nucleus (SCN). The circadian rhythm gets disrupted when an alteration occurs in the timing of food intake and diet composition. The disruption of the circadian rhythm also increases the risk of metabolic disorders. In animals, weight gain occurs due to changes in the circadian rhythm.

Consequently, (night) shift workers are at greater risk of obesity and disorders associated with obesity. Time of feeding has a significant influence on body weight. Modifying the feeding time alone can notably affect body weight [36].

Environmental Factors and Obesity: Obesity pathogenesis results from an interaction between environmental and genetic factors. Injury from trauma or incision and destructive lesions in the region of the ventromedial or the paraventricular nuclei can increase the risk of obesity. Some drugs (phenothiazines; chlorpromazine, antidepressants; amitriptyline, antiepileptics; valproate, steroids; glucocorticoids, antihypertensive agents; terazosin) may enhance the chance of obesity development [52].

Smoking cessation and Obesity: Weight gain occurs when someone stops smoking because of the removal of the pharmacological effects of nicotine to suppress food consumption. Nicotinic acetylcholine receptors are located on hypothalamic Pro-opiomelanocortin (POMC) neurons. Smokers cannot consume more food when these receptors are activated. Receptors are not activated when smokers quit smoking. This phenomenon consequently motivates people (who quit smoking) to take more food and, ultimately, weight gain results [2, 53].

Gut Microbiome and obesity: The host immune system highly depends on the gut microbiome. Changes in gut flora can bring on intestinal lining inflammation. The toll-like receptors, which recognize and destroy host microorganisms, mediate this response. Toll-like receptor (TLR5) recognizes bacterial Lipopolysaccharides in the cell walls of gram-negative bacteria. Compared to wild-type controls, the body mass of TLR5-eliminated mice increased by 20%, while the size of their epididymal fat increased by 100%. Short-chain fatty acids are formed by the microbiome-induced fermentation of dietary fiber and starch in the lower intestine. These short-chain fatty acids can control the production of gut hormones such as Peptide YY, Glucagon-like peptide-1, and Glucagon-like peptide-2. Enzymes involved in the signaling pathways for glucose are downregulated in obese individuals. Changes in specific microbial populations lead to alteration in enzyme synthesis and short-chain fatty acid synthesis, which affect insulin and glucose homeostasis and thus increase the chance of the onset of obesity [2].

CONCLUSION AND FUTURE PROSPECTS

An impaired brain circuit, along with neuroendocrine feedback, is related to pathological overeating and physical inactivity, which leads to obesity. The detrimental impacts that are imposed on human health due to obesity emphasize the need for a thorough understanding of the pathogenesis of obesity. The above-mentioned factors will help us develop a brief knowledge of energy homeostasis, positive energy balance, and food intake. We can develop preventive strategies only when we have a thorough and clear understanding of the pathophysiological mechanisms behind obesity. Such information is a probable prerequisite for their successful treatment.

Additionally, more pathophysiological explanations for obesity must be developed. We know that endocrine-disrupting chemicals (EDCs) significantly impact the activities of genes crucial for regulating adipocyte and energy homeostasis. Establishing the mechanisms through which EDCs cause obesity in humans and animals is the focus of future research. Besides, the effects of the interactions between environmental and genetic factors on obesity development need to be clearly revealed. More studies are needed to find behavioral modification strategies that are practical and accessible to people from various backgrounds. More research needs to be

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done to create safer, more effective drugs to assist obese people lose weight and maintain their ideal body weight.

ACKNOWLEDGEMENT

The Authors thank the Department of Home Science, University of Calcutta, for continuous encouragement. The author would like to thank the reviewers for their valuable comments.

CONFLICTS OF INTEREST

There is no conflict of interest regarding the review article.

AUTHOR'S CONTRIBUTION

The corresponding author would like to thank Dr. Kazi Layla Khaled, Associate Professor, Department of Home Science, University of Calcutta, for continuous support and guidance. The guide helps the corresponding author in each step of manuscript preparation.

FUNDING SOURCE

There is no funding source for this review article.

ETHICS STATEMENT

The authors have taken all necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. Journal and publisher will not be responsible for copyright infringement or plagiarism issues.

DATA AVAILABILITY

Not applicable.

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Cite this article as: Das, B.; Khaled, K.L. Pathophysiology of obesity: An extensive review. Indo Global J. Pharm. Sci., 2024; 14: 1-31. **DOI**: http://doi.org/10.35652/IGJPS.2024.14001

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Indo Global Journal of Pharmaceutical Sciences(ISSN 2249 1023; CODEN- IGJPAI; NLM ID: 101610675) indexed and abstracted in CrossRef (DOI Enabling), CNKI, EMBASE (Elsevier), National Library of Medicine (NLM) Catalog (NCBI), ResearchGate, Publons (Clarivate Analytics), CAS (ACS), Index Copernicus, Google Scholar and many more. For further details, visit http://iglobaljournal.com

Cite this article as: Das, B.; Khaled, K.L. Pathophysiology of obesity: An extensive review. Indo Global J. Pharm. Sci., 2024; 14: 1-31.
DOI: http://doi.org/10.35652/IGJPS.2024.14001