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# A REVIEW ON OBESITY AND ITS REGULATORY HORMONES

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**ABSTRACT:** Obesity is related with a number of metabolic difficulties, growing obesity may disrupt hormonal and metabolic systems, which may lead to the body storing extra energy in a variety of forms. The amount of total energy the body has stored as fat is negatively associated with the rate at which leptin circulates in the bloodstream, which is predominantly produced by adipose tissue. It is widely accepted that central serotonin contributes to the inhibition of hunger in mammals and recent reviews have elucidated the mechanisms behind these effects. The hypothalamus regulates hunger as well as energy homeostasis. The digestive tract and adipose tissues are just two examples of peripheral afferent signals that complex brain networks combine to create efferent responses that regulate food intake and energy use. Origin of ghrelin in the circulation is the abdomen and gut. Dopaminergic circuits are used to control intake of food, according to research on human brain imaging. According to the carbohydrate-insulin paradigm, adipose tissue's endocrine dysregulation rather than acting as a passive fat-accumulator as a result of overeating is the primary source of positive energy balance. Studies on mice and rats show that GLP1RA enhances energy expenditure, which results in the reduction in weight in preclinical testing. GLP-1 has considerable and powerful effects on gastric acid production and stomach emptying.

**INTRODUCTION:** Obesity is connected with a variety of metabolic issues; developing obesity may alter hormonal and metabolic functions, which may lead to the body storing extra energy in a variety of forms [1]. Since, Asian Indians exhibit a typical phenotype of obesity with a low Body Mass Index but with central obesity, BMI is unrecognized to be a reliable indicator of obesity in this population.

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According to certain theories, visceral fat in the abdominal area is more crucial to metabolism than other fat depots. Appropriately, it is accepted that measuring abdominal adiposity using waist circumference is more accurate at predicting metabolic diseases than measuring gross adiposity using BMI [2].

It is now well accepted that fat tissue will function as an endocrine organ, which secrets a wide range of growth factors, hormones, cytokines, matrix proteins, enzymes and additional factors also a diversity of systemic and local actions [3]. Studies on both humans and animals have revealed that manipulating serotonin alters eating actions. A crucial neurotransmitter in the homeostatic system

is serotonin [4]. In order to make up for lesser reward experiences, decreased dopaminergic signalling, which generally carry the satisfying components of stimuli related to food, encourages excess consumption of tempting food more what is necessary for homeostasis [5].

The gastric fundus is where ghrelin, the sole orexigenic / hunger hormone, is predominantly made. Its levels rise during fasting and the sympathetic nervous system may be able to regulate its secretion. Its secretion is reserved postprandially or in response to nutrient intake [6].

White adipose tissue mostly secretes leptin. Circulating levels are a hormonal indicator of bodily energy storage and matched up with fat mass. Insulin-mediated nutritional feedback may be weakened in this state because insulin resistance, a feature of obesity and brain disease, can arise [7, 8].

**Leptin:** Leptin is an adipocytokine, an amino acid chain that acts as a chemical messenger and was bring to light in 1994. Adipose tissue and gastric mucosa are two of the main leptin producers and secretors. Leptin promotes satiety and is essential for preserving a healthy energy equilibrium and weight [9, 10].

**Physiology of Leptin:** Leptin is principally made by adipose tissue and spreads in the bloodstream at a rate inversely correlated with the total aggregate of energy the body has stored as fat [11].

After only three days of fasting, leptin levels drop to 10% to 20% before adipose tissue falls to this range. Leptin levels are subordinate modulate by a number of other factors and are very delicate towards acute changes due to intake of calorie. Leptin mainly affects the brain, with peripheral effects coming second [12, 13].

A feedback signal that takes into account the body's energy availability controls leptin levels. Suppression of leptin gene expression is usually related to situations where low or high energy is needed like fasting subjection to the cold, type 1 diabetes with methionine restriction, or exercise [14].

When leptin levels are brought back, neuro-endocrine adaptations to various physiological situations, like fasting (for example, elevated corticosterone and adrenocorticotropic hormone, low thyroid hormone), can be back pedal or greatly muted.

On the other hand, elevated leptin gene expression is connected to a high energy level, and circulating leptin has a positive correlation with adipose tissue mass [15].

Uncertainty persists concerning the essential regulatory mechanisms that govern leptin gene expression. One of the leptin promoter regions recently contained a unique binding site that is known as Peroxisome proliferator-activated receptor referred to as the peroxisome proliferator-activated receptor, which further limits the production of the leptin gene from fat tissue [16].

Many of the findings demonstrated that the leptin gene expression is repressed by the binding of Peroxisome proliferator-activated receptor with one or more unknown factors and that adipose tissue lipolysis may likely stimulate this factor.

Energy demand conditions are marked by adipose tissue lipolysis, which relies on 3-adrenergic receptor activation. Close to this, elevated sympathetic tone inhibits leptin gene expression via 3-adrenergic receptors [17].

To fully comprehend how leptin levels are related to physiological changes in food consumption and energy use, it may be important to grasp the newly discovered involvement of glucocorticoids in promoting starvation and intake of food in response to decreasing leptin levels.

Uncertainty surrounds the ways by which cerebral circuits control leptin gene expression. These circuits, which have been specified for brown adipose tissue (BAT) and probably differ from white adipose tissue (WAT) based on the anatomical separation of pre- and post-ganglionic inputs to BAT and WAT, will probably balance sympathetic tone in adipose tissue.

Furthermore, numerous studies have shown that distinct subgroups of arcuate nucleus (ARC) neurons influenced the modulation of substrate fluxes, leptin gene expression, and variations in sympathetic tone to adipose tissues [18, 19].

**Leptin Signalling:**

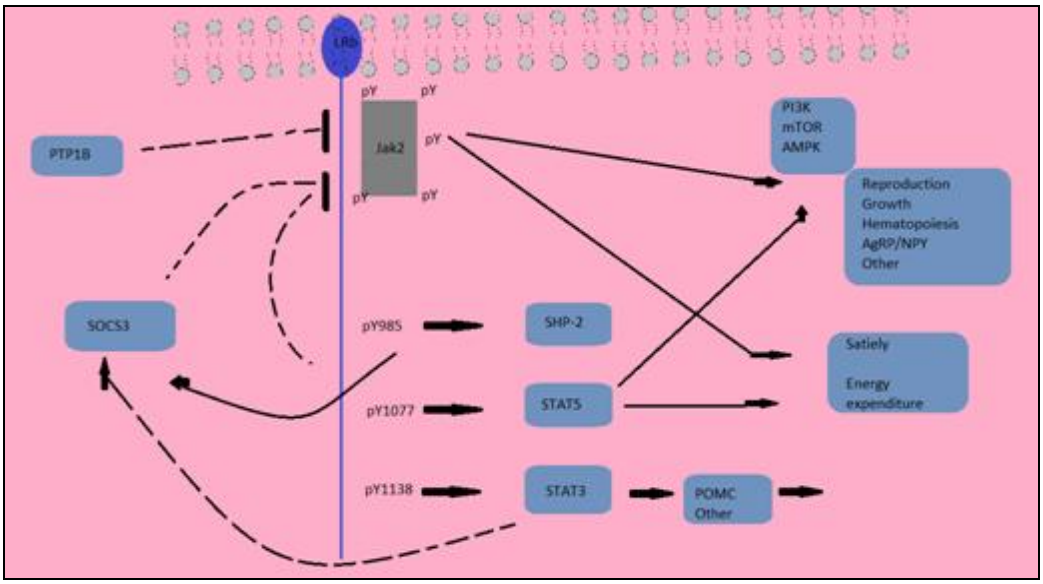


**FIG. 1: FEEDBACK INHIBITION, LEPTIN RECEPTOR SIGNALLING AND PHYSIOLOGY CONTROL. THE INTRACELLULAR LEPTIN RECEPTOR-ASSOCIATED JAK2 TYROSINE KINASE IS ACTIVATED BY BINDING OF LEPTIN TO THE EXTRACELLULAR DOMAIN OF LEPTIN RECEPTOR, THE ISOFORM OF THE FUNCTIONAL LEPTIN RECEPTOR. ON THE SURFACE OF TYROSINE RESIDUE, JAK2 GET AUTO PHOSPHORYLATE ALONG WITH THE PHOSPHORYLATION OF THREE TYROSINE FORMS ON THE INTRACELLULAR OF LEPTIN RECEPTOR: $Y_{985}$, $Y_{1077}$, AND $Y_{1138}$. IN ORDER TO MEDIATE TRANSCRIPTIONAL PROCESSES, SUCH AS THE PRODUCTION OF PRO-OPIOMELANOCORTIN (POMC) AND CYTOKINE INHIBITORY SUPPRESSOR SIGNALLING 3 (SOCS3) PROTEIN, $PY_{1138}$ ENLIST SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION (STAT) 3. $PY_{1077}$ ENLISTS AND CONTROLS STAT5'S TRANSCRIPTIONAL ACTIVATION. IN ADDITION TO BINDING TO SOCS3, $PY_{985}$ RECRUITS THE TYROSINE PHOSPHATASE SHP-2 AND CAUSES FEEDBACK SUPPRESSION OF LEPTIN RECEPTOR SIGNALLING (DOTTED LINES). ALTHOUGH NOT IN THIS WAY CONTROLLED BY LEPTIN, THE TYROSINE PHOSPHATASE PTP1B ALSO PREVENTS LEPTIN RECEPTOR /JAK2 SIGNALLING. UNCERTAINTY EXISTS REGARDING THE BIOLOGICAL PROCESSES THROUGH WHICH LEPTIN RECEPTOR RELATES TO THE CONTROL OF THE MTOR, PI3K, AND AMP-ACTIVATED PROTEIN KINASE (AMPK) PATHWAYS. LEPTIN REGULATES ANOREXIA AND ENERGY EXPENDITURE THROUGH $Y_{1138}$-MEDIATED STAT3 SIGNALLING THROUGH LEPTIN RECEPTORS (PERHAPS *VIA* POMC AND OTHER PATHWAYS). A FUNCTION FOR $Y_{985}$ AND SHP-2 IN INCREASING LEPTIN ACTIVITY HASN'T BEEN ESTABLISHED, DESPITE THE FACT THAT $Y_{985}$ OBVIOUSLY SERVES TO INHIBIT LEPTIN RECEPTOR SIGNALLING IN VIVO. LEPTIN INHIBITS NEUROPEPTIDE Y (NPY)/AGOUTI-RELATED PROTEIN NEURONS OF $Y_{1138}$ AND $Y_{985}$, POSSIBLY THROUGH TYROSINE SITES ON JAK2 OR THROUGH $PY_{1077}$. LEPTIN ALSO MEDIATES PERMISSIVE EFFECTS ON GROWTH, REPRODUCTION, HAEMATOLOGICAL EFFECTS (SUCH AS IMMUNOLOGICAL AND PLATELET FUNCTION) AND HEMATOPOIETIC EFFECTS**

**Besity-Related Leptin Resistance:** Leptin resistance is a notion that suggests mechanisms correlated with obesity interfere with leptin's functions, resulting in the development of heaviness and impeding the possible success of exogenous leptin treatment. Leptin resistance develops when leptin is unable to enter target cells, when LEP-R (leptin receptor) expression is down regulated, or when LEP-R signalling is deranged [20]. Genetic and molecular pathway may give chances to leptin resistance. Deprivation of functional changes in the leptin and its leptin genes have been set up despite their rarity. Flows in the route that control fat controller (leptin) production may be more typical processes. Leptin's effects on hunger (and body mass) are missing in a further fine or selective type leptin resistance (SLR), which has also been noticed. Autonomic (sympathetic) nervous system still shows effect of leptin. Intriguingly, SLR distinguishes obesity despite changes in leptin responses in food intake, heat production, and body weight by maintaining standard blood pressure (BP) and constant sympathetic nerve activity in the kidney [21]. For the development of SLR, two overlapping pathogenic processes have been hypothesized. Faults in

processes that control procedures that manage brain specified leptin effects, as well as defects in various leptin molecular signalling pathways that mediate selective as against to universal leptin action [22]. Furthermore, leptin acts on a limited number of interbrain place, all things appear to interrelate in the paraventricular hypothalamic nucleus (PVN), as opposed to insulin, which bring out change in SNA by action on the arcuate nucleus (ARC) as the single particular lot. Sexually dimorphic changes are among the chief impacts of insulin and leptin in obese states [23]. Current experimentation on the corelation in the middle sympathetic & sexual dimorphism in obese population of people has found that lean females have a number of changes that limit the ability of leptin and insulin to raise SNA and/or BP. Initially, proestrus leptin stimulates SNA due to the additional results of elevated oestrogen concentrations. Following leptin and insulin stimulate the increase of SNA in men, they do not in women, who experience vasoconstriction and elevated blood pressure as a result [24].

**Serotonin:** 5-HT is an ethnological antique amine that has portrayed a crucial character in managing energy balance for long era [25]. Tryptophan, an essential dietary amino acid, is required for the two-step process that creates the monoamine transmitter (5-hydroxytryptamine) 5-HT [26].

**Central Serotonin Regulation of Energy Balance:**

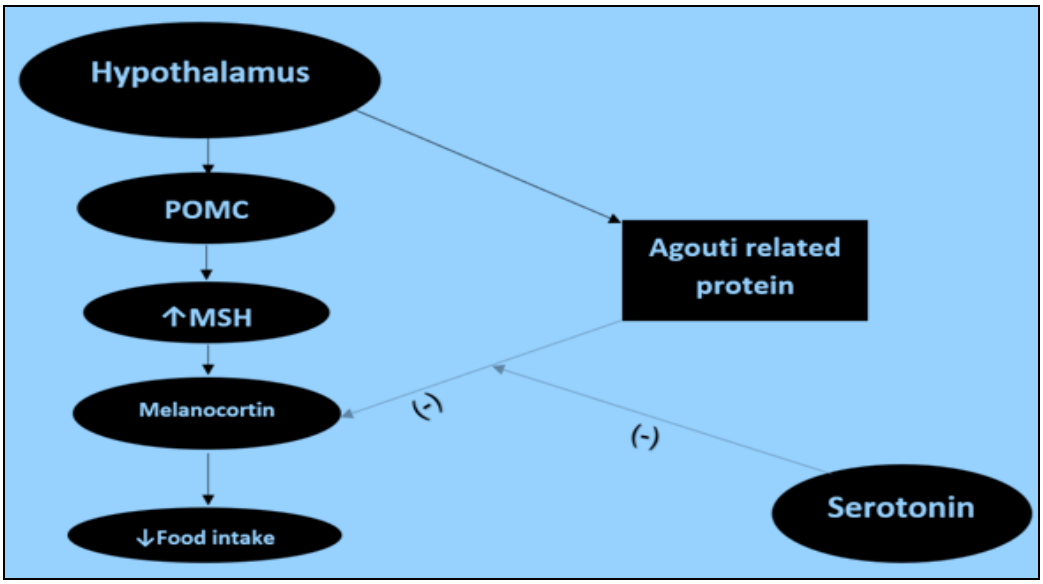


**FIG. 2: ROLE OF SEROTONIN IN REGULATION IN APPETITE SUPPRESSION**

It is generally familiar that central serotonin plays a role in mammalian appetite suppression and lot of the latest analyses have described the processes underlying these end results. Consequently, here evaluation at most offers a broad synopsis. Generally speaking, central 5-HT systems inhibit eating behaviours in spinal breed, whereas rodents develop hyperphagia and gain weight when their central serotonin levels are low. Pro opiomelanocortin indicates the hypothalamic arcuate nucleus (ARC) and brainstem, where processes innervated in the hypothalamus chiefly govern appetite [27]. POMC undergoes posttranscriptional modification to decrease hunger and food intake to produce α-melanotropin (MSH) and trigger its receptor to work.

Furthermore, agouti-related protein stops activation of melanocortin-4 receptor, which increase and eating behaviour [28]. Agouti-related protein /NPY neuron activation results in GABA release, which blocks POMC axon & dendrites and lowers hunger. Hypothalamic serotonin, which is equivalent to leptin's effects on these neurons, stimulates ARC, proopiomelanocortin neurons while inhibiting Agouti-related protein/NPY brain cells [29]. $HTR_{2C}$ appears to be the main mediator of serotonin's appetite-suppressing effects. Talcott and colleagues found that rodents (mice) need the 5-HT receptor 2C gene own greater appetites as well as more likely to become obese. After acute leptin administration, it was previously identified that 5-HT receptor 2C variant rodent (mice) likewise

showed lower eating efficacy and weight of body [30]. Studies done later showed that $HTR_{2C}$ in POMC neurons was necessary for these appetite-suppressing effects.

Central serotonin is connected to enhancing energy expenditure in addition to controlling appetite and caloric intake. According to a recent assessment, serotonin boosts activity of the brown adipose tissue and thus spends more energy. The turn on the 5-HT receptor 1A and $HTR_7$ receptors in the nucleus intermediolateral medullae spinalis may be the mechanism by which serotonin increases energy expenditure.

**Serotonin Signaling Affects Eating Behavior:** Serotonin signalling functions in eating behaviour habit and control in long periods of body weight management which is kept up by a number of lines of evidence. In animal models, it has been displayed that the experimental modification of various different subtypes of serotonin receptor affects the regulation of body weight and/or food intake [31].

Second, quantification of the availability of SERT provide evidence through molecular neuroimaging studies that reduced serotonin signaling may be the major issue in obesity and weight gain in humans; however more studies is needed for further knowledge and relationship. Thirdly, serotonin delivery throughout the body reduces appetite. Fourthly, current evidence in the investigation suggests that SSRI is used to increase the chance of weight gain for a long time. These medications impact food consumption in both people and animals. And last, several cutting-edge drugs for weight loss directly target the serotonin system [32, 33].

**Ghrelin:** Energy homeostasis and appetite control depend on the hypothalamus. Complex neural networks combine afferent signals from peripheral areas, including the digestive tract and adipose tissues, to produce efferent responses that control food intake and energy consumption.

Ghrelin that circulates comes primarily from the stomach and duodenum. Acyl ghrelin is produced by the biological catalyst GOAT the unusual post translational addition of a medium-chain fatty acid, usually octanoate, whereas deacyl-ghrelin develops after the enzyme-mediated hydrolysis of the acyl moiety [34]. Acyl-ghrelin has a variety of activities that include affect neuroprotection, glucose homeostasis, immunology and inflammation, mood, stress and anxiety, learning and memory, and olfaction. Food intake along with the growth hormone release is its major roles.

According to numerous studies, obese patients generally have lower mean serum ghrelin levels than thin people. Ghrelin level rises only during dieting so it is not easy to know long term results. Elevated ghrelin level is associated with the diet induced weight loss this can be the possible reason for the failure of many diets [34, 35].

**Goat:** Acyl ghrelin originates from the medium chain fatty acid, which the GOAT post-translationally joins to the ghrelin [36].

**Secretion:** Total plasma concentration of acyl-ghrelin rises before food intake, falls sharply after food, and rises further until the the next meal. The concentration of acyl-ghrelin was 110 pM before breakfast. After lunch it was 100 picomolar and 70 picomolar after meals when it was explored repeatedly throughout the day by participant following meal, activity and controlled sleep-wake regimen [37]. Acyl to ghrelin ratio may fluctuate at the meal's time, which is significant. Given that ghrelin has a 30-minute plasma half-life, its secretion gets suppressed after food intake [38, 39].

**Ghrelin and Weight Status:** A "reverse adiposity signal," plasma volume of ghrelin is not positively attached with body fat percentage [40]. Appropriately, recent research has shown that, in contrast to healthy, normal-weight participants, obese people have low plasma ghrelin levels, while anorexic patients have high plasma ghrelin levels. Moreover, it was linked that changes in body weight (weight increase or decrease) trigger compensatory reactions in ghrelin levels. For instance, ghrelin levels rise with weight reduction (whether brought on by decreased caloric intake or higher energy expenditure through physical exercise). Conversely, a reduction in ghrelin levels occurs along with weight gain (caused by increased calorie intake, high-fat diets, or iatrogenic or pregnancy-related). It appeared that decreased ghrelin secretion in obese patients was an adaptation

strategy to a sustained positive energy balance. Although the levels of circulating plasma ghrelin in obese participants are low, postprandial ghrelin suppression was not set up in these individuals, which may explain why they eat more than usual [41].

**Ghrelin Resistance in Obesity:** Uncertainty surrounds the function and importance of ghrelin resistance in obesity. As a defence against the greater body-weight set point that is expanded during periods of abundant food supply and to maximise energy reserves during a cycle of food shortage, ghrelin resistance has been favoured. In these circumstances, ghrelin sensitivity inhibition may help patients with obesity avoid weight gain of body. The finding that diet-induced obesity in ghrelin null mice exhibit less body-weight increase after calorie-restricted weight loss lends credence to this theory. Diet-induced obesity in ghrelin null mice has been linked reclaim less weight after less calorie food[42].

**Dopamine:**

**D2 Receptor in Food Reward/ Action of Dopamine Receptors on Obesity:** In a high study amount of edible food was given to rats which cause abnormal eating and uncontrolled weight rise develop anorexic behaviour as measured by palatable food consumption that is resistant to the suppressive effects of punishment [43]. In study rats were fed with "cafeteria diet" that included a variety of highly appetising, calorically dense foods that are generally vend in cafe and food-providing machines for human being use, such as bacon and cheesecake, which cause excessive weight gain in rodents greatly like its human counterpart. Infusion of cocaine provided to rats after prolong administration of drug exhibit similar compulsive-like consumption [44].

In addition to having too much body fat and eating compulsively, low dopamine receptor expression in the corpus striatum is observed in hypercaloric diet rats. For that reason, it was investigated even if striatal D2R detach could hasten the appearance of overeating in high-calorie diet rats. This strategy confirms that the alteration only affected the neuronal postsynaptic dopamine receptor in the striatum and not affect those in the pre-synaptic region. Striatal D2R knockdown did, in fact, hasten the formation of calorie-dense, pleasant obsessive eating behaviour. However, subject devoid of striatal dopamine receptor didn't result in harmful habit to ordinary meal, indicating that compulsivity did not develop in rats until after they had both dopamine receptor flattens and even only little subjection to the appetising meal. Astonishingly, impact of altering the signaling of striatal dopamine receptor on drug-intake behaviours resembling obsessive patterns has not yet been explored [45].

**Dopamine Signaling in Food Reward:** Abuse-related medications, in particular the dopaminergic mesolimbic system, can change our brain's reward mechanisms. It has also appeared that a delicious meal with a hyper calorie diet greatly starts the DA's reward circuitry. These results imply that drug and food addictions share brain foundations and depend on dopamine circuits. In addition, brain imaging research suggests that dopaminergic circuits play a role in the eating behaviour [46].

This finding suggests that food addiction get enhanced by the release of dopamine. Moreover, Rotiman and colleagues demonstrated that sign indicating the chance of acknowledgment for sucrose reward or sudden delivery of sucrose release dopamine in the (Nucleus accumbens) [47]. Here strongly suggests that DA signalling in the nucleus accumbens is an actual regulator of eating behaviour. Other research, however, has shown that the dorsal striatum shows more significant character in managing food reward than the NAc. For instance, the DA antagonist cis-flupentixol reduces food reward-related lever pressing in rats when injected in dorsal striatum part but not at nucleus accumbens, frontal brain, amygdala [48].

**Insulin:** The "insulin-carbohydrate" of obesity, in particular, contends that high-glucose diets increase insulin secretion, which in turn suppresses fatty acid release from fat tissue in the bloodstream and store fats in the adipose tissue rather than being disintegrated enzymatic acting cells like the muscle, liver, and heart[49]. According to one previously mentioned theory, changed fuel availability causes cells to undergo "internal starvation," which results in adaptive reductions in increased food intake and energy utilization. To address the starving of metabolically active requires inside of individual cells, insulin-driven changes in fat portioning that cause more fat to be

stored in adipocytes is believed to be the cause of the relationship between the development of obesity and positive energy balance [50]. This reduction in energy spending and rise in eating habits is believed to be the result of this process. According to the carbohydrate-insulin hypothesis, adipose tissue endocrine dysregulation is the primary factor contributing to positive energy balance. Rather than allowing yourself to cat your way into obesity 51 simply passively.

**Resistance of Insulin in Obesity:** In reaction to circulating insulin, the muscular structure exhibits impaired insulin sensitivity as a reduction in glucose transfer and muscle glycogenesis. Myocytes grabbed from overweight people or lipids from the adipocyte show action on the cultured myocytes and exhibit lower insulin sensitivity, supporting the idea that an excess lipid accumulation or its metabolic by-products reduce insulin signalling in skeletal muscle. Newly, it has been illustrated that endothelial cell-specific insulin signalling abnormalities in mice cause muscular insulin resistance, which causes impaired transcapillary transportation of insulin in diabetic and obese people. Obesity and muscle endothelial cell insulin resistance have not yet been correlated. Muscle mitochondrial respiratory chain deficiency is also attendant with insulin resistance, but this may be an effect rather than the fundamental cause [52].

Insulin resistance is very specific in liver as, it does not prevent gluconeogenesis from -happening while continuing to stimulate the synthesis of fatty acid. Impaired insulin sensitivity is also connected with a lack of mitochondrial respiratory chains in tissue and tendons, though here conceivable result in place of the original cause of impaired insulin action. So, after insulin receptor activation, obesity-related interruption of insulin signalling occurs. This insulin signalling pathway's uncoupling of lipid and glucose metabolism eventually manifests as hyperglycaemia and hypertriglyceridemia, which may give rise to other processes, more importantly of the serine or threonine-specific protein kinase, including a major role for the mechanistic target of rapamycin in hepatic lipid formation. Adipose tissue exhibits insulin resistance as diminished insulin-stimulated lipolysis inhibition and impaired insulin-stimulated glucose transfer. Similar to the liver, adipocytes show a divergence in insulin signalling, which blunts the action of insulin on glucose transporter-4 trafficking. Adipocyte insulin resistance may result from obesity all over independently along with interconnections between adipocytes and inflammatory carriers [53].

**GLP-1:** Admitting that there is ample evidence to support the title role of GLP-1 in lowering eating behaviour in both humans and animals, different species respond differently to GLP-1's effects on energy expenditure. GLP1RA expands energy expenditure, according to studies on mice and rats, which helps to explain the weight loss seen in preclinical research [54].

The effects of Glucagon-like peptide -1 on duodenum clearance and gut acid output are strong and significant. It is principally accountable for the "ileal break," a closely controlled mechanism that controls the motion of nutrients through the digestive system and is under the direction of neurological and hormonal signals. GLP-1 improves satiety and lowers caloric intake.

GLP-1 injected peripherally can promote satiety and lessen postprandial glucose excursions by delaying stomach emptying. In lean people, peripheral GLP-1 infusion is connected to increased post-meal satiety and decreased food consumption at the next meal. Both obese patients with diabetes and those without it maintain this effect. Pharmacologically simulating these effects might help people consume low-fat food, hence promoting weight loss and maintenance.

Weight reduction of roughly 3kg happens due to diabetes treatment by GLP-1 receptor agonists, depending on the clinical trial. Depending on the clinical trial, type 2 diabetes treatment with GLP-1 RAs results in a weight loss of about 3 kg. Clinically meaningful weight loss was noticed in patients with diabetes (2.8 kg, 3.4 to 2.3; 18 trials) and without diabetes (3.2 kg, 4.3 to 2.1; three trials) in a meta-analysis of 21 trials of obese patients with or without type 2 diabetes treated with a GLP-1 RA (exenatide twice daily, exenatide QW, or liraglutide up to 1.8 mg) [55]. Fasting GLP-1 levels in lean and obese healthy persons are similar, but GLP-1 production decreased in response to an oral glucose challenge, and there have been reports of

lower circulating GLP-1 levels after eating [56]. According to a recent study which found that increased GIP secretion brought on by a CBR agonist was associated with noticeably decreased GLP-1 release following a glucose challenge, Raised GIP and endocannabinoid tone may potentially contribute to obesity's impaired GLP-1 response to luminal nutrients [57]. Furthermore, in type 2 diabetic obese subjects, high dosages of exogenous GIP infusion reduced GLP-1 production after a mixture of meal challenges. These new data confirm the notion that endocannabinoids have an impact on incretins [58].

Liraglutide, a glucagon-like peptide-1 (GLP-1) agonist, was initially marketed to treat type 2 diabetes (T2D). 3.0 milligrams of it are dispensed intravenously once daily (compared with up to 1.8 mg daily for treatment of T2D) [59]. By promoting satiety by hypothalamic stimulation and delaying stomach emptying, liraglutide lift up weight reduction by causing a decrease in food intake [60]. It has received approval from the FDA and EMA to help weight loss in those with a BMI of 30 kg/m2 or less and co-morbidities related to obesity [61]. Pancreatitis and nausea/vomiting are more frequent adverse effects. Compared to the placebo, an extra annual weight loss of 5.3-5.9 kg has been spotted [62].

**Neuropeptide Y:** By encouraging energy storage in WAT and preventing BAT activation in animals, neuropeptide Y, an orexigenic neuropeptide, regulates obesity. Energy is stored in adipose tissue as a result of NPY's promotion of fat cell differentiation and increased lipid profile, effects mostly mediated by NPY receptor subtypes 1 and 2 [63].

**In Adipose Tissue, NPY Encourages Adipogenesis and Preventing Lipolysis:** *In-vitro* and *in-vivo* experiments with NPY revealed hyperplasic, adipogenicity and antilipolytic actions in adipose tissue cells as well as angiogenic actions in the vasculature neighbouring fat cells (a key factor in adipose enlargement), however in one investigation NPY administration had no effect on lipid build up in 3 T3-L1 cells at 8 days post-differentiation [64]. Although NPYR5 has also been linked to cellular responses, it was previously believed that NPY's effects on adipose tissue function mostly occurred through NPYR1- and NPYR2-mediated pathways. A high-fat, high-sugar diet and two weeks of exposure to the cold were linked to an increase in the expression of NPY and NPYR2 in the subcutaneous fat stores of mice, with the expression being localised to blood vessels, neurons, and adipocytes [65]. Adult mice with adipose tissue only conditionally knocked down NPYR2 to prevent high-fat diet-caused obesity. The knockdown did not impact body weight or food intake in mice receiving regular chow, indicating that NPYR2 is crucial for energy deterioration in peripheral tissues.

The NPYR2 germline knock-out animals were resistant to the cold stress-induced enhancement of diet-induced obesity, and nursing of wild-type rodents for two weeks with an NPYR2 antagonist given to the adipose tissue through slow-release pellets decreased visceral fat depositary clump by 40%. Similarly, after two weeks of stress-induced fat accumulation, conditional suppression of NPYR2 by an adeno - associated viral vector was delivered into the visceral fat deposits of mice. These findings imply that NPYR2 was primarily responsible for those NPY-mediated impacts on fatty tissue.

**NPY decreases brown Adiposity Formation and Activation:** NPY inhibits the development and activation of brown adiposity. Norepinephrine (NE) released from SNS terminals induces BAT thermogenesis *via* the beta 3 adrenergic receptor.

By guanosine diphosphate bonding diminution (a sign of brown fat thermal activity) to BAT mitochondrial, central injection of NPY in rats suppressed BAT thermogenesis and increased lipoprotein lipase (LPL) action to promote WAT fat accumulation, it stimulates the breakdown of low-density plasma lipoprotein into free lipids for absorption into peripheral tissues and is a rate-limiting step. Despite much research showing that NPY decreases BAT-related thermogenesis, our comprehension of the role of distinct CNS-specific nuclei and subnuclei has only recently become clear. The function of adipose tissue was shown to be influenced by hypothalamic dorsomedial NPY by Chao *et al.* [66].

**CONCLUSION:** There have been significant improvements in our understanding of the pathophysiological processes that lead to and maintain obesity. Pathological overeating and physical inactivity appear to be connected with altered brain circuits and neuroendocrine feedback that led to obesity. A monogenetic mutation that causes obesity affects a small part of the obese population. Additionally, other genes associated with obesity risk have been found in GWA investigations.

Our knowledge of the causes and progression of obesity has recently advanced, but our grasp of its pathophysiology and aetiology is still lacking. Controlled intervention trials and long-term follow-up are especially necessary to clarify causation questions. However, if preventative measures and/or efficient treatments are not accomplished, obesity has the potential to be harmful to mankind because to its speeding impacts on cancer and metabolic consequences.

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## REFERENCES:

1. Rebello CJ and Greenway FL: Obesity medications in development. Expert Opinion on Investigational Drugs 2019; 29(1): 63–71.
2. Sarma S, Sockalingam S and Dash S: Obesity as a multisystem disease: Trends in obesity rates and obesity-related complications. Diabetes, Obesity and Metabolism 2021; 23(1): 3–16.
3. Safaei M, Sundararajan EA, Driss M, Boulila W and Shapi'i A: A systematic literature review on Obesity: Understanding the Causes & Consequences of obesity and reviewing various machine learning approaches used to predict obesity. Computers in Biology and Medicine 2021; 136: 104754.
4. Saltiel AR and Olefsky JM: Inflammatory mechanisms linking obesity and metabolic disease. Journal of Clinical Investigation 2017; 127(1): 1–4.
5. Blum K, Thanos PK & Gold MS: Dopamine and glucose, obesity, and reward deficiency syndrome. Frontiers in Psychology 2014; 5, 919.
6. Kumar M, Kaushik D, Kaur J, Proestos C, Oz F and Oz E: A critical review on obesity: Herbal Approach, bioactive compounds, and their mechanism. Applied Sciences 2022; 12(16): 8342.
7. Oussaada SM, van Galen KA, Cooiman MI, Kleinendorst L, Hazebroek EJ and van Haelst MM: The pathogenesis of obesity. Metabolism 2019; 92: 26–36.
8. Kim B & Feldman EL: Insulin resistance in the nervous system. Trends in endocrinology and metabolism. TEM 2012; 23(3): 133–141.
9. Mancuso P: The role of adipokines in chronic inflammation. ImmunoTargets and Therapy 2016; 47.
10. Mendoza-Herrera K, Florio AA, Moore M, Marrero A, Tamez M and Bhupathiraju SN: The leptin system and Diet: A mini review of the current evidence. Frontiers in Endocrinology 2021; 12.
11. Park HK and Ahima RS: Physiology of leptin: Energy homeostasis, neuroendocrine function and metabolism. Metabolism 2015; 64(1): 24–34.
12. Perakakis N, Farr OM and Mantzoros CS: Leptin in Leanness and obesity. Journal of the American College of Cardiology 2021; 77(6): 745–60.
13. Farr OM, Tsoukas MA and Mantzoros CS: Leptin and the brain: Influences on brain development, cognitive functioning and psychiatric disorders. Metabolism 2015; 64(1): 114–30.
14. Obradovic M, Sudar-Milovanovic E, Soskic S, Essack M, Arya S and Stewart AJ: Leptin and obesity: Role and clinical implication. Frontiers in Endocrinology 2021; 12.
15. Münzberg H, Singh P, Heymsfield SB, Yu S and Morrison CD: Recent advances in understanding the role of leptin in energy homeostasis. F1000 Research 2020; 9: 451.
16. Zhang Y and Chua S: Leptin function and regulation. Comprehensive Physiology 2017; 351-69.
17. Zhang Y, Dallner OS, Nakadai T, Fayzikhodjaeva G, Lu YH and Lazar MA: A noncanonical PPARΓ/rxrα-binding sequence regulates leptin expression in response to changes in adipose tissue mass. Proceedings of the National Academy of Sciences 2018; 115(26).
18. Kumar R, Mal K, Razaq MK, Magsi M, Memon MK and Memon S: Association of leptin with obesity and insulin resistance. Cureus 2020.
19. Perry RJ, Resch JM, Douglass AM, Madara JC, Rabin-Court A and Kucukdereli H: Leptin's hunger-suppressing effects are mediated by the hypothalamic–pituitary–adrenocortical axis in rodents. Proceedings of the National Academy of Sciences 2019; 116(27): 13670–9.
20. Izquierdo AG, Crujeiras AB, Casanueva FF and Carreira MC: Leptin, obesity and leptin resistance: Where are we 25 years later. Nutrients 2019; 11(11): 2704.
21. Wabitsch M, Funcke JB, Lennerz B, Kuhnle-Krahl U, Lahr G and Debatin KM: Biologically inactive leptin and early-onset extreme obesity. New England Journal of Medicine 2015; 372(1): 48–54.
22. Pan WW and Myers MG: Leptin and the maintenance of elevated body weight. Nature Reviews Neuroscience 2018; 19(2): 95–105.
23. Andreoli MF, Donato J, Cakir I and Perello M: Leptin resensitisation: A reversion of leptin-resistant states. Journal of Endocrinology 2019; 241(3).
24. Obradovic M, Sudar-Milovanovic E, Soskic S, Essack M, Arya S and Stewart AJ: Leptin and obesity: Role and clinical implication. Frontiers in Endocrinology 2021; 12.
25. Shajib MS, Baranov A and Khan WI: Diverse effects of gut-derived serotonin in intestinal inflammation. ACS Chemical Neuroscience 2017; 8(5): 920–31.
26. Georgescu T, Lyons D and Heisler LK: Role of serotonin in body weight, insulin secretion and glycaemic control. Journal of Neuroendocrinology 2021; 33(4).
27. Yabut JM, Crane JD, Green AE, Keating DJ, Khan WI and Steinberg GR: Emerging roles for serotonin in regulating

metabolism: new implications for an ancient molecule. Endocrine Reviews 2019; 40(4): 1092–107.
28. Tavares GA, Torres A and de Souza JA: Early life stress and the onset of obesity: Proof of micrornas' involvement through modulation of serotonin and dopamine systems' homeostasis. Frontiers in Physiology 2020; 11.
29. van Galen KA, ter Horst KW, Booij J, la Fleur SE and Serlie MJ: The role of central dopamine and serotonin in human obesity: Lessons learned from molecular neuroimaging studies. Metabolism 2018; 85: 325–39.
30. Xu P, He Y, Cao X, Valencia-Torres L, Yan X and Saito K: Activation of serotonin 2C receptors in dopamine neurons inhibits binge-like eating in mice. Biological Psychiatry 2017; 81(9): 737–47.
31. Gafoor R, Booth HP and Gulliford MC: Antidepressant utilisation and incidence of weight gain during 10 years' follow-up: Population based cohort study. BMJ 2018;
32. Oh C-M, Park S and Kim H: Serotonin as a new therapeutic target for diabetes mellitus and obesity. Diabetes & Metabolism Journal 2016; 40(2): 89.
33. Galen KA, Horst KW and Serlie MJ: Serotonin, food intake, and obesity. Obesity Reviews 2021; 22(7).
34. Müller TD, Nogueiras R, Andermann ML, Andrews ZB, Anker SD and Argente J: Ghrelin. Molecular Metabolism 2015; 4(6): 437–60.
35. Zigman JM, Bouret SG and Andrews ZB: Obesity impairs the action of the Neuroendocrine Ghrelin System. Trends in Endocrinology & Metabolism 2016; 27(1): 54–63.
36. Sovetkina A, Nadir R, Fung JN, Nadjarpour A and Beddoe B: The physiological role of ghrelin in the regulation of energy and glucose homeostasis. Cureus 2020;
37. Jiao ZT and Luo Q: Molecular mechanisms and health benefits of Ghrelin: A Narrative Review. Nutrients 2022; 14(19): 4191.
38. Gupta D, Ogden SB, Shankar K, Varshney S, Zigman JM. "A leap 2 conclusions? targeting the ghrelin system to treat obesity and diabetes. Molecular Metabo 2021; 46: 101128.
39. Ghrelin and obesity: Identifying gaps and dispelling myths. A reappraisal. *In-vivo* 2017; 31(6).
40. Steinert RE, Feinle-Bisset C, Asarian L, Horowitz M, Beglinger C, Geary N. Ghrelin CCK: GLP-1, and PYY (3–36): Secretory controls and physiological roles in eating and glycemia in health, obesity and after Rygb. Physiological Reviews 2017; 97(1): 411–63.
41. Mihalache L, Gherasim A, Niță O, Ungureanu MC, Pădureanu SS and Gavril RS: Effects of ghrelin in energy balance and body weight homeostasis. Hormones 2016; 15(2): 186–96.
42. Cui H, López M and Rahmouni K: The cellular and molecular bases of leptin and ghrelin resistance in obesity. Nature Reviews Endocrinology 2017; 13(6): 338–51
43. Janssen LK and Horstmann A: Molecular imaging of central dopamine in Obesity: A qualitative review across substrates and Radiotracers. Brain Scien 2022; 12(4): 486.
44. Wallace CW and Fordahl SC: Obesity and dietary fat influence dopamine neurotransmission: Exploring the convergence of metabolic state, physiological stress and inflammation on dopaminergic control of food intake. Nutrition Research Reviews 2021; 35(2): 236–51.
45. Kravitz AV, O'Neal TJ and Friend DM: Do dopaminergic impairments underlie physical inactivity in people with obesity? Frontiers in Human Neuroscience 2016; 10.
46. Kleinridders A and Pothos EN: Impact of brain insulin signaling on dopamine function, food intake, reward, and emotional behavior. Current Nutrition Reports 2019; 8(2): 83–91.
47. Ruegsegger GN and Booth FW: Running from disease: Molecular mechanisms associating dopamine and leptin signaling in the brain with physical inactivity, obesity and type 2 diabetes. Frontiers in Endocrinology 2017; 8.
48. Cameron JD, Chaput JP, Sjödin AM and Goldfield GS: Brain on fire: Incentive salience, hedonic hot spots, dopamine, obesity, and other hunger games. Annual Review of Nutrition 2017; 37(1): 183–205.
49. Wondmkun YT: obesity, insulin resistance and type 2 diabetes: Associations and therapeutic implications. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2020; 3611–6.
50. Kolb H, Stumvoll M, Kramer W, Kempf K and Martin S: Insulin translates unfavourable lifestyle into obesity. BMC Medicine 2018; 16(1).
51. Hall KD: A review of the carbohydrate–insulin model of obesity. European Journal of Clinical Nutrition 2017; 71(3): 323–6.
52. Wu H and Ballantyne CM: Metabolic inflammation and insulin resistance in obesity. Circulation Research 2020; 126(11): 1549–64.
53. Barber TM, Kyrou I, Randeva HS and Weickert MO: Mechanisms of insulin resistance at the crossroad of obesity with associated metabolic abnormalities and cognitive dysfunction. IJMS 2021; 22(2): 546.
54. Drucker DJ: GLP-1 physiology informs the pharmacotherapy of obesity. Molecular Metabolism 2022; 57: 101351
55. Brown E, Cuthbertson DJ and Wilding JP: Newer GLP-1 receptor agonists and obesity-diabetes. Peptides 2018; 100: 61–7.
56. Chia CW, Carlson OD, Liu DD, González-Mariscal I, Santa-Cruz Calvo S and Egan JM: Incretin secretion in humans is under the influence of cannabinoid receptors. American Journal of Physiology-Endocrinology and Metabolism 2017; 313(3).
57. Færch K, Torekov SS, Vistisen D, Johansen NB, Witte DR and Jonsson A: GLP-1 response to oral glucose is reduced in prediabetes, screen-detected type 2 diabetes and obesity and influenced by SEX: The addition-pro study. Diabetes 2015; 64(7): 2513–25.
58. Chia CW and Egan JM: Incretins in obesity and diabetes. Annals of the New York Academy of Sciences 2019; 1461(1): 104–26.
59. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH and Pagotto U: Pharmacological management of Obesity: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism 2015; 100(2): 342–62.
60. Singh AK and Singh R: Pharmacotherapy in Obesity: A systematic review and meta-analysis of randomized controlled trials of anti-obesity drugs. Expert Review of Clinical Pharmacology 2019; 13(1): 53–64.
61. Mehta A, Marso SP and Neeland IJ: Liraglutide for weight management: A critical review of the evidence. Obesity Science & Practice 2016; 3(1): 3–14.
62. Williams DM, Nawaz A, Evans M. Drug therapy in Obesity: A review of current and emerging treatments. Diabetes Therapy 2020; 11(6): 1199–216.
63. Zhang W, Cline MA and Gilbert ER: Hypothalamus-adipose tissue crosstalk: Neuropeptide Y and the regulation of energy metabolism. Nut & Meta 2014; 11(1).
64. Huang Y, Lin X and Lin S: Neuropeptide y and metabolism syndrome: An update on perspectives of Clinical Therapeutic Intervention Strategies. Frontiers in Cell and Developmental Biology 2021; 9.

65. Wu Y, He H, Cheng Z, Bai Y and Ma X: The role of neuropeptide Y and peptide YY in the development of obesity *via* gut-brain axis. Current Protein & Peptide Science 2019; 20(7): 750–8.

66. Shende P and Desai D: Physiological and therapeutic roles of neuropeptide Y on biological functions. Cell Biology and Translational Medicine 2019; 37–47.

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