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Impact of Stress on Obesity-Targeted Signaling Pathways for Novel Drug Discovery

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Abstract

Obesity is an epidemic that affects millions of people across the world. It is a metabolic disorder that can be characterized by an excess buildup of adipose tissue. Stress can be defined as the organism's false response to any kind of demand or challenge to equilibrium. Whenever an organism comes in contact with any sort of stressor (physical, social, etc.), all the originating internal stress mechanisms are triggered to start a flight or fight response and thereby deal with the stress event. Several animal stress models are thought to exhibit unique metabolic traits, with some animals exhibiting signs of anorexia and a reduction in body weight, while others show an increase in food consumption and body weight and become more prone to disorders of metabolism. Hormones that are released by the endocrine organ gut, such as ghrelin, leptin, glucagon-like peptide-1 (GLP-1), peptide YY (PYY), pancreatic polypeptide (PP) as well as cholecystokinin (CCK), have quite an influence on the maintenance of homeostasis and energy balance by generating satiety and food termination. Leptin, a hormone that is released by adipocytes into the bloodstream is necessary for the regulation of body weight and the proper balance of energy. Obesity is caused primarily by leptin deficits or genetic abnormalities in the signaling of the leptin mechanism. A therapeutic approach by the use of probiotics as an external living system for the control of obesity is usually suggested by recent research that examined the relationship of the gut microbiota with obesity. The superfamily of mitogen-activated protein kinases (MAPK) includes the c-Jun N-terminal kinase (JNK) family. In obesity, JNK is a signal transducer that has been extensively studied. This review explores various kinds of rodent stress models and signaling pathways that affect metabolic outcomes to better understand stress-induced obesity.

Keywords: Obesity, Stress, Leptin, JNK, Nrf2 Pathways, Stress Model.

1. Introduction

The World Health Organization (WHO) reports that obesity incidence has increased twice since 1980. More people die from overweight or obesity than from underweight in most countries of the world [1]. The regulation of body weight and energy balance depends mainly on the GI tract, which is the body's largest endocrine organ and secretes a variety of gut hormones, which include cholecystokinin (CCK), ghrelin, peptide YY (PYY), as well as glucagon-like peptide (GLP-1) [2]. Obesity has become an epidemic, and it is now widely accepted. Some medical experts believe that obesity is the largest global cause of mortality that may be prevented [3]. In fact, according to some research, weight gain considerably reduces life expectancy, and those who are obese can pass away a decade or more earlier than people

who are of normal weight [4]. Stress might be one of the major environmental factors that impact metabolism and food intake that leads to obesity.
The two main glucocorticoids that are secreted as a response to stressful conditions are cortisol and corticosterone in humans as well as rats, respectively. Glucocorticoids oppose insulin's efforts to store energy in numerous tissues by partially reducing insulin secretion [5, 6]. A transitory state of insulin resistance (IR) generated by glucocorticoids inhibits the production of hepatic glucose and regulates the transport of glucose to peripheral tissue, leading to a state of acute hyperglycemia [7, 8].
This review focuses on the understanding of the pathophysiology and metabolic alterations linked with obesity and also the employment of animal models to study stress-related activities. Additionally, it also focuses on the signaling pathways that govern food consumption as well as the role of serotonin and homeostasis.

Pathophysiology of Obesity

The major fat organ, which is regarded as an endocrine organ is the adipose tissue (AT) that plays a part in the immune system's response [9]. The majority of the body's fat mass is made up of subcutaneous adipose tissue (80%) and visceral fat (20%). Triglycerides (TG) compose 90% of the lipids that make up the lean body mass, which contributes over 80% of the weight [Fig. 1] [10,11]. Based on homeostasis, AT may either carry out the lipolysis of TG by the enzyme lipoprotein lipase (LPL), which generates free fatty acids (FFA) as well as glycerol, or by generating acyl-CoA from extracellular fatty acids or glycerol-3-phosphate, it may esterify these compounds. Lipogenesis and glyceroneogenesis, respectively, are terms given to these processes [12–14]. As a result, over long periods of positive energy balance (when energy intake exceeds energy loss), AT works by engaging preadipocytes, which grow rapidly and undergo hypertrophy into full-grown adipocytes, resulting in vascular and stromal development.

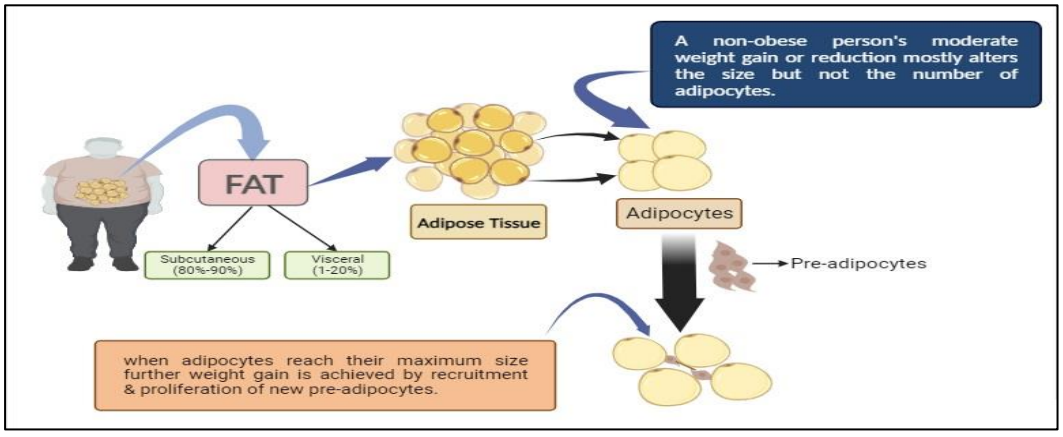

Fig 1. Subcutaneous (80%–90%) and visceral (1%–20%) adipose tissue compose the majority of the body's fat mass, respectively. Adipose tissue is made up of adipocytes, and after adipocytes reach their maximal size, the recruitment and proliferation of new pre-adipocytes allow for further weight gain.

AT induces the release of active biomarkers from stromal cells i.e. endothelial cells, fibroblasts, leukocytes, and macrophages, as well as, to a small amount, adipocytes. The proteins, hormones, and cytokines that are secreted are known to be adipocytokines or adipokines including leptin, adiponectin, resistin, visfatin, retinol-binding protein 4 (RBP-4), and many more [13–16]. Peripheral afferent system, central processing system, and efferent system control

obesity pathogenesis. The peripheral processing system, divided into peripheral appetite-suppressing and peripheral appetite-stimulating systems, is suppressed by adipocytes secreting leptin and adiponectin [Fig 2]. The central processing system, divided into central appetite suppressing and central stimulating systems, is stimulated by the gut hormones ghrelin and obestatin. NPY, a central stimulus, decreases energy expenditure and increases food intake, maintaining energy balance. Recently, terms like "adiposopathy" and "diabesity" which denote the near association between T2DM and obesity, have been developed to describe the close link between the pathology of AT and metabolic disorders [17, 18]. The main sites in which IR occurs are the muscle, liver, AT, and kidney [19]. In the community, overweight and obesity are associated with problems that increase the death risk by 2–3 times in obese people [20].

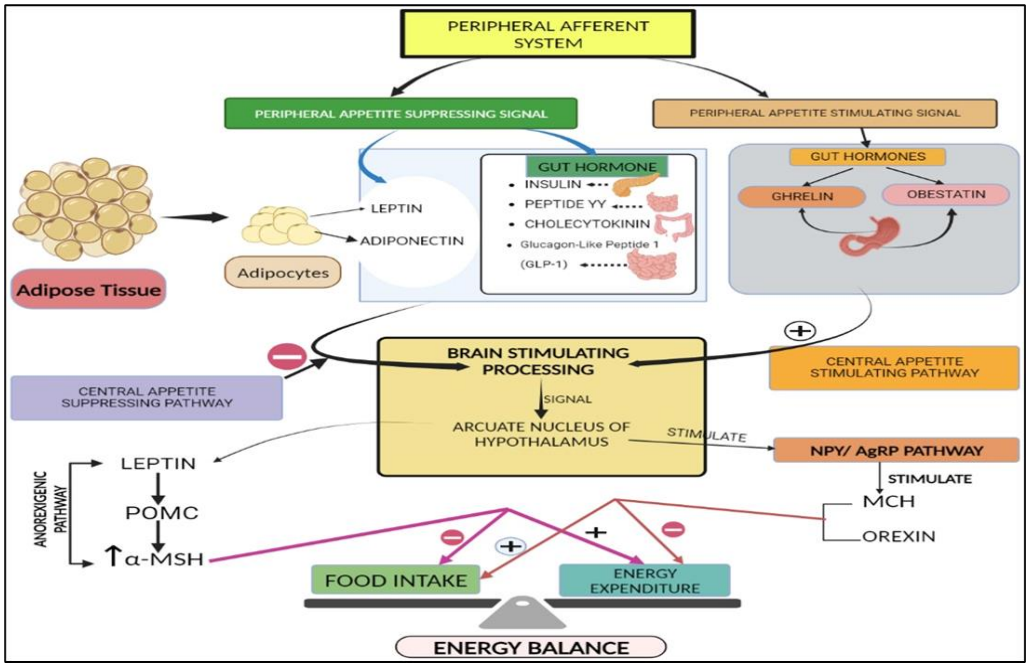

Fig 2. The peripheral afferent system, central processing system & efferent system control the pathogenesis of obesity. The peripheral processing system is divided into peripheral appetite suppressing & peripheral appetite stimulating systems. The peripheral suppressing system, through adipocytes secreting leptin & adiponectin, suppresses the central processing system. The peripheral stimulating signals including gut hormones ghrelin and obestatin, stimulate the central processing system. The central suppressing system, through α-MSH suppresses food intake and increases expenditure while the central stimulating system through NPY decreases energy expenditure and increase food intake maintaining energy balance. POMC: Proopiomelanocortin; α-MSH: α-Melanocyte-stimulating hormone; MCH: Melanin-concentrating hormone

Stress, Gut & Metabolic Hormones and Obesity

There are over 20 different hormones released by the gastrointestinal tract, which is the largest endocrine organ in the body. The main function of gut hormones is nutrition uptake, although they also perform other functions such as digestion and absorption [21]. These are a few of the most significant hormones-

- **Peptide YY (PYY)**

PYY along with pancreatic polypeptide (PP) are the neuropeptide Y (NPY) family members and the diverse system of the cell along the gut-brain axis express them. PYY is produced by a special type of endocrine cells of the distal gut and is termed PYY because it contains a tyrosine residue. In both the fed and fasted states, PYY3-36 is the predominant circulating hormone [22, 23]. With the intake of food, levels of PYY are elevated, reach their peak by 1-2 hours, and remain raised for an extended period, showing that it functions primarily as a component of satiety rather than being a terminator of food [24]. PYY mediates its effects through the Y2 receptor, which is found all over the CNS. The hypothalamic regulation of consumption of food by the brainstem and vagal afferents is affected by PYY3–36, and it may potentially directly affect this control. Recent research suggests that several brain regions except the homeostatic region may also affect hunger, which is mediated by PYY 36 [25]. Numerous cases have shown that PYY3-36 may reduce weight in part as a result of its effects on fuel partitioning and energy loss [26].

- **Pancreatic polypeptide (PP)**

The f cells of the pancreatic islets secrete PP, producing minimally in the distal portion of the gut. After food intake, the PP circulation increases for about 30 minutes and continues for minutes after the termination of the meal [27]. In contrast, somatostatin prevents PP secretion. PYY has a certain level that persists for an extended period after the meal has terminated, indicating that it may promote satiety. PP has a greater affinity for the Y4 receptor, even though it is thought that the brainstem regulates the majority of this hormone's anorectic actions [28]. Numerous earlier investigations found that repeated peripheral PP administration in animals decreased the intake of food. According to several human investigations, when normal-weight subjects are studied, their food intake is reduced by 25% [29-31]. No study has associated changes in body weight with fasting or postprandial PP [31, 32].

- **Glucagon-Like Peptide 1 (GLP-1)**

GLP-1, a member of the incretin hormone family, is a gut-derived hormone that stimulates the release of insulin in response to glucose, among other functions. Two forms of GLP-1 are produced by the intestinal L cells, GLP-11-37 and GLP-11-36 amide [33]. The major hormone in circulation is GLP-17-36. This hormone’s secretion is mainly stimulated by food. GLP-1 acts on the GLP-1 receptor (GLP-1R), found both in peripheral tissues as well as the CNS. The hypothalamus and brainstem both express c-fos, which mediates GLP-1 activity [34]. The receptors of GLP-1 are usually found in the periphery and have a significant role in the termination of meals and the feeling of satisfaction [35]. GLP-1 administration in both the peripheral and central regions significantly reduced food intake by rodents [36]. Additionally, the satiated rat's food intake was doubled by antagonistic central GLP-1 receptors [37]. Although the majority of research has shown that GLP-1’s concentration remains unchanged in both the overweight and lean subjects, there is enough proof to suggest that GLP-1 has a role in the pathophysiology of obesity.

- **Cholecystokinin (CCK):**

This is released with the help of specialized cells known as I cell. The tripeptidal peptidase II enzyme inactivates this hormone, which is formed by the posttranslational moderation of the pro-cholecystokinin gene with a combining with peptides [38]. CCK levels rise biphasically for about 25 minutes after food intake and then remain elevated for about 3 hours. CCK-1 receptor mediate CCK’s anorectic effects, according to genetic and pharmacological research. The

primary CCK receptors are CCK-1 and CCK-2, which are both present in the brainstem and hypothalamus. Satiety is generated by CCK, when CCK-1 binds to the vagus nerve [39]. According to some findings, compared to obese or lean individuals, morbidly obese individuals had lower fasting levels. The effectiveness of CCK has recently demonstrated a limited level of anti-obesity activity. CCK appears to have a greater impact on satiety than satiation [40].

- **Ghrelin**

It is a 28-amino acid neuropeptide hormone produced by cleaving a larger precursor, preproghrelin. Ghrelin is a hormone generated from the gut that is produced by the X/A-like cells of the gastric oxyntic mucosa surrounding the stomach [41]. Ghrelin specifically promotes consumption of food by triggering a several of hypothalamic, brainstem, and midbrain nuclei [42–46]. The only known peptide between the gut and the brain that stimulates appetite is ghrelin. The binding of certain molecules of medium-chain fatty acids, particularly octanoate, is involved in this alteration. This acylation is carried out by the enzyme gastric o-acyl transferase (GOAT) [47]. The orphan GH-secretagogue receptor (GHS-R1a) is the endogenous ligand through which ghrelin exerts its effects on adiposity. The acyl ghrelin (active form) can only cross the blood-brain barrier (BBB), which also activates and binds to the GHS-R1a receptor [48]. According to several studies, the ARC of the hypothalamus is where ghrelin's control of appetite functions is centrally situated [49]. The regulation of ghrelin-induced food intake is mostly dependent on the vagus nerve and brainstem [50]. Like PYY3–36, ghrelin enables us to recognize truly satisfying meals. It has been shown that ghrelin administration (both centrally and peripherally) indirectly triggers hypothalamic corticotropin-releasing factor (CRF) neurons, leading to stimulation of the HPA axis [51]. In Prader-Willi syndrome, where ghrelin levels rise and obesity develops, the pathogenic involvement of ghrelin has been suggested. However, ghrelin has been shown to be inversely correlated with BMI in non-syndromic plasma [52, 53].

- **Leptin**

The peripherally derived hormone leptin affects the consumption of food and homeostasis and is expressed according to the size and number of adipocytes. The metabolic effects of stress are also influenced by leptin. Once it is produced, leptin stimulates the ARC's anorectic POMC/ Cocaine-amphetamine related transcript (CART) neurons and regulates the ability in which ghrelin and other metabolically active hormones may cause these neurons to become depolarized [54–56]. According to one study, intraperitoneal administration of glucocorticoids (emulating acute stressor levels) reduced consumption of food and body weight by increasing concentrations of leptin [57]. When glucocorticoids were administered centrally, the same group showed that leptin had a different function since NPY expression increased along with food consumption and body weight [58].

- **Glucocorticoids**

Visceral obesity has been linked to increased HPA axis activity in both humans and rodents, as well as elevations in glucocorticoid concentrations that can have an impact on the brain and peripheral tissues [59]. As with other steroid hormones, lipophilic glucocorticoids cross the BBB and affect the production of hypothalamic peptides that regulate intake of food and homeostasis [60–62]. Numerous brain areas significantly associated with energy balance, including the ARC, LH, and PVN, have been shown to express glucocorticoid receptors (GRs) [63]. Due to their capacity to modify behaviors that affect energy intake and expenditure, glucocorticoids are thought to have a significant impact on the connection between obesity and stress [64–66]. The

relationship between glucocorticoid levels and obesity, however, might not be as clear-cut as previously assumed. In addition to stimulating, inhibiting, and interacting with other metabolically active hormones (such as insulin, leptin, CRF, and others), glucocorticoids play a significant role in controlling feeding behavior [61, 67–69]. Every stressor can initiate the release of glucocorticoids. The HPA axis reaction and the response to food intake, however, differ depending on the stressor. The duration and intensity of the current stressor have a significant role in how much the HPA axis gets involved and, consequently, how much glucocorticoids are generated in response to the stressor [70–72].

Signaling Pathway of Stress-Mediated Obesity

Obesity is a disorder of metabolism characterized by an abundant buildup of adipose tissue and has been associated with several types of molecular signaling pathways. Chronic stress can lead to a specific kind of obesity known as stress-induced obesity. The following signaling pathways [Fig. 3] have been linked to stress-related obesity:

- **Leptin Signaling Pathway:**

Leptin receptor b (LEPRb) belongs to the interleukin 6 (IL-6)-type cytokine receptor family that has three domains: extracellular, intracellular, and a single membrane-spanning domain [73–75]. LEPRb interacts with Janus Kinase 2 (JAK 2), although it lacks intrinsic enzymatic activity [73, 75]. On certain tyrosines, leptin triggers the activation of JAK2 and its autophosphorylation [76, 77]. Tyr 985, Tyr 1077, and Tyr 1138 are the three tyrosine residues of LEPRb that are phosphorylated by JAK2 [77–79].

LEPRb Tyr1138-emanated JAK2/STAT3 signaling

Leptin causes JAK2 to phosphorylate LEPRb on Tyr 1138. After that, phosphorylated Tyr 1138 then interacts with the SH2 domain of STAT3 (signal transducer and activator of transcript 3) [80]. JAK2 associated with LEPRb subsequently phosphorylates STAT3, leading to nuclear translocation and dimerization [81]. Suppressors of cytokine signaling 3 (SOCS3) and neuropeptides are two examples of target genes that STAT3 dimers regulate by acting as transcription factors in the nucleus [77, 82]. Genetic studies have shown that leptin can reduce obesity depending on the JAK2/STAT3 pathway [83,84].

LEPRb Tyr1077-emanated JAK2/STAT5 signaling

Activation of STAT5 is facilitated by JAK2, which phosphorylates Tyr1077 on LEPRb by leptin, which binds to the SH2 domain of STAT5 [85, 86]. The activation of STAT5 is also partially modulated by phospho-Tyr1138 [86]. In mice, STAT5 activation in hypothalamic neurons lower food consumption, but STAT5 elimination in the CNS result in the obesity and hyperphagia [87].

LEPRb Tyr985-emanated SHP2/ERK signaling

A binding site for the SH2 domain of protein tyrosine phosphatase 2 (SHP2) is produced by phospho-Tyr985. The extracellular signal-regulated kinase (ERK) pathway activated by leptin is mediated by SHP2 [88, 89]. Under some circumstances, SHP2 could also downregulate JAK2/STAT3 signaling [90]. Leptin's anti-obesity action acts through the SHP2 pathway, as demonstrated by the fact that mice with the SHP2 gene eliminated in the brain develop obesity at an early stage [91–93]. According to the study, the substitution of Phe for Tyrosine-985 results in the elimination of Tyr985 phosphorylation, which elevated obesity and diet-induced leptin resistance [94]. Unexpectedly, a further investigation showed that removing Tyrosine 985

phosphorylation prevents female mice from developing diet-induced obesity [95]. The outcomes of Tyr985's phosphorylation are probably influenced by the levels of intracellular SOCS3.

- **PI3K/AKT Signaling Pathway:**

The phosphoinositide 3-kinase (PI3K) pathway is also required for leptin activation [84, 96]. Mice become obese when IRS2 is deleted from the brain [97, 98]. Leptin-induced anorexia in mice is prevented by pharmacologically inhibiting PI3K in the hypothalamus [96]. The stimulation of the PI3K pathway by leptin is mediated by the adaptor protein SH2B1, which has an SH2 domain and binds to both the IRS and JAK2 proteins [99]. Leptin resistance and obesity are caused by disruptions in the SH2B1 gene [100, 101].

The forkhead box O1 (FoxO1) signaling branch

PI3K/Akt is a significant downstream effector of FoxO1, a transcription factor important for nutritional energy balance [102]. Several sites on FoxO1 are phosphorylated by Akt, which causes FoxO1 to be retained in the cytoplasm and become inactive [103]. In mice, food consumption and body weight are reduced when FoxO1 is deleted from POMC neurons [104, 105]. IRS2 null mice with removed FoxO1 are able to reverse obesity phenotypes, while LEPRb neurons with removed IRS2 become obese and have an energy imbalance [106].

The mammalian target of rapamycin complex 1 (mTORC1/ ribosomal S6 kinase (S6K) signaling branch

The mTOR/S6K pathway is a further step in the PI3K/IRS pathway's downstream processing [76]. Leptin stimulates mTORC1 to activate, which subsequently phosphorylates and triggers S6K in the hypothalamus [107, 108].

- **JNK Signaling Pathway**

The JNK signaling pathway may be activated by obesity, alcohol, and radiation to modulate inflammation, proteins, and oxidative stress [109]. JNK can be activated by the MAP2K (MKK4 and MKK7) enzymes that are present upstream of JNK. Both MKK4 and MKK7 are capable of phosphorylating JNK concurrently at the threonine-183 and tyrosine-185 sites; however, MKK4 usually phosphorylates tyrosine whereas MKK7 phosphorylates threonine. Furthermore, several upstream MAP3K is controlled by a variety of different upstream factors, such as TNFα and FFA which in turn activate MKK4 and MKK7 [110–112]. JNK is known as c-Jun N-terminal kinase as it was first identified as a kinase that mainly phosphorylates only the nuclear transcription factor c-Jun. JNK moves into the nucleus from the cytoplasm when the JNK signaling pathway is triggered, where it transphosphorylates Ser63 and Ser73 in the c-Jun transcription factor's amino-terminal active domain to activate it. The c-Jun transcription factor binds to the transcription factor activator protein-1 (AP-1) at the gene promoter after activation, triggering the expression of proinflammatory genes and protein synthesis (e.g., TNF, IL-1, IL-6, and IL-8), which leads to impaired glucose tolerance as a result of obesity and insulin resistance [113–114]. A primary function of JNK activity is to regulate metabolism by phosphorylating its substrate in the JNK signaling pathway, and it plays an important role in disease occurrence. These findings collectively demonstrate that JNK strongly influences metabolism, especially in conditions associated with inflammation and obesity [115].

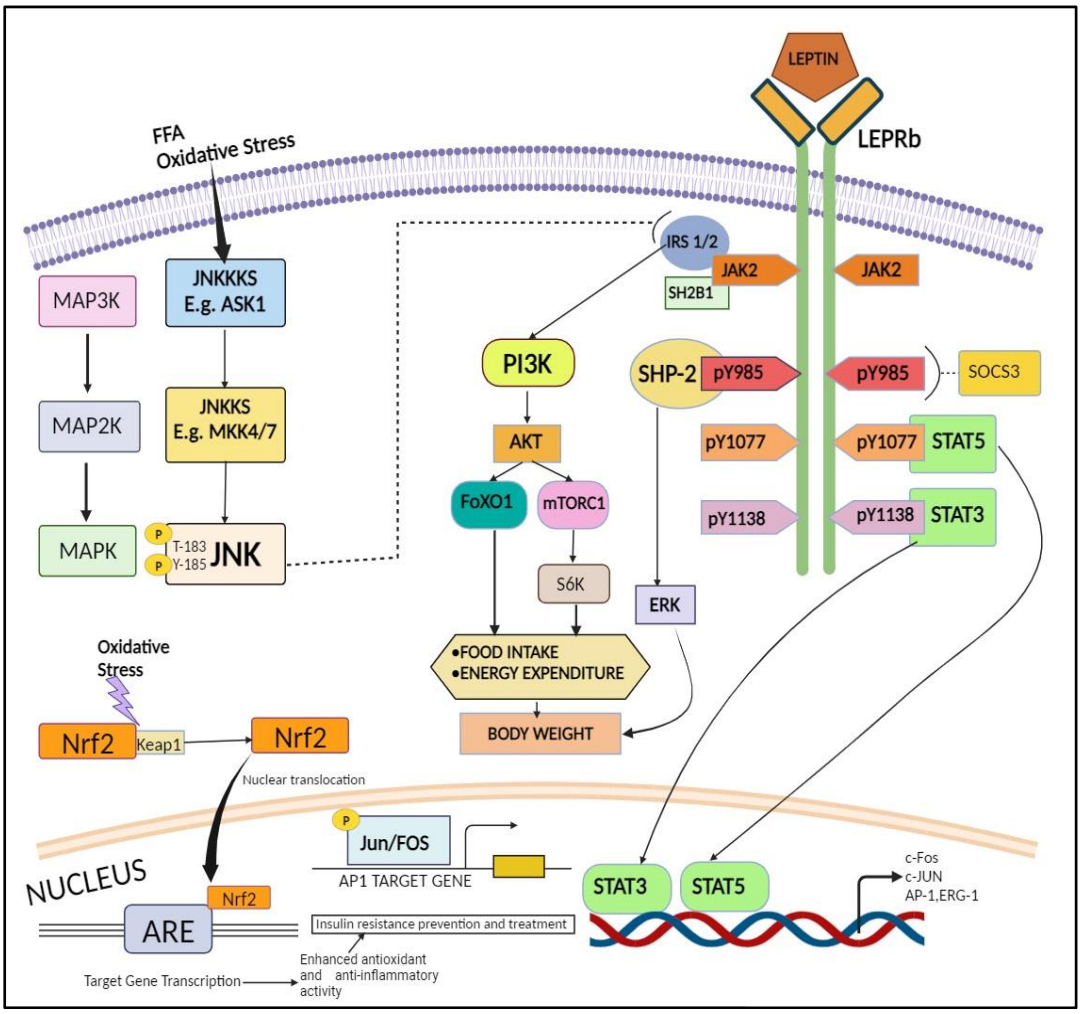

Fig. 3. The network of signaling pathways involved in stress mediated obesity. Nrf2: Nuclear factor erythroid 2-related factor 2, keap 1: kelch like ECH associated protein 1, IRS: Insulin Receptor Substrate, SH2B1: SH2B adaptor protein 1, pY985: tyrosine 985, pY1077: tyrosine1077, pY1138: tyrosine1138, ERK: extracellular signal-regulated kinase, S6K: ribosomal S6 Kinase

- **Nrf2 Signaling Pathway**

When under minimal stress, Nrf2 is cytoplasmically bound to Keap1; however, when under oxidative stress, it dissociates from Keap1 and translocates to the nucleus. Following this, Nrf2 attaches to the antioxidant response element (ARE), which triggers the transcription of the genes expressing cytoprotective antioxidants. Due to this, increased antioxidant and anti-inflammatory activity has the potential to prevent or treat insulin resistance [116].

These pathways are not exhaustive, and stress-induced obesity may include other signalling pathways. However, these pathways provide insight into the complex mechanisms that underlie the onset of obesity and might potentially serve as therapeutic targets for obesity treatment.

Stress Models

- **Visible Burrow System (VBS)**

VBS was first designed as a realistic social stress agent to study agonistic actions in rodents [117, 118]. This model imitates a rat's natural surroundings by stimulating an underground burrow

system. In the VBS, two adult female rats and four adult male rats are typically kept together. Within days, a social hierarchy forms, producing three subservient and one dominant male animal [119]. Within the VBS, subservient animals have elevated initial corticosterone (CORT), elevated testosterone and consistently reduced ~10-15% of their body mass [117, 120–124]. With other measures such as initial locomotor activity removed as contributing parameters, the reduction in body weight has been linked to changes in metabolic rate and decreased food intake [119, 124]. In the VBS, it has been shown that subservient animals produce lower levels of leptin and insulin, but the expression of orexigenic peptides and hormones is unchanged. Due to reduced food consumption and alteration in the rate of metabolism, subservient animals in the VBS show lower adiposity and a reduction in lean body mass [124]. The majority of endocrine and physiologic parameters are restored in animals who have been taken out of VBS and allowed to recuperate to enhance their metabolic phenotype, but they aren't restored to levels that are comparable to dominant or unstressed control animals in terms of body weight [119].

- **Resident Intruder**

The resident intruder model, also called as social defeat stress, has been used by researchers for a very long time to study how social dominance and subordination affect animals [125-127]. An animal is referred to as a resident when its territorial behavior toward its home cage quickly develops after being single-housed for ~1 week. The researcher introduces an entirely new, non-littermate rodent to the inhabitant within the home cage in the resident intruder model. Therefore, the new animal appears to be an invader within the cage and must compete within the social hierarchy for his position (usually held by males). While allowing for the development of a social hierarchy, it was demonstrated that keeping animals with their littermates shows no impact on anxious behavior or CORT generation in subservient animals and therefore is considered non-stressful [128]. In contrast, subservient rodent exhibit signs of stress while living with a new, non-mate rodent, including reduced immunological responses and increased food consumption, fat mass and body weight [128, 129-132].

Typically, there are two male rodents in this model- one intruder and one resident. Usually, the invader is placed in the resident's home cage, where animals are permitted to interact until one dominates another. A central barrier that divides the resident's home cage is used to separate the animals after interaction [128, 132]. This barrier allows the animals to exchange sensory information but restricts the use of physical contact. The experiment gives the animals a chance to establish a social hierarchy by removing the barrier and enabling them to interact, leading to the formation of four distinct groups: resident-dominants, resident-subordinates, intruder-dominants, and intruder-subordinate [128]. Some labs select new inmates every day of defeat in the context of persistent social defeat stress [130, 131, 133-138]. The experimental individuals are presented with a novel social order throughout each distinct incident of defeat due to the deployment of novel inhabitants. For instance, in the resident intruder model, submissive animals have elevated CORT and blood glucose levels as well as elevated levels of orexigenic/adipogenic plasma ghrelin and elevated levels of hypothalamic NPY and Agouti-related protein (AgRP) expression [132, 137]. Ghrelin signaling increases lead to further increases in hypothalamic NPY/AgRP, which stimulate adiposity and consumption of food, with a focus on visceral adiposity, which causes obesity. It is capable of decreasing stress-mediated increases in food intake, body weight gain, as well as obesity when observed in submissive rodents by interrupting the signaling of ghrelin by pharmacological blockage or genetic manipulation [132].

- **Chronic Mild Stressors (CMS)**

CMS has been demonstrated to be capable of causing depression, along with the plethora of behavioral, physical, and neurochemical alterations that often present alongside depression (such as anhedonia) [139–141]. Chronic mild stress is caused by daily stresses. The animal may experience daily stressors such as living in a congested cage, a small room or room with wet bedding, tilting the room, shock in the foot, tail pinches, living in a filthy cage, predator smell, loud noise, changes to the cycle of light/dark (for example, 24 hours of light), and more [139–145]. The induction of anhedonia is the most notable physiological effect of CMS, but this paradigm is also able to impair established location preference, decrease libido, impair immunological action, and change the sleep cycle [140]. However, only a small number of CMS-based studies show that their experimental rodents are obese. However, CMS reduces the intake of enticing meals, which has an impact on body weight [142, 144, 145]. Before attempting to mimic human obesity, it is important to think about the types of CMS that may be used in human scenarios.

Physical Stressors

- **Foot shock/ Tail pinch**

Rodent feeding behavior is influenced by two common physical stressors, such as foot shock and tail pinch. In this specific experiment, the availability of a highly palatable, calorie-dense food encouraged the rats to consume calories. Whether a tail pinch is enough to cause physiological alterations that may influence feeding behavior is unknown. The effect of general arousal is thought to be responsible for the feeding response rather than motivating feeding responses [146]. However, it has been demonstrated that foot shock increases the levels of leptin, insulin, and plasma glucose in the circulation of rats, indicating an anorectic hormonal profile [147, 149]. Animals exhibit no changes in food intake despite the anorectic hormonal profile imposed by repetitive foot shock, but they do maintain a positive energy balance and gain greater weight over time than controls not under stress [149]. According to the resident intruder paradigm, the metabolic effects of submissive animals occurred much more quickly than the body mass and body composition alterations caused by repetitive foot shocks [149].

- **Immobilization/ Restraint stress**

Two more commonly used techniques for acute physical stress are immobilization and physical restraint. According to physiologic and neuroendocrine responses, restraint stress is referred to as mild stress, yet in the hypothalamus it has been shown to enhance the synthesis of orexigenic peptides [149]. Mild restraint stress can increase AgRP-expressing neurons in the ARC while simultaneously decreasing α-MSH receptors. Particularly acute restraint activates cFos in the lateral hypothalamus, paraventricular nucleus, and ARC; however, recurrent exposure diminishes the activation, indicating adaptation to the stress model [149-150]. On the other hand, immobilization stress is regarded as an effective physical stressor causing HPA axis hyperactivity since it significantly increases CORT secretion [151]. Following immobilization stress, it has been seen that rats eat less and acquire less weight, indicating evidence of the stressors' potency. Additionally, after immobilization stress, no alterations in NPY production are observed, providing hormonal support for the food intake responses to this kind of stressor model [152]. Data on the possibility of immobilization stress habituation are contradictory [152-154].

- **Cold stress**

In the rodent and human stress paradigms, exposure to cold physical stressors has been employed. In humans, cold physical stressors cause cortisol levels to significantly increase 15

minutes after the initiation of the stressor [155]. The release of cortisol is typically associated with subsequent calorie intake in stress protocols that might induce an obese-like phenotype. It has been demonstrated that cold stress increases CORT secretion in rodents and that CORT secretion is closely associated with the upregulation of hypothalamic orexigenic peptides (such as NPY/AgRP). When cold stress and a high-fat diet are present, NPY and its receptor (Y2R) appear to significantly increase in white adipose tissue. Additionally, it was hypothesized that these modifications would cause adipocytes to proliferate and differentiate, leading to obesity and a state that resembled the metabolic syndrome [156]. Following subordination stress, similar elevations in Y2R have been seen in white adipose tissue [132].

2. Conclusion And Future Perspectives

The major focus of this study is on the impact of stressful environments on the occurrence of obesity and other similar metabolic diseases. According to studies, people eat more when they are stressed as compared to when they are happy because stress causes our bodies to release the hormone cortisol. However, stress-induced eating might be difficult to resist since eating is pleasant. The hormone leptin is important to the regulation of body weight and homeostasis, and leptin resistance is now known as the major contributing factor to obesity. In the brain, specifically in the hypothalamus, leptin promotes weight reduction predominantly through activating the LEPRb pathways. However, it is unknown how the many LEPRb pathway branches function specifically and/or in coordination to control various aspects of food intake behavior and energy expenditure.

In relation to obesity, the interaction between neuronal and hormonal communication through the gut-brain axis has a variety of physiologic aspects, including homeostasis, and might be used as a target for therapy in the future. The precise monitoring of homeostasis and consumption of food might help to produce a more individualized therapy for obesity, regardless of whether it is pharmacological or psychological.This way of treatment quite helpful in the society to control obesity associated diseases.

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