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Obesity Induced by Chronic Psychological Stress: A Review of Neuroendocrine Mechanisms and Metabolic Effects

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Abstract:

In modern society, the frequency of chronic stress states such as stress and anxiety in individuals is increasing, and the number of obese people is increasing. Multiple studies have clearly pointed out that chronic stress is positively correlated with body weight. Its core mechanism is that the prolonged activation of the HPA axis results in a long-term increase in cortisol, which interferes with the function of the hypothalamic feeding center through neuroendocrine. This review focuses on the neuroendocrine mechanism of the "cortisol-NPY" pathway in stress-induced obesity, and sorts out the signal transduction mechanism from HAP axis activation to arcuate nucleus NPY/AgRP upregulation, POMC/CART downregulation, and then to imbalanced eating behavior. At the same time, the positive feedback in the short-term relief of anxiety by high-fat and high-sugar intake is analyzed, and how this mechanism promotes the vicious cycle of stress eating. Further experiments such as TSST illustrate the individual differences in cortisol reactivity and its value in predicting metabolic risks. At the intervention level, this article explores the application prospects of drug strategies targeting NPY signals and psychological regulation programs represented by CBT. The central regulatory mechanism mediated by cortisol helps to more accurately identify susceptible individuals and formulate personalized prevention and treatment strategies for stress-induced obesity.

Keywords:-Stress-induced obesity; cortisol; feeding behavior; HPA axis; NPY pathway

I. Introduction

As the pace of modern society accelerates, individuals are increasingly exposed to chronic stress. Studies have shown that chronic psychological stress not only affects emotion regulation, but may also interfere with endocrine homeostasis and energy metabolism. In this context, feedback regulation of

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the hypothalamus-adrenocorticoid (HPA) axis, an endocrine stress response mediator, plays a key role in this chain [1]. This regulation is mediated by glucocorticoid receptors in the lower part of the brain. Chronic stress can lead to long-term increases in glucocorticoid GC (such as cortisol), which is different from the immediate negative feedback of glucocorticoid in acute stress. Long-term increases in GC can lead to failure of the negative feedback mechanism or adaptive changes. At the same time, GC enhances the reward response to food, especially high-energy food (sugar, fat), through its positive effects on the midbrain-limbic system. In addition, the World Obesity Federation's "Atlas 2025" predicts that by 2030, the total number of obese adults will more than double from 2021, from 524 million to 1.13 billion [2]. This also shows that obesity has become increasingly common in modern life, making normal metabolism even more unbalanced [3].

Although the mechanism has been preliminarily established, there is still a lack of systematic analysis and integration of the specific regulatory steps of the cortisol - neuropeptide Y (NPY) pathway in stress behavior, the relationship between the downstream effector molecules involved and their individual differences. It is generally believed that the cortisol response in the population varies greatly when responding to any given stressor. In the process of exploring the mechanism of obesity, some studies have found that the intensity of cortisol's response to adrenocorticotropic hormone ACTH varies genetically between individuals, and this difference is closely related to fat storage and metabolic regulation. Therefore, individuals with high cortisol reactivity are considered to be more susceptible to metabolic imbalance and thus show a higher risk of obesity, and this responsiveness can be used as a potential predictive indicator to assess an individual's susceptibility to stress-induced obesity [4]. Therefore, in-depth exploration of the regulatory mechanism of the cortisol -NPY pathway will not only help reveal the neuroendocrine basis of stress-induced obesity but also lays the theoretical groundwork for the formulation of personalized intervention strategies.

II. Chronic activation mechanism of the HPA axis and cortisol

A. Stress Stimulates Cortisol Release through Corticotropin-Releasing Hormones CRH and ACTH

The HAP axis is not a simple metabolic pathway, but a neuroendocrine channel that regulates stress response. It mainly regulates metabolism through cortisol and also plays a regulatory role in the energy metabolism system, rather than a metabolic pathway on the material conversion path. When individuals face stress, Hypothalamic paraventricular nucleus (PVN) neurons involved in neuroendocrine regulation are activated, releasing CRH and arginine vasopressin AVP to trigger HPA axis activation [4]. These two factors act synergistic on the anterior lobe of the pituitary gland, which in turn triggers the secretion of ACTH, and ACTH in turn promotes the release of glucocorticoids (GC) by the adrenal cortex. Cortisol is the main GC and plays multiple roles in promoting metabolic behaviors such as gluconeogenesis, fat mobilization, and protein breakdown, as well as in immune and neurological functions.

CRH is a neuropeptide that is the starting point for HPA axis activation and the key point for connecting 'neuro-endocrine-metabolism'. In the PVN and supraoptic nucleus, AVP is expressed in the magnocellular neurons; in addition, AVP and CRH were found to be co-expressed in the parvocellular neurons of the PVN.

B. Negative Feedback Imbalance Forms Feedback Passivation

Under normal circumstances, cortisol regulates the secretion of CRH and ACTH through negative feedback, forming a typical HPA axis closed loop. And under short-term stress, this mechanism is adaptive, helping to mobilize energy resources and enhance stress coping ability. However, under chronic stress conditions, such as persistent anxiety and long-term social evaluation pressure, sustained high levels of cortisol will reduce the sensitivity of the hypothalamus and pituitary gland to it, causing the HPA axis to be in a chronically activated state, forming the so-called feedback blunting phenomenon, which gradually makes the negative feedback pathway ineffective [4].

C. High Cortisol Levels Under Chronic Stress are The Core of Pathology

The HPA axis has important physiological significance in responding to acute stress, but under chronic stress conditions, the continuously activated HPA axis releases CRH and ACTH for a long time, leading to a continuous increase in cortisol; and the disorder of its own negative feedback mechanism and the decrease in the sensitivity of the glucocorticoid receptor GR make it difficult for the HPA axis to shut down, forming a vicious positive feedback loop. This state not only destroys the normal endocrine balance of the body, but also may cause a series of metabolic and neuropsychiatric diseases. Therefore, a correct understanding of the regulatory mechanism of the

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HPA axis can prevent and provide new ideas for the treatment of diseases related to chronic stress.

III. Effects of cortisol on the hypothalamic feeding center

A. NPY/AgRP and POMC/CART Show Opposite Regulatory Trends in the Arcuate Nucleus

One of the central targets of cortisol is an area of the hypothalamus called the arcuate nucleus, where there are two functionally antagonistic neuronal groups: one is neurons that co-express NPY and the Agouti-related protein (AgRP), which plays an important role in the regulation of energy; Neurons classified as another type are characterized by the co-express of pro-opiomelanocortin (POMC) and cocaine-amphetamine regulated transcript (CART), which have anorexigenic effect. Under chronic stress conditions, cortisol can promote an individual's appetite response by enhancing the expression of NPY in the hypothalamus. This mechanism may mediate appetite enhancement by acting on the Y1R receptor of NPY neurons. In a mouse chronic stress model, electrophysiological recording technology of hypothalamic POMC neurons was used, and it was found that the discharge frequency of POMC neurons was significantly reduced under chronic stress conditions, and these neurons were responsible for releasing melanocyte-stimulating hormone α-MSH, which plays a role in suppressing appetite. As the activity decreased, the experimental animals also expressed higher food intake [5]. Individuals with higher cortisol reactivity are more likely to show a tendency to consume high-energy foods after exposure to stress, suggesting that this mechanism not only exists at a general level, but also has individual differences. Chronic high cortisol exposure significantly upregulates the expression of NPY and AgRP, enhancing feeding motivation.

B. Signal Transduction Pathway Analysis

NPY achieves its function by activating the Y1 receptor, while AgRP antagonizes MC4R, blocking the binding of α-MSH to the receptor and disrupting with POMC-mediated signal transduction, thereby inhibiting the transmission of anorexigenic signals. In a classic experiment, AgRP was injected into the cerebral ventricle of mice, and the promotion of appetite and weight gain were observed, which established that AgRP is an endogenous antagonist of MC4R, competing for binding and blocking the effect of α-MSH to inhibit POMC-mediated appetite-inhibiting signals [6]. At the same time, AgRP-specific VGAT knockout mice, combined with optogenetics, have shown that AgRP can also directly inhibit the activity of POMC/CART neurons by releasing γ -aminobutyric acid (GABA), further reducing the inhibitory regulatory ability.

C. Imbalanced Appetite Regulation: Overeating, Especially Preference for High-Energy Foods

In adrenalectomized animals, cortisol replacement hormone can restore the preference for sweet foods, indicating that cortisol regulates the preference for high-sugar foods after stress. In addition, high cortisol levels will enhance the effects of orexigenic neuropeptides and weaken satiety signals [7]. Therefore, cortisol reactivity not only affects hormone levels, but also regulates feeding tendencies through central nervous system mechanisms, turning stress into hedonic eating rather than eating due to physiological hunger.

IV. High-sugar and high-fat foods and positive feedback mechanisms

A. Comfort Food Intake Regulates HPA Axis Function and Activity During Stress

In rats that underwent adrenalectomy to remove their endogenous glucocorticoid source, the researchers observed the dose-dependent effects of GC on behaviors such as feeding, reward, and locomotion, as well as dopamine activity in the brain reward system. They found that under chronic stress, the negative feedback inhibition produced by GC on the brain and anterior pituitary gland was significantly weakened, and CRH, AVP, and ACTH levels could not be regulated normally. At this time, the intake behavior of comfort foods rich in fat or sugar is greatly affected by GC regulation. Eating comfort foods can cause reward-mediated negative feedback on the HPA axis, thereby inhibiting the HPA axis and temporarily relieving stress symptoms, affecting normal metabolism and appetite regulation [8].

B. Overeating High in Sugar and Fat Will Create a Vicious Cycle of Stress Metabolism

Long-term consumption of foods rich in fat and sugar not only interferes with the body's metabolic mechanisms, but also profoundly reshapes the brain's stress-related neural circuits, especially affecting the dynamic regulation function of the HPA axis. Mice that have long consumed comfort food have significantly reduced expression of adrenocorticotropic hormone-releasing factor (CRF) in the central amygdala (CeA), a change that is associated with anxiety relief [9]. However, once these mice stop having access to comfort food, CRF expression levels rise rapidly, even higher than mice that have never had access to

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comfort food [10]. This result indicates that this increase in CRF levels is also common in rats in a withdrawal drug addiction model, indicating that comfort food may have a dependence potential similar to that of drugs [11].

In addition, it was found that mice that had been deprived of comfort food were more inclined to take risks to obtain comfort food rather than easily obtain ordinary food, even in an environment without obvious threats [10]. This phenomenon shows that comfort food can also enhance the drive for reward at the behavioral level. Even if there are potential negative consequences, individuals are still willing to take risks to obtain comfort food, which is highly consistent with the addiction mechanism.

At the physiological level, a long-term high-fat diet can increase basal cortisol levels and reactive cortisol levels, while interfering with the negative feedback mechanism of the HPA axis, weakening its regulatory function. Due to the reduced expression of corticosteroid receptors (GR) and mineralocorticoid receptors (MR) in the hypothalamus, the inhibitory feedback of the hippocampus to cortisol becomes sluggish, the negative feedback inhibition of the hypothalamic endocrine cascade that mediates cortisol release is weakened [11]. Dysregulation of corticosteroid receptors can lead to increased HPA axis activity and increased anxiety behaviors. This further consolidates the " stress-eating-relief-withdrawal-binge eating " cycle. Comfort food temporarily relieves stress and reduces CRF levels through the reward system, but subsequent withdrawal will trigger a stronger stress response and anxiety, prompting individuals to binge eat again to seek relief.

V. Individual Differences—Predictive Values of Cortisol Responsiveness

A. Metabolic Risks of High Responders

In all species, there are significant differences between individuals in the cortisol response to stressors. When faced with stressful stimuli, individuals with significantly elevated cortisol levels, higher-than-average response concentrations, and slower recovery are defined as hyper-responders 4, which is one of the factors for visceral fat accumulation. The high sensitivity of the HPA axis function is positively correlated with visceral fat accumulation and insulin resistance, and cardiovascular disease, mainly due to the destructive effects of long-term excessive exposure to cortisol on the metabolic system.

B. Trier Social Stress Test (TSST)

Using the TSST as a stress induction model, a group of healthy premenopausal women were evaluated for stress response. It was found that stress-induced cortisol reactivity was positively correlated with increased calorie intake after exposure to a new laboratory stressor. It is worth noting that under the same social evaluation stress conditions, women with high cortisol reactivity consumed more food during the stress recovery process than those with low reactivity, and consumed significantly more high-fat sweets. They were also more likely to have abdominal fat accumulation, decreased cortisol metabolic efficiency, and higher self-perceived stress scores *[12]*. This shows that different individuals have different levels of HPA axis activation, which can not only be used as a response to psychological state, but also a direct biological indicator of metabolic health.

The cortisol response pattern has potential clinical predictive significance. Early standardized tests such as TSST can identify high cortisol responders, which may become a marker for predicting susceptibility to chronic diseases. At the same time, through the different states of individual stress response, such as impulsive eating, poor emotion regulation, and overeating, it provides a solution direction for personalized psychological-physiological joint intervention in the future.

VI. Future Directions and Application Prospects

A. Potential Therapeutic Strategies Targeting NPY

Low-dose NPY can mimic the anxiolytic effects of benzodiazepines and barbiturates by acting on the common core processes of fear and stress-related behaviors and emotions [13]. NPY can achieve acute anxiolytic effects by activating Y1 receptors to promote neural stem cell proliferation and induce neurogenesis, and can also exert long-term antidepressant effects by enhancing neural plasticity. NPY is also involved in stimulating hippocampal neurogenesis, and stimulating neurogenesis in the hippocampus is almost all clinically effective antidepressant treatments. This further demonstrates the prospect of the NPY system as an antidepressant target.

B. Individual Biomarker Screening

Cortisol concentration is an effective indicator of HPA axis activity. At basaline or in response to acute stressors, there are differences in the regulation of the HPA axis under disease conditions such as depression and post-traumatic stress disorder compared with healthy people [14]. When examining individual psychotherapy or obesity treatment, using the HPA axis and cortisol as auxiliary

biomarkers to diagnose the disease may have certain advantages, and psychotherapy interventions can alleviate the symptoms by regulating the function of the HPA axis and the autonomic nervous system ANS and affecting the levels of biomarkers such as cortisol and α-amylase.

C. Intervention Recommendations

Cognitive behavioral therapy (CBT) is based on the cognitive behavioral model, which stems that an individual's anxiety stems from an interaction between negative thoughts and avoidant behaviors. It aims to change patients' thinking, beliefs and behaviors by identifying and re-understanding negative thoughts and attitudes and positive self-guided behaviors [15]. It is currently widely used in clinical practice to treat depression, anxiety and psychological disorders. For example, a community randomized controlled trial of patients with tuberculosis showed that after two months of CBT intervention, the anxiety GAD-7 and depression PHQ-9 scores of patients were significantly reduced, and the quality of life scores were significantly improved, indicating that CBT can effectively improve individual stress management and anxiety reduction [16].

In the actual application of stress-induced obesity, CBT can help individuals understand through cognitive reconstruction that "I can only relieve my mood by eating something sweet and high in calories" is a wrong cognition under long-term or high-intensity stress, and help them understand that this unhealthy eating behavior is a response to anxiety or lack of control, rather than a real hunger signal from the body. Then, through intervention training, individuals can learn to be aware of emotions and actions, and take the right and healthy way to relieve stress instead of eating, thereby significantly reducing the frequency of stress-induced eating and the trend of weight gain.

This process not only involves cognitive adaptation, but also indirectly regulates HPA axis reactivity by reducing chronic stress, lowering cortisol levels, and improving the sensitivity of the central feeding regulatory system.

VII. Conclusion

This study sorted out and demonstrated the core role of the cortisol-NPY mechanism in stress-induced obesity. The HPA axis responds to stress by increasing CRF and cortisol levels, which in turn triggers the NPY-mediated feeding response.This reveals a central pathway linking stress, neural regulation, eating behavior and metabolic disorders. In particular, the NPY system, through its Y_1 receptor, not only promotes high-fat and high-sugar feeding behavior under stress, but may also further promote the vicious cycle of "stress-eating-relief-binge eating" by regulating hippocampal neurogenesis and emotional state.

Dynamic assessment of cortisol can be used as a biomarker screening method for high-risk individuals, and new drug intervention strategies targeting the NPY system, such as the use of Y_1 receptor antagonists or agonists, are also becoming the direction of future treatment. In addition, combining CBT with dietary structure management also provides a realistic and feasible solution to alleviate the psychological-metabolic imbalance of such individuals. In-depth understanding of this pathway is not only a breakthrough in basic research, but also an important starting point for individualized intervention in the era of precision medicine.

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