



The Serotonergic System in Diet, Obesity and Mental Health



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Abstract

Mental health and obesity research seldom intersect despite that poor diet and serotonergic system disturbances are common in both etiologies. Many interplaying factors lead to a concomitant dysregulation of the feeding centers and the limbic emotional processing centers. Leptin resistance, poor diet and lifestyle, inflammation, and psychological stress Interwine to disrupt these functions. Despite that many neurotransmitters play a role in these processes; the serotonergic system appears to be at the heart of these disturbances. Therefore, shedding the light on these factors and their effect on the serotonergic system may support a comprehensive therapeutic approach. Another goal for this review was to evaluate the cellular and molecular derangements associated with feeding disturbances and mental health to better shed the light on the intricate factors leading to their development.

Keywords: Leptin; Serotonin; Diet; Exercise; Inflammation; Stress; Obesity; Anxiety; Depression

Abbreviations: BBB: Blood-Brain Barrier; IL: Interleukin; 5-HT: 5-Hydroxytryptamine; HPA: Hypothalamic Pituitary Adrenal; PVN: Paraventricular Nucleus of the Hypothalamus; Tph: Tryptophan Hydroxylase; KO: Knockout; CNS: Central Nervous System; GABAergic: Gamma Aminobutyricacid Ergic; LNAA: Large Neutral Amino Acids; EPA: Eicosapentaenoic Acid; DHA: Docosahexaenoic Acid; CV: Cardiovascular; NPY: Neuropeptide Y; AgRP: Agouti Related Protein; POMC: Proopiomelanocortin; CART: Cocaine and Amphetamine Regulated Transcript; NMDA: N-methyl-D-aspartate

Introduction

The fields of mental health and obesity research are less likely to interconnect despite that both conditions have poor diet and serotonergic system disturbances as a common etiology. Obesity is usually linked to dysregulation of the hypothalamic neural circuits of the feeding centers. Mental distress, namely anxiety and depression, appear to be linked to dysregulation of neural circuits in the limbic regions such as the hippocampus and the amygdala. However, neural circuits involved in both morbidities are activated by the same set of neurotransmitters. Monoamines such as dopamine, norepinephrine and serotonin are the major target for psychiatric drugs. The same neurotransmitters are also the target of some weight loss medications that regulate the hypothalamic feeding centers. Although dopamine, and to a lesser extent norepinephrine, have been reported to have some effect on the feeding center, their main role is in the limbic reward system. On the other hand, serotonin appears to play a key role in the dysregulation of both systems. Additionally, obesity and mental distress have been both associated with increased risk for dementia and cognitive decline [1]. Poor diet increases systemic inflammation which contributes to the etiology of cognitive impairment. [2] Consequently, the brain becomes susceptible to oxidative stress due to the limited endogenous antioxidant enzymes and the tight

regulation over transport of antioxidants and others across the blood-brain barrier (BBB). Inflammation in the brain has been linked to leptin resistance [3] and to mental distress [4,5]. Patients with mental disease and those with a body mass index within obese ranges commonly have activated inflammatory pathways manifested by increased pro-inflammatory cytokines such as interleukin (IL)-6, and/or C-reactive protein as positive markers of acute-phase proteins [4,6]. Inflammation and subsequent oxidative stress disturb homeostasis by altering redox signaling and gene expression [7].

The purpose of this review was to elucidate the different components of the serotonergic systems that control the limbic and the feeding centers. Another goal was to evaluate the cellular and molecular derangements associated with feeding disturbances and mental health to better shed the light on the intricate factors leading to their development.

Discussion

The serotonergic system: the interface between feeding behavior and mental health

Serotonin, or 5-hydroxytryptamine (5-HT), and its receptors play a vital role in the regulation of nearly all brain functions despite

that the majority of serotonin is produced in the gut [8]. However, many of the serotonergic neuronal projections within the cortical, limbic, midbrain, and hindbrain regions appear to originate from the brainstem [9]. There are currently fifteen identified serotonin receptors which are grouped into seven families based on their intracellular signaling mechanisms [10]. In addition, all brain regions express several serotonin receptors with typically specific subtype patterns [11]. However, individual neurons also express different serotonin receptors with disparate effects to modulate neuronal activity [12].

Serotonin regulates brain regions responsible for emotional processing (which include the prefrontal cortex and the limbic system) and the hypothalamic feeding centers such as the hypothalamus, the extended amygdala and brainstem [13,14]. In fact, dysregulation of the serotonergic system in these brain areas has been implicated in the pathogenesis of many psychiatric conditions and disordered eating [15,16]. Alternatively, chemicals that promote the increase in 5-HT neurotransmission are typically prescribed for the treatment of depression, anxiety, and in some instances obesity. At night (or in dim light), serotonin is metabolized further into melatonin in the pineal gland. Therefore, 5-HT also contributes to the circadian rhythm. A mutual functional interface exists between central 5-HT system and the hypothalamic-pituitary-adrenal (HPA) axis under normal physiological conditions. Therefore, serotonin plays a significant role in the HPA axis regulation to turn off centrally the stress response through a negative feedback loop [17]. In fact, the hippocampus and the paraventricular nucleus of the hypothalamus (PVN), part of the limbic serotonergic system, are regions in which components of the HPA axis and the 5-HT systems interact extensively. Multiple central and peripheral inputs converge on PVN to modulate the HPA axis where corticotropin-releasing hormone is synthesized. Subsequently, adrenocorticotropin signals the pituitary gland to release cortisol from the adrenal cortex [18]. The steady rise in plasma cortisol concentration attenuates the stress response in the hypothalamus and pituitary gland via a negative feedback loop. Consequently, dysregulation of HPA and 5-HT systems contributes to the pathophysiology of mental diseases. Therefore, dietary or pharmacological therapies need to address this dysregulation to produce a healing effect [19].

Tph2 and brain serotonin synthesis

Serotonin is synthesized in the brain and in the peripheral tissue by a rate-limiting enzyme: tryptophan hydroxylase (Tph). Tph exists as two isoforms, Tph1 and Tph2, which are encoded by two separate genes. Tph1 is the rate-limiting enzyme that controls 5-HT synthesis in the periphery (gut, pineal gland, spleen and thymus); whereas Tph2 is more localized to the brain [20]. In humans, Tph2 is highly expressed in frontal cortex, thalamus and hypothalamus and less expressed in the hippocampus and amygdala, and hardly detectable in peripheral tissues [21]. Evidence from the literature reveals that Tph2 gene expression is highly inducible and is closely related to the stress response. However, glucocorticoids effect on Tph2 expression appears to be species-dependent and

may be tissue-specific [22]. Additionally, daily fluctuations in glucocorticoids levels modulate the circadian rhythmic Tph2 expression, which explains the reduction in brain serotonin with sleep deprivation. This phenomenon was demonstrated through adrenalectomy in lab animals which led to a total suppression of the daily rhythmic Tph2 mRNA expression in the raphe nucleus. In contrary, glucocorticoid restoration in the same models reinstated Tph2 expression [23]. In fact, serotonin-receptor knockout (KO) studies reflect these critical functions of 5-HT in different organ systems such as the central nervous system (CNS), GI, heart, endocrine functions and others. Autonomic functions such as sleep, respiration, body temperature, blood pressure and heart rate are severely altered with disrupted Tph2 expression or absence of 5-HT [24]. To better understand the effect of Tph2 gene expression in relation to 5-HT functions, KO mice studies completely lacking 5-HT in the brain, reported growth retardation and increased lethality in early life stages. These findings suggest that Tph2 gene expression is closely associated with the biological clock and the stress response. Additionally, sleep quality may affect levels of Tph2 expression and thus 5-HT concentrations.

Function of 5-HT_{2C} receptors

CNS serotonergic neurons exert a moderating effect on an extensive neural network through modulation of the gamma-aminobutyric acid-ergic (GABAergic) neurons activity. This extended control explains the widespread effect of serotonin on human behavior [11]. These behaviors include mood, feeding and appetite, reward, aggression, perception, memory, sexuality, anger and attention, among others. Although the neural circuits responsible for these behaviors have not been all elucidated, it appears that different brain regions control specific behaviors via an explicit concoction of serotonin receptor subtypes. 5-HT_{2C} expression is particularly high in the limbic system which implies its fundamental role in mental distress and disordered feeding. In fact, 5-HT_{2C} receptors KO in mice studies induce concomitant hyperphagia [25], and anxious behaviors [26]. Additionally, 5-HT_{2C} receptor regulates reward processing, locomotion and energy balance [27]. Weight loss and psychiatric medications are often associated with several side effects and in most instances; they exhibit an opposite effect on the other co-morbidity. For instance, weight loss medications increase the incidence of mental distress, and several psychiatric medications promote weight gain. Therefore, therapies that support treatment of both conditions simultaneously are warranted. Taken all evidence collectively, Tph2-derived 5-HT multitasks between behavior regulation, autonomic control and modulation of metabolic pathways which implicates it in the pathophysiology and pharmacology of mental disease.

Effect of diet and exercise on serotonin

Dietary composition and exercise have a significant effect on serotonin synthesis. The essential amino acid tryptophan is the precursor for 5-HT production. Tryptophan shares with the other large neutral amino acids (LNAAs) a common carrier across BBB. Therefore, tryptophan/LNAA ratio determines the amount of tryptophan supplied to the brain. A protein-rich diet provides

copious endogenous amounts of amino acids which lower the tryptophan/LNAA ratio. Subsequently, serotonin production decreases. On the other hand, a complex carbohydrate-rich diet induces a steady rise in serum insulin, which promotes a continuous amino acid uptake by peripheral tissue. Consequently, tryptophan/LNAA ratio increases which leads to a constant rise in central 5-HT synthesis [28]. This explains the reason behind increased carbohydrate cravings with a negative mood. Therefore, dietary interventions to promote mental wellbeing and weight control need to assess the ratio of protein to carbohydrates as well as the quality of carbohydrates consumed.

Inflammation induces leptin resistance which has been linked to obesity and mental distress [3,29,30]. A healthy ratio of essential fatty acids omega-6/3 is needed to prevent low chronic inflammation. In fact, a high ratio of omega 6/3 has been linked to mental distress severity and obesity [31,32]. Dietary omega-6 fats are precursors for arachidonic acid from which pro-inflammatory prostaglandins are derived. Marine omega-3 fats (eicosapentaenoic acid (EPA eicosapentaenoic acid) exhibit an anti-inflammatory effect through production of anti-inflammatory prostaglandins. Increase in cortisol levels associate with reduced levels of EPA [33], which add to the inflammatory response. Another important omega-3 fat is docosahexaenoic acid (DHA), which is one of the most abundant fats in the brain. Low levels of DHA have also been linked to mental distress in animal and human models [34,35]. Therefore, a balance between omega-6 and omega-3 fats is needed to prevent chronic low-grade inflammation and improve mood as well as leptin sensitivity [36,37].

Exercise promotes muscle use of branched-chain amino acids (BCAA), a type of LNAA, which reduces the competitive transport of tryptophan to the brain [38,39]. In fact, brain stem and hypothalamus synthesis of 5-HT significantly increases with acute cardiovascular (CV) exercise. It appears that serotonin synthesis in the cerebral cortex and hippocampus remains low with acute CV exercise. However, chronic CV exercise induces sustainable adaptation that leads to increased synthesis and metabolism of 5-HT in the cerebral cortex and in the hippocampus [39]. Therefore, the antidepressant effect of CV exercise typically comes from chronic exercise and not much from occasional activities [40]. CV exercise also sensitizes the muscle to efficiently oxidize glucose for energy which reduces inflammation and improves mood as well as body weight.

Serotonin and the gastrointestinal system

Discussion on feeding behaviors cannot be complete without addressing the gut hormones. The gut is the largest endocrine organ in the human body which contributes numerous peptide hormones critical for the short-term feeding behaviors. These hormones mainly control meal initiation and termination. The key peptides include cholecystokinin, ghrelin, pancreatic polypeptide, and others [41]. All gut hormones have an anorexic effect except for ghrelin, which increases hunger and promotes regulation of energy metabolism. In fact, ghrelin is an endogenous ligand for the growth hormone secretagogue receptors primarily found in the pituitary gland, on hypothalamic neurons in the brainstem and recently

reported in immune cells [42,43]. Additionally, the growth hormone is of importance for maintaining synaptic plasticity, especially with sleep deprivation [44]. Therefore, during stressful times, when sleep quality declines, ghrelin may have a protective effect on the neural circuit integrity involved in emotional processing and feeding centers. Additionally, ghrelin acts on the innate and adaptive immune systems to suppress inflammation and induce an anti-inflammatory profile. However, ghrelin actions differ between peripheral tissue and the brain. Peripheral daily administration of ghrelin in lab animals induced weight gain through reduced fat utilization. However, intra-cerebroventricular administration of ghrelin in the same experimental models led to a dose-dependent increase in food intake and body weight. Moreover, ghrelin seems to have an anxiolytic effect. In animal studies, ghrelin administration attenuates anxious behavior through the modulation of the HPA axis [45]. Like serotonin, ghrelin modulates HPA axis by integrating central circuitry involved in anxiety and psychological stress. In human models, high cortisol levels lead to higher production of ghrelin to support the negative feedback loop described earlier. Like serotonin, circulating ghrelin levels are also reduced in patients with mental distress. Taken all together, ghrelin is at the juncture between feeding, growth, energy metabolism and stress response [46]. Based on the given facts, experiencing intermittent low dose ghrelin secretion may have a positive effect on stress and mood. However, higher ghrelin levels may induce an increase in feeding behavior and body weight [47]

Feeding Centers

Feeding behaviors are regulated by a complex network that covers different areas of the brain. However, the hypothalamus is the main regulatory component of this network. The arcuate nucleus of the hypothalamus houses two major types of neurons that regulate feeding behavior. The orexigenic neurons neuropeptide Y (NPY)/agouti-related protein (AgRP) promote feeding upon stimulation. The anorexigenic proopiomelanocortin (POMC) and cocaine-and-amphetamine-regulated transcript (CART) peptides inhibit feeding when activated [48]. Both systems work through the cAMP second messenger system. Additionally, the two systems project fibers to different areas of the brain that control feeding behavior. NPY/AgRP neuronal projection extends to POMC neurons acting as an inverse agonist to stimulate feeding.

Leptin

Leptin, a hormone produced by the adipose tissue, is a long-term regulator of feeding behavior. The 16-kDa hormone enters the brain through the cerebrospinal fluid at low nanomolar concentrations (10–20 nM) [49]. Leptin mRNA has been localized in neuronal populations including the hippocampus [50], which suggests confined production as well. Leptin is believed to be part of the set-point theory which describes an increase in food intake and a decrease in energy expenditure with a decrease in serum leptin levels and vice-versa [51,52]. Leptin exerts its effect on hypothalamic as well as brainstem serotonergic neurons which proposes that these regions are closely associated with regulation of food intake [53]. Precisely, abundant leptin receptors exist in

the hypothalamic orexigenic neurons NPY/AgRP as well in the anorexigenic POMC and CART peptides [48]. AgRP neurons have direct inhibitory effects on POMC neurons; however, a reciprocal synapse from POMC neurons to AgRP/NPY neurons does not exist [54]. Therefore, this dual presence of leptin receptors in the microcircuit is crucial for modulation of the feeding response. The integration of peripheral and central inputs produces an integrated response necessary for the inhibition of NPY/AgRP neurons and stimulation of POMC/CART neurons [55]. The leptin-dependent inhibition of AgRP/NPY neurons is believed to involve modulation of the voltage-gated K⁺ channels. Diet-induced obesity in animal models has been associated with continuous activation of NPY neurons due to inability of leptin to hyperpolarize the resting membrane potential.

Psychological stress and leptin levels

Animal and human studies suggest that leptin and stress interact through a closed loop. Low leptin levels associate with increased symptoms of depression in young females, independent of body fat or weight [30]. Additionally, those with clinical depression exhibit lower levels of leptin after controlling for fat mass or body weight. Leptin acts as an anti-stress hormone by attenuating the response of the adrenocorticotropic and corticosterone hormones to stress and by inhibiting glucocorticoid synthesis and its release from the adrenal cortical cells [56]. Acute stress does not affect leptin levels in lab animals. However, chronic stressors decrease basal plasma levels of leptin independent of body weight [57]. Remarkably, previous negative life experiences sensitize leptin secretion response to acute stress. Reduced serum leptin levels with psychological stress correlate with behavioral alterations indicative of mental distress. Mechanistically, leptin regulates gene expression in the limbic brain areas, particularly the hippocampus, which is implicated in the pathophysiology of major depressive disorders [57]. Direct activation of the leptin receptor in the hippocampus but not in the hypothalamus produces antidepressant-like behavioral effects in experimental models, suggesting that the hippocampus is a neuroanatomical substrate for leptin's antidepressant-like actions. Therefore, as part of a therapeutic approach, an initial stress reduction is needed to support the anti-stress effect of leptin to consequently improve mood and metabolism.

Inflammatory Cytokines

The challenge with inflammatory cytokine assessments is that their production follows a circadian rhythm [58]; therefore, variation in assessment timing in research may explain the inconsistent findings described in the literature about the association between inflammation and comorbidities. Characteristically, BBB is a robust interface between peripheral tissues and the brain. Cytokines are large molecules that cannot penetrate BBB, and mostly work in a paracrine fashion. However, evidence suggests that systemic inflammation generates leaky regions in BBB which allow the entry of cytokines [59]. Additionally, the brain endothelial cytokine-transport molecules and activation of vagal afferent fibers

transmit cytokine signals to specific brain nuclei, which add to the inflammatory response. Stereotypically, these fibers contain in their perineural sheath macrophages and dendritic cells that express membrane Toll-Like Receptors and produce IL-1 β when activated [60]. Cytokines are important part of the innate immunity that is crucial for a normal brain function. However, elevated levels of cytokines modify the neurocircuitry and neurotransmitter systems; consequently, behavioral alterations lead to mental distress and feeding problems. Mechanisms of cytokine induced-behavioral changes involve variations in monoamine, glutamate, and neuropeptide systems and reduction in growth factors namely the brain-derived neurotrophic factor. Evidence suggests that tryptophan metabolism in the CNS is modified by inflammatory cytokines and high cortisol levels to produce a range of toxic kynurenine metabolites by the glial cells. In neuroinflammation over 98% of the kynurenine formed in the brain is derived from local production [61]. Some excitotoxic metabolites activate the N-methyl-D-aspartate (NMDA)-type glutamate receptors and increase oxidative stress as well as neuronal damage. In fact, kynurenine metabolism has been related to several human behavior disorders [62]. Additionally, peripheral kynurenine competes with tryptophan and other LNAA transport to the brain adding to the etiology of lower central 5-HT production [63].

Insulin resistance ensues from a systemic inflammation and is a potential contributor to altered feeding behaviors and mental distress [64,65]. Insulin receptors have been localized in areas of the brain crucial to food intake regulation and energy homeostasis [66]. However, unlike leptin, insulin is thought to play a feebler effect on feeding. Pharmacological interventions that promote insulin sensitivity such as Metformin reduce food intake and promote weight loss in animal and human models. Metformin's action is mediated through inhibition of NPY and AgRP neurons in the hypothalamus [67,68]. Taken all together, systemic inflammation and chronic stress reduce brain serotonin levels by shifting tryptophan metabolism into toxic metabolites that further disrupt brain circuitry. Insulin resistance adds to the deranged communication in the brain by increasing hunger and promoting mental distress.

Leptin and Serotonin: What's the Link with Mental Health?

Leptin exerts its anorexic effects through multiple mechanisms. Leptin modulates the effect of Krüppel-like factor 4 KLF-4 (a zinc finger transcription factor) which typically activates AgRP neurons [69]. Leptin stimulates POMC neurons to reduce feeding [52] and moderates brain and peripheral serotonin levels [70]. However, the intricate functions of leptin make studying feeding behaviors challenging. In animal models, leptin administration increases serum serotonin levels and reduces hypothalamic and hippocampal serotonin concentrations. This inhibitory effect on serotonin synthesis mechanistically regulates appetite. Hypothalamic serotonin signaling inhibits up-regulation of key genes needed to

induce satiety [71]. Therefore, selective targeting of serotonin in the hypothalamus might be a viable solution to treat hyperphagic diseases. The hypothalamic 5-HT_{2C} receptors regulate energy balance and modulate glucose homeostasis [72]. Particularly, hypothalamic 5-HT_{2C} and 5-HT_{1B} receptors control POMC neurons. Therefore, a comprehensive approach that targets hypothalamic 5-HT_{2C} may enhance leptin and insulin sensitivity. Reducing diet-induced inflammation appears to be key in enhancing metabolism, mood and feeding behaviors [3,29].

Conclusion

The evidence provided in this review suggests that addressing mental distress and altered feeding behaviors requires a multistage approach. Dietary interventions require healthy ratios of protein to complex carbohydrates and of omega-6 to omega-3 fats. Additionally, regular cardiovascular exercise is warranted to improve leptin and insulin sensitivities and increase central 5-HT levels. Exercise also reduces stress which supports the multi-actions of leptin. During exercise, feeding is halted which may contribute to an intermittent rise in ghrelin. The slight increase in ghrelin levels supports its anti-stress function: Exercise also promotes fatigue and improves sleep which may increase Tph2 expression to boost brain 5-HT levels. Based on work from our lab, mood improvement will likely support motivation to improve diet and increase exercise frequency [40]. These proposed steps may become eventually a virtuous cycle that supports further stress reduction and improvement in central 5-HT. This approach could be used as an alternative medicine therapy or in conjunction with a pharmaceutical agent.

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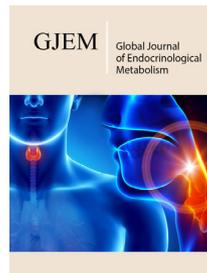
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