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"SEROTONERGIC SIGNALING IN OBESITY AND THERAPEUTIC IMPLICATIONS"

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Declaration and Certification

I do hereby attest that I am the sole author of this thesis and that its contents are only the result of the readings and research I have done.

Melisa Karabeyoglu

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Abstract

Awareness of the (global) rise in obesity (primarily in the western hemisphere) has generated current research which focuses on the impact of serotonin in food intake.This intake is controlled by our brain's two circuitries: homeostatic and hedonistic. The homeostatic circuitry matches energy intake to energy expenditure; the hedonistic circuitry involves the reward and motivational aspects of energy consumption. Serotonergic signaling purports metabolic signals to convey energy status, thereby making homeostatic circuitry the main purpose in regulating food intake in humans by suppressing the drive/need for food intake when energy needs are met. In addition, serotonergic signaling in the body can work to reduce reward in hedonistic circuitry. Therefore, observed health conditions arising from disturbances in serotonergic signaling require moderation. Furthermore, although much literature has been generated on obesity and its deleterious effects, little research exists on the impact of serotonin signaling upon energy consumption. This thesis seeks to fill this gap in the literature by providing a systematic review of eleven research studies evaluating the overview of the effects of serotonergic signaling in the brain and its effects in homeostatic and hedonistic circuitries, along with evaluating serotonergic signaling in obese individuals. Preliminary findings suggest that lower serotonergic signaling and receptivity in obese individuals may have a positive causal relationship. This research aims to further examine the etiology and causality of obesity in terms of serotonergic signaling, to be a determinant or symptom. Implications for further research may include but not be limited to examination of portion control/increased energy consumption by overweight and/or obese individuals as a consequence of serotonergic signaling.

Keywords: serotonin, signaling, obesity, caloric intake, nutrition, therapy, overweight, emotional eating, diet, tryptophan

Chapter 1. Introduction

1.1 Obesity Epidemic and Food Choices

The obesity epidemic originated in the USA from 1976 to 1980 and then spread across the remaining nations in the western hemisphere (Bray et al., 2017). The World Health Organization (WHO)'s classification of body mass index (BMI) shows that worldwide an estimated 39% of adults aged 18 or over worldwide are overweight and 13% are obese (NCD Risk Factor Collaboration, 2017). The prevalence rates for overweight and obese people differ according to each region, with North America as well as the Middle East, Central and Eastern Europe, having correspondingly higher prevalence rates than does the eastern hemisphere (Adriaenssens et al., 2019). Research shows that in Asia for example, normal range BMIs are more prevalent (i.e, 18.5 to 22.9 kg/m2 rather than 18.5 to 24.9 kg/m2). For children, the newest population in the epidemic, the International Obesity Task-Force age-, sex-, and BMI-specific cutoff points are increasingly applied. To further compound the seriousness of the issue, the health risks of being overweight or obese are greater than those risks associated with being underweight (Adriaenssens et al., 2019).

The etiology of the obesity epidemic is speculated to be due to either an increase in energy intake from food or a decrease in physical activity (or a combination of both factors). In addition, researchers agree that it may be unlikely that a decrease in physical activity has played a significant role in the epidemic (Temple, 2022). Instead, foods which are thought to be related/associated/contributing to the epidemic are identified as ultra-processed foods (UPFs), and high calorie foods with a content that is not only highly caloric but also high in salt, sugar, and fat as well as low in fiber. In addition, sugar-sweetened beverages (SSBs) are also linked with higher energy intake and more weight gain (Ng et al., 2013).

Individuals choosing to consume such dietary options may experience an increase in serotonin, which is a neurotransmitter that regulates mood, appetite, memory, and social behavior (Inam, et al., 2016). Therefore, the boost in serotonin as well as sugar levels lead to increased feelings of happiness. However, this experience, while pleasant, produces two negative outcomes: the sensation is only short-lived/is fleeting; moreover, in order to achieve the same effect, i.e., similar feelings of happiness, individuals may feel the need to increase their consumption of sugary foods (Inam, et al., 2016). In addition, individuals with generalized lower levels of 5-hydroxytryptamine (5-HT; serotonin) in the brain may experience sugar cravings. These cravings can be offset by consuming a sugar rich diet and thus improving mood and alleviating anxiolytic effects (Lopes et al., 2008).

1.2 Evaluating Serotonergic Signaling in Obesity

The hypothalamus area of the brain uses mechanisms to control appetite and food intake, and thereby manages hunger and thirst. In the basal hypothalamus, there are several nuclei regulating daily energy homeostasis working to control appetite. Human appetite is inherently controlled by neurotransmitters which are chemical messengers helping nerves communicate with each other. Research studies have demonstrated that moderating food intake is due to the hypothalamus's ability to activate/via the activation of gamma- aminobutyric acid (GABA), glutamate, acetylcholine, dopamine, and serotonin (5- hydroxytryptamine [5- HT]) neurotransmitters (Lam et al., 2010).

Hunger and appetite control are also controlled by the hormone leptin-also located in the hypothalamus and involved in fat cell regulation. Leptin is derived from **adipose tissue** and helps regulate energy in the small intestine in enterocytes, acting to **suppress hunger,**

decreasing the fat mass in adipocytes (Al-Hussaniy, Alburghaif & Naji, 2021). Heiman et al (1997) show the leptin hormones' receptors are in the ventromedial and arcuate nuclei within the **hypothalamus** and feeding center. Leptin also plays a role in the regulation of fat cells in obesity, which can become increasingly insensitive to leptin receptors, resulting in an inability to experience satiety and consequently increased food consumption (Yu et al., 2019).

Leptin, along with energy deficiency or surplus signaling hormones and their substrates, n is involved in metabolic signals that reflect the body's energy state (Cady et al., 2017). When an individual undergoes fasting, for example, a decrease is observed in glucose, insulin, and leptin levels as well as an increase in free fatty acids (FFAs), ketone bodies, glucagon, growth hormone, and catecholamines (Kang et al., 2021). The metabolic signature of fasting helps to provide the brain with feedback and restores energy levels by food- seeking behavior and increasing food intake (Sucquart et al., 2021). Research study by Romon et al. evaluated 22 healthy young individuals with recognized postprandial leptin response who showed leptin levels to be higher after a meal, a finding which significantly correlates to insulin response (Romon et al., 1999). Both hormones, leptin and insulin, directly work to regulate each other. In blood glucose homeostasis, leptin inhibits insulin; whereas, insulin stimulates leptin synthesis and its secretion from adipose tissue (Amitani, 2013). Giovambattista et al. (2000) demonstrate that leptin is capable of stimulating hepatic gluconeogenesis and hepatic insulin sensitivity via the hepatic branch of the vagus nerve.

Research regarding **leptin resistance** demonstrates how obese humans have high leptin levels but do not decrease food intake and are resistant to other metabolic signals reflecting the energy state. In summary, reward and homeostatic pathways are altered in the individuals with obesity, along with multiple effectors and pathways. Historically, the hypothalamus has been researched for its leptin signaling in human regulation of appetite (Yadav, 2009). Oury et al.

(2011) evaluate studies to show that recent findings shed new light in redefining the roadmap of leptin signaling in the brain and the selective inhibition of the leptin-serotonin axis to treat appetite disorders. For reasons of simplicity and clarity , this systematic review will solely focus on serotonergic signaling specifically in obesity, and not leptin functioning.

1.3 Correlation between Serotonergic Signaling Capacity of Food and Weight Gain

Research studies assert that serotonin signaling can modulate feeding behavior and therefore regulate body weight in animal studies (Lam et al., 2010). Miller (2017) argues that neuroimaging studies allude to the correlation of human obesity with decreased serotonergic signaling, leading to increased serotonin seeking food intake and higher body weight. Research by Peroutka and Snyder (1979) indicates that brain serotonin inhibits food intake; whereas, depletion promotes food intake (hyperphagia) and results in weight gain. Molecular neuroimaging studies posit that human obesity is correlated with decreased serotonergic signaling, via spatial visualization and locating and quantifying the central serotonin receptor or transporter (SERT) availability; nevertheless, Elmquist et al. (2005) conclude that further research may be necessary to determine causality.

In addition, research regarding serotonin administration and decreased food intake proposes that the antidepressant intake of selective serotonin reuptake inhibitors (SSRIs), may also affect food consumption of both humans and non-human animals (Woods, 2009). Research analysis of 10 year follow up studies concludes that these pharmacological therapies are associated with weight gain (Mountjoy, 2010).Consequently, Mounjoy's (2010) research has then examined the degree to which weight loss drugs selectively influence the serotonin system.

Nakatani et al. (2008) demonstrate that serotonin system arrays via the central and peripheral nervous system areas, with opposing effects on energy homeostasis. Overall, the central

serotonergic signaling is appetite-reducing and therefore termed “anorexigenic” and characterized by increasing energy expenditure through the stimulation of thermogenesis activity in brown adipose tissue (Donovan & Tecott, 2013). Peripheral serotonergic signaling, on the other hand, is linked with an increase in body weight; in reviewing literature on serotonergic signaling and receptor activity, this thesis will also discuss the (neuro)anatomy and physiology of central serotonin- mediated regulation as well as its effect on food consumption and/or weight gain in obese individuals (Yabut et al., 2019).

1.4 Evaluating the impact of disturbances in serotonergic signaling in obesity

Food consumption and its related behaviors are modulated by multiple brain regions, neurotransmitters (of which serotonin is one), neuropeptides, as well as the input and effectors of the peripheral nervous system. The analysis of the brain circuits is crucial for the purpose of understanding how serotonin signaling may determine an individual's energy consumption.

Homeostatic and hedonistic stimuli determine food intake and related behaviors. Homeostatic regulatory circuits focus on matching individuals’ energy intake to their expenditure so that their energy balance of calories is equal and thus they can maintain a particular weight. If individuals aim to lose or gain weight, they can use calorie deficit or surplus diets to achieve their desired goal. However, when individuals use their reward circuit to consume food, they are utilizing their hedonic motivation. When the body’s energy is depleted, homeostatic and hedonistic circuitry can work to regulate food intake. Evolutionarily, there is a high motivational drive to consume food to increase health, survival, and reproduction/reproductive rates. Yet in today’s modern obesogenic environment, operating via hedonic rewards where individuals are able to consume an amplitude of nutrients may be disadvantageous as such strategies can lead directly to unhealthy weights.

1.5 Delimitations of the Study

This systematic review summarizes existing evidence regarding serotonergic signaling in obese individuals and its therapeutic implications. The choice of this method aims to provide an objective rather than narrative view in order to minimize bias. This systematic review offers a **precise estimate** of the effect of the size of serotonergic signaling in obese individuals. As a result, this research seeks to obtain findings that add measurable/concrete value to the existing literature.

Nevertheless, this systematic review approach has particular constraints in certain aspects. Findings are limited because this research seeks to proffer conclusive instead of inconclusive results. In deriving conclusions for this systematic review, the possibility of bias in the shaping design of the study is acknowledged. Issues such as the selection criteria for research subject matter, the susceptibility in selecting particular studies, the choice of one journal publication over another; and the legitimacy of the eligibility criteria for selecting studies--all these factors/biases and others are acknowledged/yet human frailty/researcher bias is always present. Even though this systematic review combines findings from multiple studies, it still cannot eliminate bias.

1.6 Assumptions

In constructing this systematic review, the following assumption were made:

1. The *independent* as well as a *dependent* variables are respectively defined in the studies, as serotonergic signaling capacity and obesogenic body weight

2. Research consulted in this study defines independent variables in terms of their capacity to signal serotonin; dependent variables are defined by obesogenic body weight. In this systematic review, for reliability and validity, units and objects (such as, body weight) are clearly denied in terms of the effect that they will produce on serotonin signaling.

1.7 Organization of the Study/Thesis

This systematic review study has four components: obesogenic population, serotonin signaling as an intervention, receptor sensitivity as a comparison, serotonin firing as a specific outcome, pharmaceutical and comprehensive medicine practices to manage decreased serotonin signaling, and lastly, therapeutic implications.

Chapter 2. Review of Related Literature and Research

2.1. Neurochemicals Present in the Modern Brain

The human brain utilizes 20% of a person's daily caloric intake and constitutes 60% fat in its makeup, containing a high concentration of cholesterol and polyunsaturated fatty acids (PUFAs) such as Omega-3s. There is the production of monoamine neurotransmitters such as serotonin, norepinephrine, dopamine, all important in understanding the management of serotonergic creation and uptake in obesogenic populations.

In order to understand the pathophysiology of mental illness, the relationship between the foundational role of amino acids and mineral dependent cofactors and the production of monoamine neurotransmitters such as serotonin, norepinephrine, and dopamin should be examined. The methylation cycle requires Folate and other B vitamins in order to produce a cofactor crucial for monoamine neurotransmitter synthesis (Stahl, 2008). The value of a robustly operating methylation cycle is its ability to prevent cardiovascular disease and depression by lowering raised homocysteine levels. are linked to cardiovascular disease and depression.

The primary functions of the central nervous system are influenced by Omega-3 fatty acids which form an integral part of neuronal cell membranes. To be clear, in the central nervous system, Omega-3 fatty acids regulate neurotransmission, influence gene expression, and directly impact neurogenesis as well as many essential processes. Omega-3 fatty acids possess crucial anti-inflammatory qualities and furthermore perform as antioxidants.22 Balancing Omega-6 and Omega-3 fatty acids is furthermore pertinent in addition to Omega-3 consumption. Western diets are rich in Omega-6 fatty acids, and deficient in Omega-3s, an

occurrence that has coincided as these countries' transition from the shift towards industrialized and pa corn oil and soy oil (Simopoulos, 2011). These oils are popularly used in restaurant and packaged foods. Foods not popular in the typical American diet are fish, seafood, and grass-fed beef--all of which contain rich sources of long chained Omega-3 fatty acids. Nuernberg et al. (2002) delineate the Omega-3 composition of grass fed beef in that it contains 100 mg of long-chained omega-3 fatty acids per 100g serving, much less than a similar sized portion of fatty fish. The above example underscores the necessity for appropriate patient nutrition information, in particular healthier alternatives to mass-processed beef (Daley. Et al, 2010).

Therapeutic agencies for illness such as ADHD, PTSD, and depression disorders, such as bipolar and major depressive episodes have employed Omega-3 fatty acids solely or in conjunction with other agencies (Bloch & Qawasmi, 2011). Mischoulon & Freeman's (2013) research shows that moreover, these depressive disorders, in particular major depressive disorder, as well as ADHD reveal an elevated omega-6 to omega-3 fatty acid ratio in the blood. Sorgi et al. (2007) show that subsequent studies have argued that ameliorating ADHD symptoms can be accomplished by reduction in omega-6 to omega-3 ratio with omega-3 supplements. This argument is supported by the knowledge that conversion of both the biological mechanisms of short chain omega-3 and omega-6 fatty acids to their long chain biologically active versions requires identical enzymes. When the body possesses excessive omega-6, omega-3 manufacture is obstructed; i.e., longer chain forms cannot be transformed (Sorgi et al., 2007) .

Lachance & Ramsey's (2015) comprehensive research evaluating the implications for the modern clinician on food, mood, and brain health, propose that as part of the clinical assessment in engaging client to complete a dietary history, individuals report that they often misreport, or even forget to eat due to a rushed or busy day. As a result, an unbalanced diet consisting of the Standard American Diet (SAD)'s selection of quick convenience food such as granola bars, pizza, and soda's lack of complete macro and micronutrients can be a determinant in negatively affecting one's well being (Savarino, Savarino & Corsello, 2021). Moreover the SAD diet does not contain foods that are rich sources of nutrients crucial for brain health. When considering neurocognitive health, omega 3 sources of walnuts, hemp seeds, flaxseeds, seaweed, fish and seafood are rich. green-pigmented, chlorophyll rich vegetables, greens, and legumes are excellent sources of folate, as are fiber, and B-vitamins. In terms of professional preparation and development, medical pPractitioners (physicians) are not currently encouraged as part of their curriculum to engage in the diet of their patients and assess their omega-3 and B vitamin intake values (Lachance & Ramsey, 2015); yet, it may be beneficial in inquiring as this can help advise patients' diets.

In addition to a nutrient-rich diet, evaluating inflammation in patients may play an important role in mediating the link between diet and mental health (Galland, 2010). Multiple lines of research support the pathogenic role of neuroinflammation in mental illness (Najjar, 2013). Lucas et al. (2014) used several inflammatory biomarkers including CRP, TNF alpha receptor 2, and IL-6 and data from food frequency questionnaires to derive an inflammatory dietary pattern from a sample of over 12,000 participants from the Nurses Health Study. Participants who consumed a diet consistent with the inflammatory dietary pattern had a statistically significant increased risk of developing depression over time after adjusting for multiple confounders (Lucas et al., 2013). Specifically, over twelve years of follow up, participants with the highest adherence to the inflammatory dietary pattern had a relative risk of 1.41 (1.22–1.63)

of developing depression according to the strict definition by physician diagnosis and antidepressant use (Lucas et al., 2013). Lucas et al. 's (2013) research shows that the inflammatory dietary pattern was high in sugar-sweetened soft drinks, refined grains, red meat, diet soft drinks, and margarine and low in wine, coffee, olive oil, green leafy, and yellow vegetables.

2.2. Serotonergic Firing

Serotonin, also known as 5-hydroxytryptamine, is produced by humans and other living forms in the nervous system in both the enteric nervous system and the central nervous system (CNS). Serotonin is secreted throughout most of the axis of the central nervous system and acts to regulate mood and anxiety, along with cognitive, autonomic, and other functions maintaining homeostasis to help increase survival and reproduction (Lv & Liu, 2017).

Serotonin is stored in presynaptic vesicles and when the nerve is activated by nearby impulses, serotonin is released into the synaptic cleft and will bind to postsynaptic receptors, known as 5-hydroxytryptamine receptors and will act as G-couple protein receptors; or, otherwise, as ligand-gated ion channels (Lv et al., 2017). When serotonin is activated, there will be a second intracellular messenger cascade that can produce an excitatory or inhibitory response. Refer to Haney et al.'s (2013) diagram below detailing serotonin's neurotransmission and uptake.

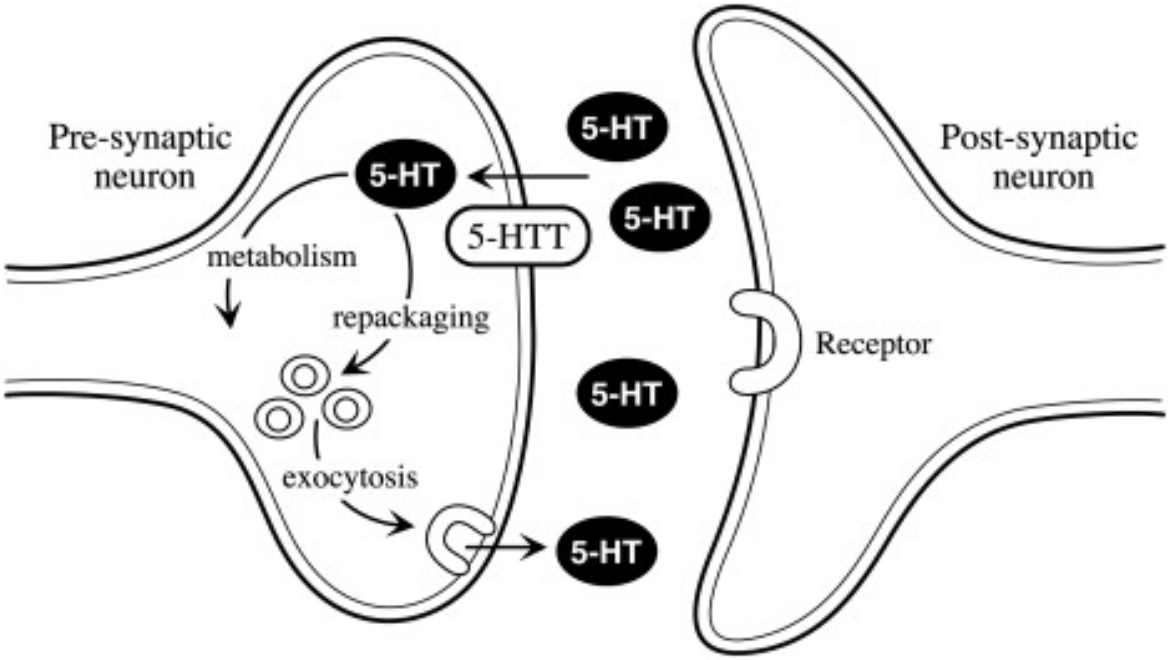

Figure 1: *"Synthesis and Function of Serotonin in the Nervous System"* (Haney et al. 2013)

Serotonin's main signaling pathways include 5-HT or agonist/antagonists for each receptor that interact in the extracellular and changes of 5-HTRs to modify the activity of the specific intracellular enzyme; thereby altering other target states which lead to different responses from cells (Amireault et al., 2011).

Humans store around 90% of their serotonin in the enterochromaffin cells in the luminal and basolateral section of the gastrointestinal tract. When serotonin is secreted and absorbed by circulating platelets, it is activated and acts on both mobility and the direction of intestine contraction, known as "gut motility" and peristalsis (Arous et al., 2009). Around 10% of serotonin production in humans will be produced by neurons in the CNS and preserved for brain functioning and include sleep, hunger, mood, memory and learning (Berger et al., 2009).

When there is excessive serotonin released by the enterochromaffin cell, serotonin is introduced into the bloodstream, where it interacts with platelets and is absorbed and stored until a clot forms (Christie et al., 2013). Serotonin will be released back into the blood when the clot forms so that it can regulate homeostasis and clotting. When serotonin levels are high, serotonin will contract smooth vascular muscle cells and constrict vessels; therefore, the state of "vasoconstriction"occurs; whereas, at lower serotonin levels, serotonin will cause the endothelial cells to release nitric oxide, and relax vessels, producing"vasodilation" (Bianchi et al., 2002).

Serotonin can affect food intake by brain serotonin in the neuroanatomy and basic functioning of the brain serotonin system, the evidence of regulating food by the brain's internal serotonin, and the mechanisms that serotonin does to improve food intake via the actions of serotonin receptors and neuronal mediators (Carhartt-Aris & Nutt, 2017).

2.3. Research regarding Serotonin seeking behaviors in humans

The nature, degree, and kind of food intake all regulate the degree and quantity of the neurotransmitters released by serotonin-releasing brain neurons. Serotonin release is increased when carbohydrates, not proteins, are consumed through insulin secretion and the "plasma tryptophan ratio" (Cassidy, 2020). How are protein and carbohydrate consumption regulated? It is the neuron's capability of linking food intake to neuron signaling properties. The role of neurons is thus one of a regulator (De Mello, 2018). Apart from this crucial activity; the abilities of the human body to enter the sleep cycle, handle emotions and moods, control blood pressure and respond to pain necessitate serotonin release (Neff, 2019). It is understandable then that these abilities of serotonin lead to excessive consumption of carbohydrate dense foods,

particularly when under stress or premenstrual, to achieve mood equilibirium (White, 2017). Other such instances are evidenced in patients who quit smoking or suffer from winter blues--these individuals to gain weight from the search for serotonin inducing sensations.

The similarity between nicotine and carbohydrates is quite interesting: both substances increase serotonin secretion. For smokers, the application of dexfenfluramine has been proven successful; this treatment increases the sensation of satiety and the increased intake of carbohydrates (Zawertailo et al., 2020). The phenomenon of food addiction is being more commonly recognized within scientific communities and parallels are being drawn between food and other addictive behaviors such as drug, tobacco, and alcohol addictions. Unhealthy diets and smoking are a risk factor for disability and death and therefore a greater understanding is necessary to be researched. Zawaertailo et al. (2020) surveyed current literature pertaining to the finding that each disorder can occur together as well as separately and have the commonalities of neurocircuitry, gut microbiota, childhood adversity, and attachment insecurity.

2.4 Research regarding homeostatic circuitry

The pathophysiological condition in which food intake cannot be controlled (i.e., consumption exceeding dietary needs), is considered to be due in part to lower serotonin signaling. Weight gain is the inevitable result of such a malfunction. The significance of serotonin and homeostatic regulation have led it to be a research focus during the past forty years. That the process is a complex one with multiple neurotransmitters across various areas of the brain makes it a fertile area of research for decades to come (Wang et al, 2014).

The key regions of the brain which input data concerning the various responses to hunger and sensations of satiety as well as the sorts of nutrients available in the body are the hypothalamus and brainstem (Al-Zubaidi et al., 2019). These two areas integrate these three pieces of information for the individual's nutritional state. The hypothalamus and the brainstem are further divided into the raphe nuclei, nucleus tractus solitarius (NTS), and parabrachial nucleus (PBN) of the brainstem and the arcuate nucleus (ARC), paraventricular nucleus (PVN), ventral medial nucleus (VMN), dorsomedial nucleus (DMN), and lateral hypothalamic area (LHA) of the hypothalamus. These, in turn, are strongly (inter)connected and receive central and peripheral input (van Galen, ter Horst & Serlie, 2021).

2.5 Research regarding hedonistic circuitry

Dopamine is a significant neurotransmitter in the hedonic system; serotonin, for the homoeostatic system as well as food intake that is reward-related or motivational in nature--according to recent research.131 In the former system (?), dopamine and serotonergic signals work synergistically and signal through other neurotransmitters (Miguelez et al., 2014).

The term the reward pathway describes the mesolimbic system, which includes the VTA, the nucleus accumbens (NAc) of the ventral striatum, and the CeA. O'herty et al.'s research (2014) asserts that it has been posited that these regions share in the interaction of the homeostatic and hedonic regulation of food consumption: a major area in which habitual consumption behaviors evolve is the dorsal striatum, where also serotonin receptors are expressed. It has been suggested that when food intake is limited by time, the dorsal striatum operates as a food-entrained oscillator/the result is that the food anticipatory activity of a circadian rhythm that operates in line with the time schedule of food availability. Lartigue & McDougle (2019) discuss how serotonin signaling operates in this sort of activity, as earlier work had offered the

theory that the development of food anticipatory activity is suppressed by serotonin signaling. Current work by Gallardo, Martin & Steele (2020) posits a different scenario: food anticipatory activity is autonomous to serotonin signaling. Motor behavior is managed by serotonergic signaling in the dorsal striatum; furthermore, many pathological motor conditions are related to perturbed serotonergic signaling within this region.

Chapter 3. Methodology

3.1 Purpose of Methodology

This thesis conducts a systematic review of research studies analyzing serotonergic signaling in obesity and the further implications of such activity in terms of eating behavior. Because peripherally acting serotonin promotes energy absorption and storage, disturbed serotonergic signaling is thus associated with obesity; therefore it is important that this research study undertake the evaluation of the significance of serotonergic signaling in food intake. Disturbed serotonergic signaling in obesity has been researched and analyzed; however, conclusive evidence regarding the relationship between the variables has not been provided and therefore will not constitute the main focus of this thesis.

3.2 Purpose of the Study

The condition of obesity is the consequence of energy intake being greater than its expenditure. The relevant literature has been proposed that a contributor to this condition/obesity is attenuated homeostatic inhibition and/or increased hedonic drive for energy consumption. In this situation, the role of serotonin signaling is key as it regulates food intake. Any disruption in serotonergic signaling is suggested to facilitate the pathogenesis of disturbed feeding behavior in chronically obese individuals. Several research studies corroborate the phenomenon of disturbed serotonin signaling in animals and humans with obesity (van Galen et al., 2021).

Both research from Meguid et al. (2000) and Routh, Stern & Horwitz (1994) demonstrate the finding that obese animals have a reduced release of hypothalamic baseline serotonin. In addition, when changes in the binding to serotonin receptors (5-HT1A, 5-HT1B and 5HT2A) are observed in rats fed an obesogenic diet with high-fat feeding, research reveals a reduced serotonin release and decreased activity of serotonergic neurons (van Galen, 2021). This thesis therefore aims to go farther than the work of previous research studies by explaining the significance of serotonin's contribution to obese individuals' food intake.

3.3. Research Question

This thesis aims to answer the questions *"What is the significance of the contribution of dietary habits of obese individuals in decreased serotonergic signaling?"* and "*What are the potential implications of therapeutic benefits for obese individuals with decreased serotonergic signaling?"* Science denotes that a higher BMI is positively correlated with decreased serotonin firing (van Galen, 2021). In addition, research shows that dietary habits associated with obese individuals, such as over-eating and frequent eating lead to decreased serotonin firing. Therefore, it is still unknown as to the significance of how much of decreased serotonin signaling is due to obesity, or if higher obesity is due to decreased serotonin signaling. As a review study, this thesis aims to perform an evaluative review of research on obesity and serotonin signaling up to date, and to offer insight into the significance of the contributing factor of serotonin.

3.4 Systematic Review of Current Research

In this systematic review we will use/employ/apply a qualitative and formal study design to systematically assess the results of previous research on serotonergic signaling in obesity. Our aim is to derive conclusions about that body of research. A good deal of the energy of this research inquiry has been directed by the very rigorous study done by van Galen et al. (2020). The writer of this thesis thus applies van Galen et al (2020) as a foundational study to support the line of this research in assessing the relationship with causality and the consequence of obesity and serotonin signaling.

With this line of enquiry in mind, this research offers an overview which focuses upon the effects of serotonergic signaling in areas of the brain containing homeostatic and hedonic regulatory systems on food intake.A second, but equally important aim in this research focuses upon identifying disturbances in serotonergic signaling in obesity and its potential therapeutic implications.

3.5 Data Collection and Analysis

Each research study that is cited in this dissertation has provided information regarding a serotonergic signaling in obesity, and as researchers, we gather data regarding the serotonergic firing in the relationship with food intake body obesity. This process allows us to evaluate the multiple brain effector pathways that mediate the effects of serotonin and food intake.

Van Galen et al. (2021) research postmortem immunohistochemistry analysis of serotonin and its metabolites in the cerebrospinal fluid (CSF), the molecular neuroimaging techniques of positron emission tomography (PET) and single photon emission to evaluate the changes occurring in serotonergic signaling in human obesity. Results offer evidence that

overweight/obese individuals had lowered levels of SERT protein in nuclei and additionally, obese women, in comparison to lean women, had lower levels of serotonin and its metabolites in CSF (van Galen et al., 2021). Serotonin Reuptake Transporter is a key regulator of serotonin neurotransmission and targeted by antidepressants, such as SSRIs (discussed furthermore in Chapter 4) and blocks SERT function.

Hesse et al. (2014)'s research reveals that SERT binding in the diencephalon is reduced in insulin-resistant subjects regardless of body weight; yet, hypothalamic SERT binding is lowered in obesity. Hesse et al.'s (2014) research offers evidence that the metabolic perturbations associated with obesity are independent of insulinergic functioning in regards to SERT binding. Serotonin has been shown to be a factor in controlling body weight and behavior: Koskela et al. (2008) examine the association between obesity and serotonin by studying the brain serotonin transporter (SERT) in monozygotic twins with different BMIs. Results show that twins with higher BMIs had higher SERT binding than did twins at a lower BMI in the hypothalamus/thalamus. Koskela et al. 's (2008) research discovered a significant difference in females in comparison to males, etiology unknown; yet offering directions for possible future research. As both Hesse et al (2014) and Koskela et al. (2008) research studies indicate similar findings, i.e., that a higher body weight is associated with a decreased serotonin absorption (increased SERT). In parallel, (Versteeg et al., 2017) found that individuals had increased SERT when following a 4-week hypocaloric diet during which most calories were consumed at breakfast and dinner . Koopman et al. (2013) track a 6-week hypercaloric high fat/high sugar snacking diet,and observe a reduction in SERT in lean men.

As the dietary habits can include physical, neurochemical, and emotional factors, a mutli-disciplinary approach must be utilized. Banskota et al. (2019)'s research argues for priority in research regarding serotonin concentrations in the enterochromaffin cells to that of those in

the brain: as 95% of serotonin is in the gut; whereas, 5% is in the brain. Banskota et al. (2019) demonstrate that binge eating individuals may have lower circulating serotonin; whereas, individuals restricting food may have higher serotonin. Wu et al. (2017) offer additional research comparing serotonin transport between obese and non-obese individuals without an eating disorder to posit the finding that there is a significant difference in SERT availability in the midbrain areas between morbidly obese and non-obese adults. In terms of the serotonergic approach of weight management in obese young adults, Garfield and Heisler's et al. (2009)'s research evidences a significantly altered serotonin receptor availability in obese individuals, suggesting that individual behavioral responses and internal cues may be affected. Therefore, one may conclude that obese individuals have lowered serotonin reuptake; yet, it is still undetermined whether obese individuals have lowered serotonin uptake due to inhibited food intake or, instead, due to serotonin seeking behaviors.

This thesis review is interested in evaluating the serotonergic signaling in obese individuals in order to understand the impact of dietary habits in decreased serotonin signaling. In total, eleven research studies were closely analyzed to understand how obesity affects serotonergic receptors. Additional research is needed to determine a linear relationship between BMI and serotonin signaling, to separate the co-dependence of the effects of dietary habits and body weight in determining the variable of serotonin signaling.

For the sake of clarity and comprehensiveness, Table 1 offers a schematic breakdown of the work to date on this relatively under researched topic. Other variables can be constructed besides those chosen. In any case, Table 1 offers the opportunity to engage in comparison.

Table 1: "Comparison of Reviewed Research Studies Pertaining to the Study of Serotonin Signaling in Relationship to Obesity"

Research Study	**Location**	**Participants**	**Independent Variable**	**Dependent Variable**	**Findings**
Banskota et al., 2019	USA	Mice	Gut-derived 5-HT	Pathogenesis of inflammation in the gut	Inflammation of the gut is increased when serotonin transport is decreased
Garfield and Heisler et al., 2009	USA	Mice	The binding of 5HT to the 5HT2c receptor on neurons	Food consumption	Binding of 5T to the 5HT2c receptor decreases the 5HT-induced inhibition of food consumption
Hesse et al., 2014	Germany	23 Patients with multiple	Psychiatric symptoms of MS	Serotonergic transmission	Serotonin regulation is decreased in

		sclerosis and 22 healthy individuals			patients with MS, due to induced psychiatric changes from serotonin decrease
Koopman et al., 2013	The Netherlands	25 lean, male subjects	High-fat-high-sugar (HFHS) or high-sugar (HS) with increased meal size or -frequency (=snacking pattern)	SERT-binding in the hypothalamic region	SERT binding is decreased in individuals following a High-fat-high-sugar (HFHS) and increased snacking
Koskela et al., 2008	Finland	16 monozygotic twin pairs with	Varying body mass index (BMI) differences	Brain serotonin transporter (SERT) binding in the hypothalamu	Serotonin regulation is decreased in twins with a higher BMI

				s/thalamus	
Meguid et al., 2000	USA	Research review of (NE) and serotonin (5HT) neurotrans mitter systems in depression and anxiety disorders	Hypothalamic abnormality	Appetite and libido	Appetite and libido are affected by hypothalami c abnormalitie s, contributing to depression and anxiety
Routh, Stern & Horwitz, 1994	USA	1-wk genetically obese vs. lean Zucker rats	Fat composition (adipose tissue percentage of rats) and rat body weight	Serotonin release, plasma insulin levels.	Serotonin release is compromise d in genetically obese rats
Van Galen et al. 2018	The Netherlan ds	Research overview of the effects of serotonergi	Serotonergic signaling in brain regions of homeostatic and hedonic regulatory	Food intake	Serotonergic signaling is decreased in obese individuals in

		c signaling in brain regions	systems		hedonic circuitries
Van Galen et al. 2020	The Netherlands	Research overview of disturbed serotonin signaling in obese individuals	Serotonin Signaling	Serotonin-mediated regulation of food intake	Serotonin signaling is constantly disturbed in obese individuals
Versteeg et al., 2017	Republic of Korea	33 healthy nonobese subjects	SERT availability from brainstem	Glucose and placebo loading	SERT availability is negatively correlated with BMI after glucose loading in humans
Wu et al. 2017	USA	Mice	Serotonin Receptor: 5-hydroxytryptamine	Binge-like eating behaviors	Activation of Serotonin 2C Receptors in

			(5-HT) 2C receptor (5-HT2CR)		Dopamine Neurons Inhibits Binge-like Eating in Mice

3.6 Conclusion

As mentioned above, obese individuals are found to have a lowered serotonergic signaling; yet, whether this is the consequence or cause of obesity is not known. The research studies mentioned above {(Banskota et al., 2019); (Garfield and Heisler et al., 2009); (Hesse et al., 2014); (Koopman et al., 2013); (Koskela et al., 2008); (Meguid et al., 2000); (Routh, Stern & Horwitz, 1994); (Van Galen et al. 2019); (Van Galen et al., 2021); (Versteeg et al., 2017); (Wu et al. 2017)} do not have a linear correlation between BMI and serotonin signaling, it thus is difficult to conclusively determine causality. Van Galen et al. (2021) denote that the lack of a linear relationship between BMI and indirectly serotonin signaling may be due to obesity associated factors such as diet composition and meal timing. The factors of frequent meals and overeating have shown to have lower serotonin, as shown in Banskota et al. (2019); therefore, van Galen et al. (2018) suggest obese individuals may have lower serotonergic functioning due to their dietary habits, not BMI, or due to a combined effect of both dietary habits and BMI. Galen et al. (2018) denote that science aims to examine why obese individuals continue to consume an excess of calories, and conclude that such consumption may be due to decreased dopamine-mediated reward and serotonin signaling in response to eating.

Additionally, the research studies mentioned above {(Banskota et al., 2019); (Garfield and Heisler et al., 2009); (Hesse et al., 2014); (Koopman et al., 2013); (Koskela et al., 2008); (Meguid et al., 2000); (Routh, Stern & Horwitz, 1994); (Versteeg et al., 2017); (Wu et al. 2017)} propose that changes in an individuals' serotonergic signaling can develop early during the overconsumption of food. Therefore, behavioral patterns of individuals can vary the development and/or persistence of obesity. This denotation of serotonin signaling in feeding behaviors affecting BMI has served to make serotonin the target of the pharmaceutical industry to increase stimulation for central serotonergic signaling. Mentioned in Chapter 4, the drugs

fenfluramine, dexfenfluramine, and sibutramine were marketed to help obese invidiausl's central serotonergic signaling increase. The unfortunate side effect of pharmaceutical treatment has caused issues such as "serotonin syndrome", amongst others, to be of concern.

Drugs acting as agonist lorcaserin (5-HT2C receptor) have been shown to help obese individuals reduce food intake and body weight (Bohula et al., 2018). ; yet, these drugs were removed from the market by the FDA due to increased cancer risk (Sharretts et al., 2020). Due to the peripheral side effects of centrally acting stimulators and peripheral serotonin stimulation, a new development in pharmaceuticals targeting the inhibition of peripheral serotonin was proposed as a treatment of obesity (Oh et al., 2015). Serotonergic drugs show promising results in humans with obesity; however, due to their serious side effects, further research is required to determine if this pharmacological approach/system can be safely treated in obesity.

Chapter 4: Serotonin Regulation

4.1 Serotonin Regulation

Serotonin can be regulated through the exogenous consumption of food, pharmaceuticals, and lifestyle changes. Research provides evidence for different methods to regulate and improve the reuptake of serotonin (Iqbal, Osmany & Iqbal, 2015). Therapists advising clients to regulate their serotonin without the use of pharmaceuticals may advise a combination of dietary and lifestyle changes that this thesis dictates/advocates as well (Iqbal, Osmany & Iqbal, 2015). In the following section, this approach is discussed in regards to complementary diet, exercise and sunlight exposure. Obese individuals with decreased serotonin seeking treatment may explore complementary medicine and lifestyle change as a transitory therapy, under the practice of a physician (Iqbal, Osmany & Iqbal, 2015).

4.2 Tryptophan

In recent years, tryptophan metabolism has gained attention for the metabolic control of immune and psychological systems in the body (Klieber et al., 2011). Research evaluating the relationship between tryptophan availability and systemic responses can be helpful for monitoring disease and therapeutic interventions as well as to provide an understanding as to how the functioning of our immune system affects human behavior, stress, mood, thought and cognitive status (Widner et al., 1997). Tryptophan is broken down via the kynurenine axis and is accelerated when the immune system is attacked; therefore, in this state, the rise of chronic inflammatory disorders can lead to decreased quality of life, altered states of mood, and depression (Geisler et al, 2015). When serotonergic transmission is provoked by cytokines with neurotransmitter storage, this transmission can cause indirect metabolite concentrations for

tryptophan catabolites (Geisler et al, 2015). Changes in the kynurenine metabolites have been correlated with the onset of CNS disorders, including AIDS-dementia as well as Huntington's andAlzheimer's diseases (Widner et al., 1997). Additionally, the modulation of the tryptophan-kynurenine pathway via the activation of the immune system due to stress can be seen as a control of epidemiological factors of cognition and behavior (Widner et al., 1997).

Tryptophan, as one of the essential amino acids, is least available in protein and therefore is dependent on protein biosynthesis; thus, the immune system will utilize tryptophan to restrict the tryptophan-degrading enzyme as a defense mechanism (Schröcksnadel et al., 2005). Tryptophan metabolism in addition to immunity helps to slow down T cell proliferation, aiding in the cessation of overwhelmed immune systems and helping to decrease illness (Schröcksnadel et al., 2005). In patients with HIV-1, lupus, cardiovascular, and neurodegenerative disorders, all are associated with biomarkers of tryptophan bioavailability concentrations (Schröcksnadel et al., 2005). Research shows that low tryptophan concentrations with high levels of neopterin (a biomarker of oxidative stress and immune activation) were associated with the shorter survival of cancer patients (Jenny et al., 2011).

The search to identify in foods the natural sources of the amino acid, tryptophan, which produce serotonin is one approach in increasing serotonin levels (Zhu et al., 2020). Food intake of cheese, turkey, salmon, pineapple, nuts and seeds as well as tofu constitutes a diet rich in tryptophan (Zhu et al., 2020). However, consuming the above food items does not singlehandedly raise serotonin levels (Zhu et al., 2020). Insulin must be released in order to absorb amino acids, so carbohydrates are a necessary component in this diet. In order to be absorbed into the brain (for regulatory activity), tryptophan must compete with other amino

acids (Zhu et al., 2020). Thus, the complexity of the process of eating tryptophan-containing foods in order to boost serotonin levels requires further research (Zhu et al., 2020).

4.3 Mediterranean Diet Approach

A diet rich in animal food in comparison to plant-based diet contains differing amounts of macronutrients (protein, carbohydrates and fats) and has therefore been shown to have a different effect (that is to say, positive) on the gut microbiome (Zhu et al., 2020). Zhu et al. 's research (2020) evaluating the fecal DNA of participants participating in a mediterranean versus western diet shows the results of differing bile-tolerant microbial genera and species, suh as Collinsella, Parabacteroides, and Bilophila. Fiber fermenting bacteria, including Lachnospiraceae and Butyricicoccus, increased significantly after following a Mediterranean diet in comparison to a Western diet. Taking into account interindividual variety in bilophila response shows a relation to saturated fat content in a Western diet (Zhu et al., 2020).

An individual’s state of mind and his or her nutritional health are affected by the consumption of both the pro-active benefits of a plant based diet as well as the deleterious consequences of an animal based one. As a mental illness, depression has been associated, according to research studies from the late twentieth century until today, with neurotransmitters that are chemically imbalanced and may cause inflammation in the brain (Sadowsky, 2020). For this reason, the nutritional community has posited the inclusion of plant foods in one’s diet because of their high antioxidant and phytochemical composition that offers anti-inflammatory properties (Matotoka, et al., 2023).

A plant based diet supports enzyme balance in neurotransmitters such as serotonin, dopamine, and norepinephrine that balance mood, in particular preventing high levels of monoamine oxidase (MAO) that would result in these particular neurotransmitters having a lower level

(Matotoka et al., 2023). Plant foods similarly inhibit MAO because only this food group contains the phytochemical quercetin. This phytochemical block MAO (Matotoka et al., 2023). Working much like a natural antidepressant, quercetin can increase the amount of serotonin, dopamine, and norepinephrine in the brain (Ugwu et al., 2022). Quercetin acts as a natural antidepressant by raising norepinephrine, dopamine, and serotonin levels (Ugwu et al., 2022). Diets containing apples, kale, grapes, onion, and berries as well as green tea supply individuals with substantial amounts of quercetin (Ugwu et al., 2022).

If we turn our attention to the origins of inflammatory chemicals in our diet choices, an examination of the impact of animal products on our biochemistry is now necessary. Arachidonic acid signals inflammatory conditions; this fatty acid is located only in animals (Munyangi & Lutgen, 2020). Consumption of, for example, beef, pork, chicken, and chicken by-products triggers chemical reactions (Nardella et al., 2022). When eating foods high in arachidonic acid, such as chicken, eggs, and other animal products, we set off a cascade of chemical reactions in our body, one of which is increased inflammatory mediators in the bloodstream (Nardella et al., 2022). An overactive immune response results from this general inflammation. When inflammation reaches the brain, subsequent negative states of anxiety, stress, hopelessness, negative emotional states, arise when the brain becomes inflamed (Arden, 2023). Studies detailing the presence of elated, positive moods indicate diets high in arachidonic acid. Eliminating inflammatory animal foods from the diet ensures not only physical health, but Arachidonic acid, a type of fat found only in animals, serves as a precursor to inflammatory chemicals in our bodies (Martiniakova et al., 2023). By eating foods high in arachidonic acid, such as chicken, eggs, and other animal products, we set off a cascade of chemical reactions in our body, leading to an increase in inflammatory mediators circulating in the bloodstream (Martiniakova et al., 2023). The result is general inflammation, or an overactive immune response. When inflammation reaches the brain, subsequent feelings of

anxiety, stress, hopelessness, and depression arise (Korn, 2016). Individuals who avoid foods high in arachidonic acid tend to report a happier, more positive mood (Korn, 2016). Eliminating inflammatory animal foods from the diet ensures not only physical health, but mental health as well (Korn, 2016).

Common advice on nutrition and depression is to increase consumption of omega-3 fatty acids, generally through fatty fish. While the anti-inflammatory effects of omega-3 fatty acids are valid, evidence supports that a diet free of fish and all animal products is optimal for mood improvement (Wall et al., 2010). Beezhold, Johnston & Daigle (2009) performed a randomized controlled trial presented at the American Public Health Association (APHA)'s annual conference in 2009, in which they assigned participants to three groups. The control group maintained a diet with regular intake of animal products, the fish group consumed three to four servings of fish and shellfish per week but restricted meat and poultry, and the vegetarian group restricted most animal products (Beezhold, Johnston & Daigle, 2009). The trial lasted only two weeks and showed the vegetarian group to have statistically significant improvements in Profile of Mood Scores (POMS) and on the Depression Anxiety and Stress Scale (DASS) (Beezhold, Johnston & Daigle, 2009). While participants in the fish group increased their intake of omega-3 fatty acids, arachidonic acid levels remained higher than those following a vegetarian diet. Their mood scores showed no significant change from baseline (Beezhold, Johnston & Daigle, 2009).

In terms of advocating dietary changes to combat depression, the standard medical/nutritional advice to patients has been to consume more food containing omega-3 fatty acids, with the general suggestion of fatty fish (Govers, 2021). There is no argument, however, that these recommendations are valid (Wall et al., 2010). Quite conversely: if optimal changes in mood are desired, eliminating fish from the diet has been observed to yield mood improvement as

demonstrated by Beezhold, Johnston & Daigle (2009); released in the 2009 American Public Health Association annual conference. Here, apart from a control group with regular intake of animal products, three groups were devised: a group solely consuming 3 to 4 daily servings of fish; a vegetarian group which avoided animal products; and, lastly,a group regularly consuming animal products. Beezhold, Johnston & Daigle's (2009) experiment ran only for two weeks; the third group, the vegetarian group, evidenced robust improvements in mood states on two standardized tests: the Depression Anxiety and Stress Scale (DASS) and the Profile of Mood Scores (POMS). Group Two, the fish and shellfish eaters, registered increased intake of omega-3s fatty acids, their arachidonic acid levels were higher than those in the Group 3 vegetarian diet; and emotional mood scores witnessed no change from the baseline (Beezhold, Johnston & Daigle, 2009).

Findings derived by the same researchers one year later, performing a cross-sectional study on the diets of Seventh-day Adventists yielded close results (Beezhold, Johnston & Daigle, 2009). As with the findings obtained from the dietary patterns from the 2009 APHA conference, vegetarian diets indicated more positive mood profiles than did the group consuming animal and animal by-products (Beezhold, Johnston & Daigle, 2009). Adventists consuming a vegetarian diet scored higher on the mood profile despite lower levels of omega-3 fats, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in their diets (Beezhold, Johnston & Daigle, 2009). The reason for the disparity is the nutritional component of fish: despite its healthy EPA and DHA fats, fish also contains arachidonic acid, cholesterol, and saturated fat (Beezhold, Johnston & Daigle, 2009). Because a well-planned vegan diet contains alpha-linolenic acid (ALA), this diet eliminates the need to consume animal products because the body uses ALA from walnuts, flax seeds, chia seeds, and leafy green vegetables for conversion into healthy EPA and DHA fats (Beezhold, Johnston & Daigle, 2009).

The argument for a plant based diet to ameliorate depression and anxiety again is found in the abundance of tryptophan in a vegetarian diet (Wurtman et al., 2003). This chemical is employed by the brain to manufacture serotonin, a neurotransmitter enabling positivity and sense of comfort (Wurtman et al., 2003). Tryptophan is obtained in seeds such as sunflower and pumpkin, leafy greens such as watercress, vegetables such as broccoli and mushrooms, and, lastly, legumes such as soybeans and peas (Wurtman et al., 2003). Although tryptophan is found in meats such as turkey, the human body experiences difficulty in converting it into serotonin (Friedman, 2018). As other amino acids enter the bloodstream, the arterial space grows smaller, due to the competition of various amino acids (Friedman, 2018). The opportunities for tryptophan's entrance to the brain is restricted, and less serotonin thus emerges (Friedman, 2018).

Tryptophan, however, can more easily enter the brain (and thus raise serotonin levels) if insulin production increases, as typically in the case after meals high in carbohydrates. Increased insulin enables other amino acids to be absorbed by muscle cells (Strasser & Fuchs, 2016). This sort of diet may shed light on the link between depression and carbohydrate cravings (Strasser & Fuchs, 2016). Consuming a meal rich in carbohydrates causes insulin to be released from the pancreas so that excess blood sugar can be stored in the liver, muscle and fat tissue (Strasser & Fuchs, 2016). Insulin decreases levels of the branched-chain amino acids (BCAA) therefore in the bloodstream, increasing a competition with tryptophan to cross into the brain as illustrated in Figure 2 below (Palego, 2016). Similar levels of BCAA and tryptophan entering the brain, the brain will choose to utilize the BCAA; thereby, leading to a reduced serotonin level in the individual (Terry & Margolis, 2017). Low levels of serotonin therefore may cause humans to crave carbohydrates, also called “the carbohydrate craving syndrome” as to inherently increase tryptophan over BCAA levels, increasing tryptophan availability and therefore serotonin (Palego, 2016).

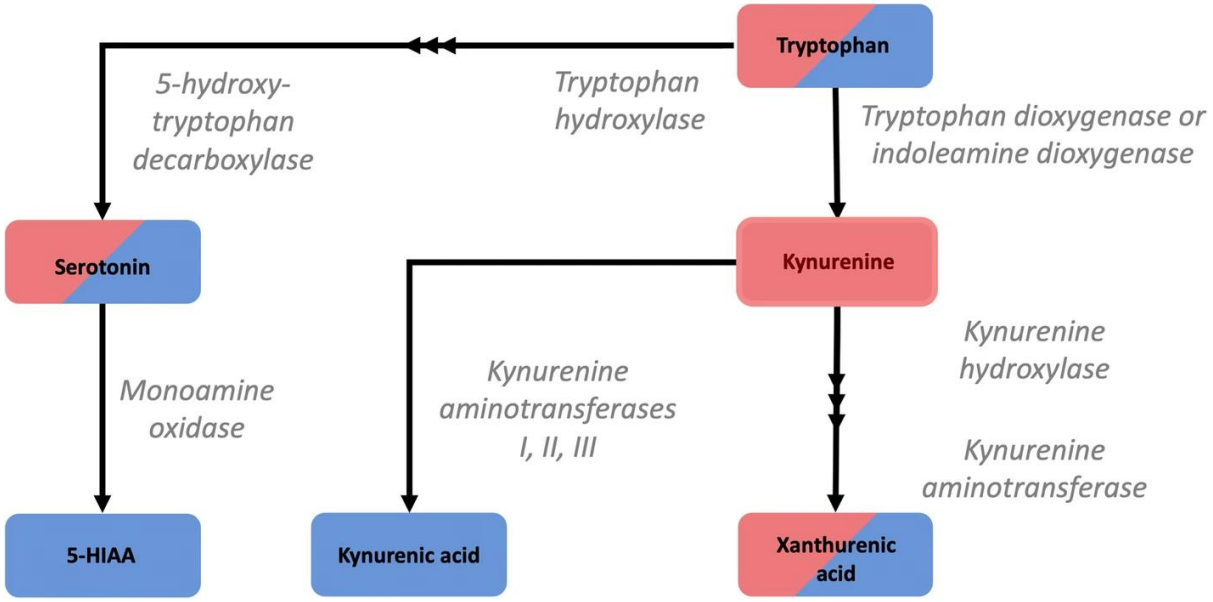

Figure 2: Tryptophan pathway (Wiley et al., 2021)

Since serotonin production is limited in diets high in protein and/or animal products, to encourage serotonin production, a plant protein based diet accompanied by ample quantities of complex carbohydrates such as whole grains, vegetables, legumes, and fruits is recommended (Villas-Boas et al., 2021). A health-appropriate approach for ideal levels of tryptophan in the brain is to focus on plant proteins along with generous amounts of complex carbohydrates, such as vegetables, fruits, whole grains, and legumes should yield ample serotonin (Villas-Boas et al., 2021). Recent evidence revealing the serotonin and tryptophan link in these food sources strengthens the argument for plant-based diet to combat depression and anxiety evaluating plant and animal protein intake and its association with depression, anxiety, and stress among Iranian women (Sheikhi et al., 2023).

4.4.1 Pharmaceutical Sources of Serotonin

The nerve cells in our brain and spinal cord secrete serotonin acting to regulate attention, behavior and body temperature; whereas, the intestinal cells produce serotonin acting to regulate digestion, blood flow, and breathing (Terry & Margolis, 2017). In the treatment of depression, anxiety and appetite-regulating obesity, drugs and supplements may be prescribed to regulate serotonin production (Berger et al., 2009).

"Selective Serotonin Reuptake Inhibitors" (SSRIs), are a class of drugs used to treat depression by increasing levels of serotonin in the brain (Berger et al., 2009). Serotonin is a chemical messenger (neurotransmitter) carrying signals between neurons to block the reabsorption of serotonin. SSRIs include antidepressants such as citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), escitalopram (Lexapro), paroxetine (Paxil, Pexeva, Brisdelle) and sertraline (Zoloft) (Getz et al., 2011).

Serotonin and norepinephrine reuptake inhibitors (SNRIs) are a class of antidepressant medications used to treat depression, anxiety, obsessive-compulsive disorder, social phobia, attention-deficit disorder, chronic neuropathic pain, fibromyalgia syndrome and menopausal symptoms (Sansone & Sansone et al., 2014). SNRIs work to ease depression by reducing chemical messengers (neurotransmitters) used to communicate between neurons, ultimately affecting brain chemistry and regulating mood to help relieve depression. Some SNRIs are desvenlafaxine (Pristiq), levomilnacipran (Fetzima), milnacipran (Savella), duloxetine (Cymbalta, Drizalma Sprinkle) and venlafaxine (Effexor XR) (Sansone & Sansone et al., 2014).

In addition to SSRIs and SNRIs, there are other medications used to regulate serotonin production and uptake. Some notable medications are: Bupropion (Zyban, Wellbutrin SR, Wellbutrin XL) an antidepressant used in tobacco addiction and tobacco-addiction medication; tricyclic antidepressants**,** such as amitriptyline and nortriptyline (Pamelor); and Monoamine oxidase inhibitors (MAOIs)**,** antidepressants such as isocarboxazid (Marplan) and phenelzine (Nardil) (Stahl et al., 2004). Anti-migraine and pain medications such as opioids (codeine, fentanyl, hydrocodone, and oxycodone). Mood stabilizers such as Lithium, are used to regulate serotonin by blocking the transporter protein and clear serotonin at the synapse between the sending and receiving cells (Hughes et al., 2014). Additional pharmaceuticals regulating serotonin are some over the counter cough and cold medications with dextromethorphan (Delsym), anti-nausea medications, the antibiotic linezolid, and the anti-retroviral medication to treat HIV, Ritonavir (Schwarz et al., 2008).

Illicit drugs such as LSD, ecstasy, cocaine, and amphetamines regulate serotonin production and uptake. Herbal supplements may be alternatively and additionally prescribed to regulate serotonin production, including St. John's wort, ginseng and nutmeg (Sofuoglu & Sewell, 2011).

4.4.2 Serotonin Syndrome

In the human body, an excessive accumulation of serotonin can create "serotonin syndrome", the situation in which and an individual has overactive reflexes and muscle spasms, along with high body temperature, sweating, shivering, clumsiness, tremors, confusion and other mental changes. (Ener et al., 2003). The administration of pharmaceutical drugs regulating serotonin levels can cause serotonin syndrome in individuals, commonly occurring when combining

medications, such as antidepressant with migraine medication or opioid pain medication. Individuals may also potentially overdose antidepressant medications (Gilman, 2007).

For example, serotonin syndrome may occur if an antidepressant with a migraine medication are combined or an antidepressant with an opioid pain medication (Albers et al., 2000). Another cause of serotonin syndrome is intentional overdose of antidepressant medications as Serotonin Syndrome is a potentially life-threatening drug reaction causing the body to have too much serotonin, a chemical produced by some nerve cells (Amitai & Frischer, 2006).

Serotonin Syndrome may cause mild symptoms (such as diarrhea or nausea) to severe symptoms, such as high fever or seizures (Anderson, 1998). In some cases, severe serotonin syndrome can be fatal if not recognized (Thomas et al., 2012). In the 1960s, healthcare providers first recognized serotonin syndrome in the 1960s, after the approval of the first antidepressant medications (Baumann et al, 2004). Due to the large number of serotonin-affecting medications available, there has been an increased number of reported cases of serotonin syndrome (Baumann et al, 2004).

4.5 Exercise

Muscle activity uses branched-chain amino acids, usually in competition with tryptophan which is the precursor of serotonin to be carried across the blood-brain barrier (Patrick & Ames 2015). As a result of decreasing competitive amino acids crossing the blood-brain barrier, it also has the potential to increase serotonin in the brain (Patrick & Ames 2015). Serotonin metabolism is time-course dependent and differs between brain regions; exercise boosts the striatum, hippocampus and midbrain areas (Thomas et al., 2012). In research evaluating 30

minutes of daily exercise that time period appears to be enough to increase serotonin synthesis and metabolism in the cerebral cortex and brainstem (Patrick & Ames 2015).

As a complementary or alternative therapy to the management of serotonin levels in individuals, exercise may be encouraged (Ranabir & Reetu, 2011). Research has shown that regular exercise increases one's mood and cognitive functioning; the neurobiological basis of these results have concluded that serotonin is a dominant hormone in mood change (Patrick & Ames 2015). Thirty minutes of aerobic exercise five times per week, along with two strength training sessions per week has been shown to improve mood disorders and heart health. Exercise promotes the release of multiple hormones, including dopamine, endorphins and serotonin; synergistically working to improve mood, cognition and concentration (Patrick & Ames 2015).

Wipfli et al's research study evaluating a 7-week exercise intervention demonstrated that individuals divided into exercise versus stretching had differing post-test serum levels (Wipfli et al., 2011). Individuals participating in stretching had significantly lower post-test serum levels than individuals assigned to aerobic exercise (Wipfli et al., 2011). The reduction in blood serotonin post-exercise is similar to the effects of selective serotonin reuptake inhibitors; concluding percent change in serotonin partially mediated the relationship between exercise and depression (Wipfli et al., 2011).

4.6 Psychological Stress

Research shows that stress may be a beneficial factor in regulating serotonin uptake in humans (Niellon, 2002). Chronic and acute psychological stress can show tryptophan hydroxylase levels to be upregulated in the brains of rats, leading to improved serotonin creation and

secretion (Sparling et al., 2003). Research shows that chronic stress leads to higher levels in the hippocampus, hypothalamus, frontal cortex, and striatum (Vaida et al., 1999). The cause is presumed to be decreased serotonin transporter levels in the raphe nuclei after acute and prolonged stress (Vaida et al., 1999). The serotonin transporter responsible for transporting serotonin into the synaptic cleft (BDFN) is seen to be decreased in post-stressful situations, concluding that prolonged stress can lead to decreased serotonin and depression (Wurst et al., 2000).

Whereas psychological stress can increase serotonin creation, the state can also extend its creation towards depletion, and therefore should be encouraged in acute durations (Wurst et al., 2000). As stress and depression are characterized by high circulating cortisol and changes in psychological functioning, the origin and development of depression was evaluated by researchers, Tafet, Toister-Achituvadn Shinitizky (2001). Findings offered elevated cortisol induced stress showing increased serotonin uptake when resting and also stimulated nerves, resulting in symptoms of depression (Tafet, Toister-Achituvadn Shinitizky, 2001). Therefore one can induce that long periods of elevated cortisol and increased serotonin uptake can lead to depression. Acute exposures of elevated cortisol and psychological stress can lead to improved mood; whereas prolonged exposure to stress can lead to symptoms of depression (Tafet, Toister-Achituvadn Shinitizky, 2001).

4.7 Sunlight Exposure

Insufficient sunlight exposure, also known as seasonal affective disorder, may exacerbate mood disorder (Kent et al., 2013). Research shows that sunlight entering the human eye stimulates the retina to cue the brain to produce serotonin, allowing for mood, emotion, appetite and digestive regulatory processes (Val-Laillet et al., 2015). Research shows suprachiasmatic

nuclei affect both serotonin and melatonin (for sleep) and are both essential for mood along with cognitive functioning involved in pathways potentially affected by sunlight exposure (Kent et al,. 2009). Evaluating participants exposed to periods of sunlight and periods of isolation show that depressed participants experienced lowered cognitive functioning in lower levels of sunlight exposure; researchers concluding seasonal depression may be to blame for lowered serotonin uptake due to decreased sunlight exposure (Kent et al,. 2009).

Bright light is used to treat winter depression and might also have positive effects on mood in some healthy individuals (aan het, Moskowitz, & Young, 2007). We examined possible links between bright light exposure and social interaction using naturalistic data (aan het, Moskowitz, & Young, 2007). For 20 days in winter and/or summer, 48 mildly seasonal healthy individuals wore a light meter at the wrist and recorded in real-time their behaviors, mood, and perceptions of others during social interactions (aan het, Moskowitz, & Young, 2007). Possible short-term effects of bright light were examined using the number of minutes, within any given morning, afternoon or evening, that people were exposed to light exceeding 1000 lux (average: 19.6min) (aan het, Moskowitz, & Young, 2007). Social interactions were labeled as having occurred under conditions of no, low or high bright light exposure (aan het, Moskowitz, & Young, 2007). Independent of season, day, time, and location, participants reported less quarrelsome behaviors, more agreeable behaviors and better mood when exposed to high but not low levels of bright light (aan het, Moskowitz, & Young, 2007). Given that the effects were seen only when exposure levels were above average, a minimum level of bright light may be necessary for its positive effects to occur (aan het, Moskowitz, & Young, 2007). Daily exposure levels were generally low in both winter and summer. Spending more time outdoors and

improving indoor lighting may help optimize everyday social behavior and mood across seasons in people with mild seasonality (aan het, Moskowitz, & Young, 2007).

The issue of decreased exposure to natural, bright light and the corresponding lessened serotonin production appears to be a phenomenon which is culturally and historically bound (Salmon, 2001). Only until very recently, prior to the industrial revolution, has most of the world's population labored out of doors, primarily in agricultural settings (Salmon, 2001). Populations thus received sufficient bright light exposure, even during the darkened winter months (Salmon, 2001). For example, light outside can exceed 1000 lux even on a cloudy day; this brightness is often not obtainable indoors (Salmon, 2001). In a recent study in 2007, implemented at an approximate latitude of 45° N, daily exposure to light more than 1000 lux averaged about half an hour during winter and only, during summer, an hour and a half, in summer amongst workers laboring a minimum of 30 hours weekly; (weekends were included) (Salmon, 2001). In this group, the light exposure characteristic of summer was probably considerably less than was the winter exposure of our agricultural ancestors. It is possible to then argue that today's population inhabits a world devoid of bright light (Salmon, 2001). A good deal of literature across disciplines discusses this topic of the many benefits of bright light for populations; the volume of which is beyond the scope of this thesis (Salmon, 2001). Testimony to this points to the phenomenon of lighting specifically created for addressing seasonal affective disorder. Such lamps offer more lax than what can be obtained with conventional indoor lighting (Salmon, 2001). Apart from individual consumer use, on the broader national level, light deprivation has been addressed in Scandinavia's "light cafes" and this phenomenon has made its way to the UK (Leidig, 2005). In terms of communities addressing the issue, an Austrian village in a valley built a series of giant mirrors during winter to increase daylight brightness (Leidig, 2005). In our modern day world, an understanding of the serotonin - natural light connection has directed the architectural design of our homes and

buildings so that indoor labor is not associated with natural, bright light deprivation (Salmon, 2001).

4.8 Conclusion

In summary, and in review of factors contributing to serotonin regulation in humans, research points to pharmacological and complementary health factors (Zhang et al., 2021). As serotonin regulation is correlated with regulation of both mood and appetite, its functioning is valid for both the improvement of mental as well as dietary health (Zhang et al., 2021). Pharmacological drugs offering serotonin uptake regulation can offer solutions to individuals with malfunctioning serotonin creation, secretion and uptake; yet, research shows that prolonged administration of such drugs may improve yet not enhance the cognitive behavioral attributes leading to the development and duration of depression and mood disorders (Panossian, et al., 2021). Whereas complementary therapy such as dietary habits including a tryptophan-rich, balanced meal plan, adoption of omega-3 and the PUFA rich Mediterranean meal plan can offer beneficial results in individuals' serotonin uptake (Panossian, et al., 2021). However,the implementation and persistence in the adoption of such a meal plan requires effort (Panossian, et al., 2021). Unfortunately some individuals may lack the physical, financial, and psychological support in adopting lifestyle changes. Additionally, engaging in regular aerobic exercise, short periods of stress, and exposure to natural sunlight are also therapies in which individuals may engage to adopt a serotonin balanced lifestyle (Dai et al., 2022). As Chapter 4 has presented qualitative and quantitative research findings addressing the management of serotonin uptake, Chapter 5 presents conclusions, discussion and recommendations for future research.

Chapter 5. Conclusion

5.1. Introduction

Two research questions have structured the direction of this thesis. The first question relates to overweight and obese individuals' consumption of a diet higher in calories than their homeostatic requirements and "*What is the significance of the contribution of dietary habits of obese individuals in decreased serotonergic signaling?"* For years, researchers have concentrated on endocrinology and hormonal disturbances which may occur due to higher body mass (Srivastava et al., 2019). Yet, current research in the psychology field regarding food intake has the potential to shed new light as to why obese and overweight individuals consume more calories than their homeostatic requirements (Srivastava et al., 2019). Therefore, the second question in this thesis regards "*What are the potential implications of therapeutic benefits for obese individuals with decreased serotonergic signaling?"* The second question that directs the course of this thesis asks if there is a causality factor between. Pharmaceutical interventions may outnumber the natural treatment of improving serotonin signaling in obese populations due to lack of research and therefore could be encouraged to be explored (Srivastava et al. 2019). The pharmaceutical approach in pursuing this line of research does of course yield valid outcomes to the scientific and medical community but this approach offers insights for mental health care practitioners as well. Research in the field of psychology and nutrition share an overlap in the areas of binge eating, overeating, and emotional eating (Lattimore, 2020). Although the causality between emotional eating and obesity is similar to serotonin disturbance, further research determines that the previous literature can also be recommended to scientists interested in exploring the inner workings of hedonistic circuitry (Lattimore, 2020). Overweight and overweight individuals in consuming a caloric excess diet for pleasure may also engage in overconsumption due to decreased serotonin signaling;

therefore, a decreased sense of pleasure (Niccolai et al., 2019). An exponential decrease in serotonin signaling and consequently in decreased pleasure in every fat mass gained can lead to the "lack of pleasure,' ' loss of taste', the symptoms that obese and overweight individuals claim (Niccolai et al., 2019). This decrease in cessation is also common in depressed people. Although depression can and does exist in all body types however, the obese and overweight individuals share common attributes that depressed individuals do, such as decreased physical activity, decreased struggle to identify a correlation between blood sugar and obesity (Niccolai et al., 2019).

5.2. Summary

Chapter 5 provides conclusions based on research findings from data collected on eleven research studies, as well as discussion and recommendations for future research. This chapter will review the purpose of the study, research questions, literature review, and findings of the study. It will then present conclusions, a discussion of the conclusions, and recommendations for practice and for further research.

The work of Chapter 5 serves to offer summative conclusions derived from research findings obtained from data collection on eleven research studies. We also identify trends for future research. This chapter assesses the study's aims, lines of research enquiry and the established research to which they below, and, lastly, the findings. Chapter 5 proceeds to offer and discuss conclusions as well as recommend future lines of research and therapeutic implications.

5.3 Recommendations for Therapeutic Implications

There is an absence of training in both neuroscience and psychology. Interdisciplinary approaches can yield richer findings and directions combining the efficacy of drugs plus the therapeutic/individual based (Steiger, 2004). Emotional eating has recently received more attention in nutrition and psychology research; revolutionary practices are employing emotional eating awareness, mindfulness and connecting with one's body and mind (Lattimore, 2020). Clients who engage in emotional eating, gain weight, and continue to increase their food consumption due to decreased serotonin signaling may also be suitable for this interdisciplinary/multi-pronged approach (Steiger, 2004). Therefore, attention to mindfulness and awareness in eating behaviors is crucial for further directions and recommendations to practitioners, as detailed below.

Before continuing with this line of inquiry, it is worth noting that In cases where clients with serotonin signaling disturbance require support for extreme stress, anxiety, depression, or binge eating, nutritionists, health coaches, and exercise professionals should be aware that treatment of these disorders extends beyond the limits of their practice (Steiger, 2004). Therapeutic diagnoses are required in these situations by mental health professionals.

In light of these discussions, exploring the distinction between binge eating and emotional eating is worthwhile in so far as the topic provides directions for professionals.

Binge eating is characterized by multiple episodes of eating where there is a loss of control. In these situations, the individual should be referred to a medical and/or mental health professional for treatment (Karakurt et al., 2014). Offering support in mindful eating

techniques is beneficial; nevertheless, registered dieticians, therapists or mental health professionals are best suited as they specialize in such cases (Karakurt et al., 2014).

In addition to the above discussed modifications in food choices(plant based diet), sunlight therapies (individual or community based initiatives to increase bright natural light indoors), and distinguishing patterns of eating behaviors (binging vs emotional eating), there are strategies that may support individuals experiencing serotonin signaling disturbances (Yau & Potenza, 2013). These strategies can be therapeutically administered in counseling strategies (Yau & Potenza, 2013). Since stress, for example, triggers emotional eating/hedonistic circuitaries, there are behavioral and cognitive strategies to manage stress or any other negative emotions that may preclude overeating (Yau & Potenza, 2013). Some techniques to modulate serotonin disturbance include physical activity, counseling, and mindfulness exercises. The latter, mindfulness exercises, because of the breadth of strategies, deserves a separate section of this thesis.

Before entering into a discussion of these strategies, it should be noted that as with all therapies, individual clients need to determine a particular course of action (Karakurt et al., 2014). Counseling that enables patients to mediate between strategies is a ‘win-win’ situation in the sense that patients gain understanding of themselves in managing their responses to stress triggers (Karakurt et al., 2014).

Frayn, Livshits and Knäuper (2018) advocate skill building in managing unpleasant emotions for patients by transitioning from the numbing behaviors to mindfulness; in this way, they adopt healthier patterns of coping with stress and healthier eating behaviors. One such mindfulness adoption practice the researchers advocate is a client self check-in in which s/he inventories behavior to ensure stress is being managed (Frayn, Livshits and Knäuper, 2018).

Consistent application of these management techniques can support behavioral changes which prevent spiraling (Czuczor-Bernat et al. 2019). Mindfulness takes on many aspects. These behaviors include but are not limited to recording one's experiences in a diary, deep breathing when under stress, talk therapies, and gentle physical movement--something as stress-free as stretching, taking a walk or yoga movements. Apart from the insights gained in professional counseling, suggesting clients avail themselves of their established friendships and reach out to those who care for them when under stress and thus avoid experiencing the impulse to numb pain with food and reacquaint oneself with the joys/benefits of human interaction (Czuczor-Bernat et al. 2019).

A similar switching off from negative to positive behaviors would be engagement in hobbies that stimulate brain pathways other than hedonistic ones. Such outlets would stimulate/invigorate creativity and self-expression, thereby reducing the urge to numb oneself (Czuczor-Bernat et al. 2019). In addition to the above discussions, regarding the association of regulation of serotonin signaling in good nutrition, further common sense management strategies are the time honored benefits of listening to music--'soothing the savage beast' as Shakespeare would say. Sleep in regulating serotonin disturbances is a category deserving of separate consideration (Czuczor-Bernat et al. 2019).

Since mindful eating is a relatively new topic (see above), it would be best to define the practice and explore the associated therapies that serve obese and overweight clients (Frayn, Livshits, & Knäuper, 2018). . Mindfulness uses two criteria: firstly, observation--of fullness (instead of unpleasant sensations of feeling stuffed or sick) and hunger cues; secondly, speed--eating more slowly so as to achieve natural satiety and experience the sensation of eating (Frayn, Livshits, & Knäuper, 2018). While research on emotional eating and the use of mindfulness-based

interventions in weight loss is relatively new, several studies have investigated the benefits of mindful eating on emotional eating and weight loss (Frayn, Livshits, & Knäuper, 2018).

The value of mindful eating in terms of weight loss has been examined in a 2019 study, for example, for overweight and obese adult females (Czepczor-Bernat et al., 2019). A year earlier, Salvo et al's 2018 clinical trial achieved similar findings in terms of pairing the strategy with others for weight loss. Mindfulness's significance in its ability to decrease emotional eating and attune oneself to prevent susceptibility to cues was also noted in a literature review from the same time (Warren, Smith and Ashwell, 2017).

In order to ensure that the technique benefits obese and overweight individuals, practitioners are encouraged to encourage clients to focus upon the act of eating so as to understand fullness (Frayn, Livshits, & Knäuper, 2018). This focus includes recognizing hunger and meeting one's needs. A fullness scale, termed "A Hunger Scale", see Figure 2. For example, it is one such technique that enables clients to focus upon the act of eating and swallowing as well as discerning hunger as a sensation separate from one's emotions (Frayn, Livshits, & Knäuper, 2018). The Hunger Scale also enables one to identify emotions instead of repressing them with food. This technique offers a safe space that enables the obese and overweight individual to explore painful emotions (Warren, Smith, & Ashwell, 2017).

Figure 2. *The Hunger Scale (Cardello et al., 2005).*

In terms of recognizing one's emotions and the compulsion to eat, the Hunger Scale works hand in hand with another therapeutic practice, that of journaling as indicated in Figure 3 below. Journalling, similar to The Hunger Scale, requests client buy-in to the process so they can autonomously understand situations that prompt them to eat (Cardello et al., 2005). By ranking their hunger (The Hunger Scale), the time of eating, what they ate, and how they felt, clients become aware of the connection that arises between what they eat and how they feel. Clients may also identify their predilection for various kinds of food (savory, sweet) and, on a simpler level, realize that the volume/quantity of what they eat if binding is an issue (Cardello et al., 2005). Clients may further notice events that trigger eating when not hungry and thus incorporate other non-eating strategies (van Strien, 2018). Sessions with skilled practitioners enable clients to plan strategies that do not employ eating while not hungry (Cardello et al., 2005). They can be some of the activities described above, engaging in a hobby, physical exercise, initiating contact with friends and family to manage powerful or unpleasant emotions (Warren, Smith, & Ashwell, 2017). Other behavior strategies may incorporate the technique of

hydration: recognizing the difference between thirst and hunger, consuming water to help one prevent emotional, not hunger based, eating (Cardello et al., 2005). Furthermore, if clients do eat out of emotional and not hunger based needs, discussions between client and professionals could deal with the emotions arising after the eating episode has passed (van Strien, 2018). Having clients discuss the emotions following a binge or episode of emotional eating may help strengthen their understanding of the factors leading them to eat.

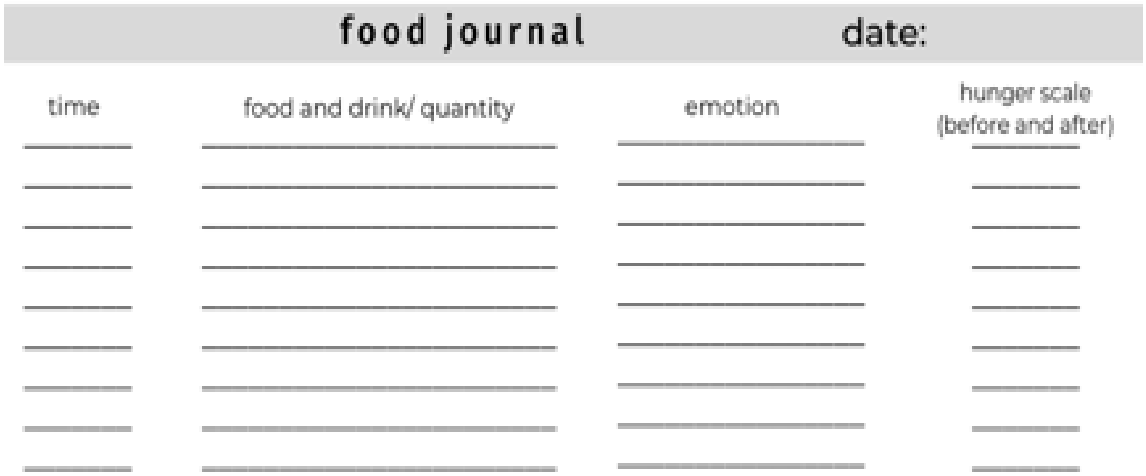

Figure 3. *Sample Food Journal (*Arnold & Sobal, 2000)

Practitioners counsel their patients to adopt behavior changes: to eat more slowly, stop before feeling overly full, and prepare meals that are protein and fiber rich (Salvo et al., 2018). On another note regarding food choices, clients can be encouraged to disabuse themselves of the tendency to demonize particular kinds of foods, i.e., calorie dense sweets (Salvo et al., 2018). In adopting this practice, certain kinds of foods do not acquire power and thus control over the client.

In conclusion, as a cautionary note, dieticians and therapists utilize these management strategies with the full awareness that patients and clients may be experiencing such severe trauma or other mental disorders to the degree that the above strategies this thesis discusses may not be fruitful. In such cases, professional help is needed.

5.4 Suggestions for Further Research

Unfortunately, the obesity epidemic shows no signs of cessation. Therefore vigorous, ongoing, innovative, and eclectic studies are required to shed light on this problem and propose solutions. Therefore, the latter criteria are particularly important. Since recent research has pointed to a rise in obesity in the Near East, innovative and eclectic research which focuses upon different or new subject populations, geographic locale and age groups will prove particularly insightful (Di Cesare et al., 2019). The Near East is one such example as well as the rise in obesity in children across the globe (Di Cesare et al., 2019). Ironically, the exponential speed at which the obesity epidemic has spread across the globe yields multiple directions for research avenues. For researchers this poses a rich yet troublesome paradigm. "Healthy obesity" is now being called into question as children and teens face being overweight. For example, the cautiously optimistic term "healthy obesity" would benefit from long term studies which follow dietary patterns and weight of healthy obese children and adolescents as they progress into adulthood (Di Cesare et al., 2019). Another direction future research might take would be in quantitative broad based cross country comparison of obesity. Inherently, biogenic mechanisms in the human body possessing some part in the cause of obesity need to be researched in detail.

Similar to obesity, serotonergic signaling in the body and the human body's responses to its signaling must be evaluated in further detail of serotonin's significance and relationship to other important hormones playing in weight gain, such as insulin. Depression, along with obesity are common disorders brought by both epidemiological and environmental factors of modern living (Blasco et al., 2020). Since the pharmaceutical treatments of mental illness and weight gain have an overlap, the causal effect of these drugs must be evaluated to determine the causality and identity of the dependent versus independent variables (Rajan, 2017). Future research focusing on addictive behavior and serotonin can shed light on dietary consumption and response-control (Rajan, 2017). In conclusion, the current landscapes suggests an eclectic/multi prong research approach in which streams of research conjoined and commingled to uncover or understand the complexity of these issues. However, other mechanisms are also possible. The challenge of future research is to delineate them in the complete elucidation of the complex neurocircuitry underlying the serotonergic control of appetite and body weight.

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