Preprints.org

Review

Not peer-reviewed version

Premier Obesogenic Factors: Overeating and Food Addiction

Muhammad Aslam * and Mubashir Abbas

Posted Date: 14 February 2023

doi: 10.20944/preprints202302.0223.v1

Keywords: Obesity; Hyperpalatability; Adipose tissue; Hormonal imbalance

Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 February 2023 doi:10.20944/preprints202302.0223.v1

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Review

Premier Obesogenic Factors; Overeating and Food Addiction

Muhammad Aslam *, Mubashir Abbas

Laboratory of Neurophysiology, Graduate School of Health Sciences, KOC University, Istanbul, 34450 Turkey; MASLAM21@KU.EDU.TR; ORCID iD: 0000-0002-5701-3721

FQDMF College of medicine, Lyceum Northwestern University, Dagupan city,2400, Pangasinan, Philippines; mubashirabbas92786@gmail.com; **ORCID:** 0000-0002-5808-6666

* Correspondence: maslam21@ku.edu.tr

Abstract: Obesity is characterized by surplus buildup of body lipids primarily in adipose tissue. Prevalence and incidence of obesity are ascending persistently at an alarming rate. Unusual eating behaviors like compulsion to eat (food addiction) and excessive consumption are the premier contributors to obesity. Both are under influence of a variety of stimuli, mainly being stress, emotions, dietary restrictions, sweetness, hyperpalatability, neural pathways, hormonal imbalance and genetics. This review summarizes the potential driving factors behind overeating and food addiction for understanding and exploring obesity linked novel agents and processes as an endeavor to advance treatment approaches. Obesity has been studied extensively throughout the world due to high incidence and association with several metabolic disorders including cardiovascular disorders. The food addition has considered one of potential key factor of obesity and excessive weight gain. Sedentary life style and availability of food also induce obesity.

Keywords: Obesity; Hyperpalatability; Adipose tissue; Hormonal imbalance

Introduction

Obesity is under extensive investigation throughout the world owing to high incidence along with induction of several obesity-associated disorders. Obesity is generally linked with non-homeostatic feeding behavior correlated with overconsumption of food (mainly palatable) for the sake of pleasure rather to fulfill biological requirements. Enhanced caloric intake resulted by failure to control over feeding regardless of knowing the consequences suggested that hyperphagia is a form of food addiction [1]. Out of a wide range of obesogenic factors, the greatest contribution associated with over consumption of energy dense foods due to abnormal eating behaviors [2]. Food addiction (FA) has been emerged as one of the potential key factors of obesity [3].

Food addiction is a chronic and relapsed state characterized by unnecessary consumption of high calorie food in a dysregulated manner. The condition associated with the interactions among different complex fundamental factors that amplify the desire for certain specific dietary items in order to attain the state of excitement, pleasure, energy or to relieve stress [4]. Craving and impulsivity are the main underlying mechanisms of FA. Food craving is a forceful desire to ingest some particular food with minimal resistance [5], while impulsivity is defined as an unintended response to any internal or external stimulus without considering negative impacts [6].

Food addiction has been recognized as fundamental factor in chronic overeating and obesity [7]. With the passage of time human beings are becoming inclined to FA as a result of hedonic system, excessive consumption of food over the requirements [8] mediated by desire and drive neural pathways. Optimum circumstances directing towards food addiction include an abundant supply of energy dense foods, nominal physical exercise and different socio-cultural principles that encourage over ingestion of various products [9,10]. One of the most reliable tools to access food addiction is Yale Food Addiction Scale (YFAS) comprised of 25 measures which are used to evaluate different addictive eating disorders [11].

© 2023 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 February 2023 doi:10.20944/preprints202302.0223.v1

A study from the field of bariatric surgery has found more than 60% of presurgery patients having histories of grazing like behaviors, exhibiting strong connection with food addiction [12] Some of the most important and potential driving factors behind overeating and food addiction include stress, emotions, neural pathways, dietary restrictions, sweetness, palatability, and genetics.

Stress

Stress being a state of endangered homeostasis triggers diverse behavioral and adaptive responses to stabilize the condition. Stress, weather physiological or environmental in nature, has significant influence on eating behavior. Several studies in animal models have revealed considerable increase in food intake following some stressful condition [13]. Human eating behavior is much similar with animals in sensitivity and response to stress, depending on type and duration of stressor [14]. Meanwhile, lower attraction towards food has been noted in case of some physical harm, illness or fear [15].

Corticotropin-releasing hormone (CRH), norepinephrine and their peripheral factors including pituitary-adrenal axis and divisions of autonomic nervous system, are the premier regulators of stress response. Upon the activation of stress system, multiple behavioral and peripheral changes happen in order to support organism to regulate homeostatic mechanisms [16]. For survival, it is mandatory to cope with stress, an energy consuming process. Multiple processes start in the body including hyperglycemia as a result of glucogenolysis, gluconeogenesis, reduced glucose uptake in tissues; mobilization of amino acids from tissues other than liver, lipolysis and hypermetabolism to enhance available energy [17]. But untreated and recurring stress may lead to serious threats to health and well-being. Repeated exposure to stress stimulates food cravings especially for sweet foods even in the absence of hunger [18].

The hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) are the principal effecter pathways of the stress system. According to existing records, chronic stress with mild hypercortisolemia and chronic CNS activation excite fat accumulation in body in addition to eliciting multiple pathologies including diabetes, inflammation and other metabolic syndromes [19]. Higher risk of abdominal fat deposition is seen in case of chronic stress due to HPA axis dysregulation causing continuous over production of glucocorticoids [20]. Glucocorticoids stimulate activity of lipoprotein lipase in adipocytes, thus help in promoting fat storage in adipose tissue [21]. Moreover, they also increase serum insulin, leptin, ghrelin [22] and some hypothalamic neuropeptides [23] stimulate preference for food.

The key endocrine mediator of stress in human is hypothalamic–pituitary–adrenal (HPA) axis with cortisol as end product. Frequent and unmanageable stress stimulates hypercortisolemia by deregulating hypothalamic-pituitary-adrenal axis ultimately influencing food intake behavior and energy homeostasis by inducing glucose intolerance [24] and insulin resistance [14]. Cortisol shows acute as well as chronic effects on metabolism, central nervous system (CNS) and cardiovascular system [25]. Cortisol has shown to be high in about 50% of US population due to their involvement in unhealthy activities including smoking, dietary irregularities and intake of certain medicines like prednisone [26].

Emotions

Emotions play an important part in determining overall human behavior including food choice, liking or disliking of particular food and extent of food consumption. Similarly, mood and feelings of people can also be influenced by the type of food consumed, indicating some intricate relationship between emotions and food intake [27,28]. Both share complex interactions including a number of physiological factors, reward mechanisms, psychological factors, social factors, cultural factors and eating tendencies [29]. Eating in response to emotions, noticeably interrelated with BMI as higher or lower intake of food is parallel with gain or loss of weight respectively [30]. Individuals with high level of emotional eating are at the verge of developing overweight and obesity [31].

Food addiction being similar to drug addiction resulted by strong emotions and ingestion of specific foods, attempt to regulate emotions [32] rather fulfilling their physical requirements [33]. Various investigations have proposed that food choice and consumption are even more affected by emotions rather than profound traditional factors such as liking and desire [34,35]. Furthermore, food

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 February 2023 doi:10.20944/preprints202302.0223.v1

choice and eating desire is also associated with positive emotions [36] in addition to negative emotions. But, experiments have revealed a tendency to over consume highly processed foods in food addicts, is attempt to cope with negative emotional state [37,38]. Effects of negative emotions on ingestion behavior are comparatively severe and found greater in females while positive emotions related overeating are found similar in both genders [39].

Negative emotions especially when not regulated properly, guide to overeating [40], prominently in obese rather than normal persons [41]. Negative emotions-triggered hyperphagia coupled with an improvement of mood [42] as elevated level of serotonin was detected in food addicts following energy intake [43]. Hyperphagia in response to anxiety is considered most cited emotion while hyperphagia in response to happiness considered least frequently described form [44]. Emotions associated hyperconsumption suggested to act as mediator between negative emotional status and expected weight gain in female individuals [45]. Healthy as well as eating disordered women demonstrate affinity for overeating due to emotion-oriented handling and disrupted preventive attempts [46]. However, another study has contradicted the idea by revealing overeating as a result of attention and focus for food rather than negative mood [47].

Parental feeding manners and eating restrictions also exert critical impact on children feeding strategies and weight status by directly influencing their emotional eating patterns [48]. Higher caloric intake without hunger by preschool children has been noted while experiencing negative mood whom parents were consuming sweet palatable foods as an attempt to regulate emotions [49]. Stress further ameliorates emotional eating guiding towards building abdominal stores and development of co-morbid medical disorders [50]. Hence, these findings appeal considered emotional management while designing preventive and treatment strategies against obesity [51].

Neural Pathways

Brain reward pathway is one of important circuit related to obesity and addiction. Both share similarity as confirmed by functional brain imaging studies expressing analogous activation patterns of neural pathways when obese and addictive individuals were exposed to certain food or drug of abuse [52,53]. Many other neurological studies have also revealed some shared neural pathways between abnormal food consumption and substance dependence [54,55] by discovering similar hyperactivity in reward related areas and diminished activity in inhibition related areas [56]. Dopamine acts as premier regulator of brain reward circuit. Sufficient concentration of dopamine is released in limbic system [57] and mesolimbic regions following administration of various addictive substances, in humans following exposure to palatable foods [58]. Striatum has also implicated in the regulation of such behaviors revealed by positron emission tomography studies by comparing dopamine D2 receptors between obese and lean individuals [59]. Obese individuals are likely to over consume foods to compensate blunted striatal sensitivity [60]. Brainstem also contributed a greater extent in the regulation of energy homeostasis by receiving neural and hormonal signals from peripheral parts about the nutritional status and adiposity [61].

Currently we are living in an obesogenic environment as highly palatable foods are available everywhere. Exposure to such foods aggravate our desire to consume them, consequently contributing to weight gain [62]. Experimental studies on animals have uncovered same neural mechanisms found in human food addictors after they were allowed a rapid access to sugar, fat and processed food [63,64,65]. Dysregulated food reward mechanism related with the threat for future weight gain especially in case of an unhealthy food environment [66]. Prolonged intake of certain high calorie diets induce molecular and behavioral changes in brain reward centers similar to drugs abuse reinforcing their discriminatory preference [67]. Several neural mechanisms have been implicated in regulation of stimulatory effects of sugar on caloric intake including special peptide systems in hypothalamus like neuropeptides Y and agouti-related protein. Moreover, these appetite stimulant peptides are found effective in inducing fat rich diet intake [68].

Overconsumption of foods affects neural reward pathways, lead to increased salience and seeking for such foods, similar to the processes observed in high alcohol and drug intake [69]. Parallel pattern of activation /inhibition of different brain areas has been noted in obesity and substance addiction, including hyper activation of amygdale, pallidum, putamen, striatum and superior frontal

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 February 2023 doi:10.20944/preprints202302.0223.v1

gyrus and inhibition of central operculum and postcentral gyrus [70]. Moreover, excessive activity in amygdala, putamen and thalamus being connected with compulsive eating [71]. Amygdala serves as a meeting point for most important information [72] and it has been extensively investigated for its contribution in emotional processing, fear and anxiety [73]. Based on available evidence important role of amygdala has been proposed towards the development of compelling quest for desirable substance [74]. Besides this, an electroencephalogram study, revealed similar types of brain alterations have been in people with addictive disorders [75].

Desire and appetite pathways work side by side along with hunger pathways [76] and exert potential effects on strength of satiety [77] to access the amount of food consumption for one day, depicting their vital role in eating behavior [78]. The prefrontal cortex is one of the many regions involved in the regulation of eating behaviors by integration with sensory and visceral afferents as well as interacting with hypothalamus and limbic areas through feedback system. In obese people these functional associations altered and control over feeding behavior is lost, leading to unnecessary overeating [79]. It has been observed in recent studies that dietary alterations during gestational period lead to long lasting developmental changes in offspring. A comparative study at embryonic stage has indicated higher expression of different neural substances including hypothalamic orexigenic peptides linked with enhanced stimulation of hypothalamic neuronal precursors and neuroepithelial cells, lead to higher food intake as a consequence of various physiological and behavioral changes [80].

Generally, the central melanocortin system being considered one of the best-characterized neuronal pathways concerned with regulation of energy homeostasis. This complex neuronal network retains the ability to sense stimuli from a range of substance like hormones, nutrients and other neural inputs and regulates long lasting adipostatic signals mainly from insulin and leptin in hypothalamus. Acute regulations are linked with the control of hunger and satiety in the brainstem. Considering the potential regulatory role of these system, serves as a dynamic target for drug developers for treatment of obesity [81].

Dietary Restrictions

Dietary restriction are concerned with intended limitation for food intake and omitting meals even in the presence of hunger [82]. Dieting is a form of energy restriction, related with management of weight loss. Both food restriction and dieting exert their effects on eating habits leads to abnormal eating [83]. In addition to food restriction and dieting, food deprivation also encourages reinforcing value of food [84].

In normal individuals, the food restriction is risk factor for hyperphagia while in the individuals already suffering from some eating disorder, the ongoing illness further prolonged [85]. Experimental studies on laboratory animals have revealed reliable and consistent increase in food intake following food deprivation and food restriction strategies [86]. Although the exact mechanism need to be uncovered, however, food cues and stress may also be underlying factors in this exacerbate eating [38].

Dieting is more often observed in teenage girls as an attempt to improve their appearance resulting nutritional deficiencies and restricted growth [87]. Early age food restrictions are linked with overeating in adolescence thus posing threat for the development of obesity [82]. In addition, maternal restriction can also encourage overeating in early age overweight girls that may be genetically liable to environmental cues [88]. Following a short term restriction of carbohydrates and proteins, participants under observation expressed higher consumption of respective diet [89] indicated dieting individuals experience powerful cravings and difficulty in resistance of foods restriction compared to non-dieters [90]. Desire of sugar consumption continue to ascend as the duration of self-restraint prolongs [91].

Evidence has suggested a history of food restriction and stress promoted abnormal over intake of food even with normal satiation and body weight [92]. Severe and short term energy deficiencies cause modifications in appetite and appetite–regulating hormone concentrations leading to compensatory increase in energy intake thus regaining lost weight in non-obese individuals [93]. Restrained eaters with limited inhibitory control are more likely to failure while attempting to restrict

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 February 2023 doi:10.20944/preprints202302.0223.v1

intake, increasing the probability of overeating [94]. Both caloric restriction and overeating have been shown to affect neural processes associated with reinforcement. Both preclinical and some clinical studies have provided evidence that food restriction may increase reward sensitivity similar to drug abuse [95].

Sweetness

Evidence of available knowledge reported that sweet foods encourage appetite, facilitating overeating. Sweet taste exerts its effect through G-protein coupled receptors (T1R2 and T1R3) found in mouth and intestine and secrete different peptides aid in metabolic activities and satiety [96]. Hormonal and metabolic modifications have been noted in individuals taking high glycemic index food, reduces availability of metabolic fuels and stimulate overeating mainly in obese subjects [97]. Energy rich foods are efficient source of daily energy intake and stimulate release of various neuropeptides to elevate mood [98]. Signals for high fat and high sugar diets stimulate food ingestion desire, gradually lead to overeating [99]. Conclusively concentrated sugars rich food and fats act as addictive substances [66].

Carbohydrates, mainly disaccharides like table sugar are considered the most potent addictive dietary substances out of all macronutrients [100]. Sugar encourages the synthesis and release of dopamine in nervous tissue, one of the premier neurotransmitters of addiction pathway [101]. Elevated dopamine secretion has been observed in nucleus accumbens in high sugar fed animals, parallel to the outcome of certain drugs abuse. In addition, a delayed response of acetylcholine neurotransmitter for satiety is noted in such animals [102].

In a series of experimental investigations, role of sugar as an addictive substance has been confirmed owing to similarity of its behavior with well documented effects of addictive drugs [103]. Foods rich in energy, mainly high sugar and high fat diets, are mostly highly palatable in nature. Rewarding mechanisms are the key contributors in sensing these substances more desirable over certain low caloric foods. Resultantly these energy dense highly palatable diets revealed an addictive potential [104]. Inclination towards excessive consumption of hyperpalatable foods with time, specifically sugar rich, fat and salt, associated with their high processing and rapid availability [105].

Different foods have different capacities to induce addiction, based on their processing and composition [106]. Processing along with addition of sweeteners and fats enhances addiction potential of many food items. Although, FA is categorized under both behavioral as well as substance related addiction, however symptoms better fit with later one [56]. An increased level of calmness and reduced levels of anger and tension have been reported after consuming carbohydrate-rich foods. Consumption over long term induces adaptations in the neural reward and stress pathways ultimately encourage depression and opioid-like withdrawal symptoms in case of unavailability of such foods [107,108]. Furthermore, in some animal models anxiety, aggressiveness and teeth chattering has been prominent [103].

Besides the foods, sweetened soft drinks also highly contributed in the pathogenesis of overweight and obesity [109,110]. In a recent meta-analysis, a strong relation between soft drink utilization and higher energy consumption has been proposed [111]. The primary ingredient of these soft drinks is high fructose corn syrup, an important contributor of obesity, due to its sweetness, cheapness and wide availability [112]. Taking sugar sweetened beverages (drinks with added sugars, excluding milk and pure fruit juices) are coupled with surplus caloric intake and higher obesity prevalence due to their little role in regulation of satiety mechanism [113]. A clinical examination has reported that alcoholic beverages are more potent in stimulating total energy intake as compared to soft drinks. In addition, over use of alcoholic beverages at a meal induces thirst owing their diuretic properties [114].

Hyper-palatability

Energy density of a food largely depends on amount of fat in it. High fat foods modify the satiety mechanism [115] and insist an uncontrolled eating drive [116]. Obese people are more prone to overfeeding [117] as claimed by Liu and his colleagues after noticing a delay in satiety signal in obese individuals using functional magnetic resonance imaging technique [118]. Energy efficient diets containing either high proportion of sugars or fats are usually highly palatable in nature. Such diets

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 February 2023 doi:10.20944/preprints202302.0223.v1

provoke more portrait for their ingestion by affecting brain reward circuits in comparison to low calorie foods, progressing towards addiction behavior [104]. Chronic over intake of hyperpalatable diets has also stimulated by their high processing and rapid availability [105].

Some palatable and energy efficient foods are consumed as snacks and desserts, contributed obesity development because of continuous intake stimulated by their appetizing nature and their ability to reduce sensitivity of satiety mechanism [119]. Higher salivary secretions have been reported in restrained objects as exposed to sight and smell of palatable foods [120]. Even hyperpalatable foods revealed many dissimilarities with traditional drugs of abuse but still share some of the important features [105]. Utilization both of substances are associated disorderly overuse despite knowing the potential side effects. Consequently, individual fails to control over intake and unable to cut down the consumption [55].

High fat diets act in similar way to enhance sensitization of reward pathways as addiction drugs, rising search for hyperpalatable foods and addictive substances, resulting their overconsumption [32]. Induction for over consumption of hyperpalatable foods has been attributed to hypothalamic neuropeptides mainly being neuropeptide Y (NPY), melanin-concentrating hormone (MCH), agouti-related protein (AgRP), orexin, ghrelin and dynorphin [121]. Food reward, instead of hunger has become central motivational factor for eating today. Even being aware of the potential negative consequences, people consume highly palatable foods, generally rewarding and dense in energy, to seek pleasure. Such foods exhibit numerous similarities to drug cravings observed in both obese and lean drug addicts [122].

Summarizing both historic and current perspectives, a number of processed palatable items express addictive properties analogous to drugs such as nicotine, alcohol, and other neural stimulant [123]. Brain opioid peptide system within the ventral striatum has observed to play important role in regulating responses to highly palatable energy dense foods as confirmed by over intake of palatable foods following stimulation of opioid receptors [124]. Why sweet and palatable foods are difficult to resist? could be answered by sensory properties of sugars and fats. These foods have an uncontrollable sensory appeal that might be natural or learned. Fats impart characteristic texture, flavor and aroma to many foods making them highly palatable. Olfactory perception of volatile fat-soluble molecules is involved in driving towards hyperphagia [125].

Genetics

Along with a number of other important factors, genetics also play major role in energy homeostasis by contributing in maintenance of body energy stores and caloric intake. Genetic mutations can lead to uncontrolled food intake stimulating excess fat deposition ultimately derived to obesity [126]. Using modern technological approaches more than 20 obesity linked genes, primarily active in central nervous system and adipose tissue, have been discovered [127]. The most widely adopted method to investigate role of eating tendencies associated genes comprised of sequencing twins and comparing them with singletons. High palatability, availability and cheapness of food items further support food consumption in genetically susceptible individuals [128]. With the passage of time our genome has evolved according to our lifestyle and environmental conditions in order to ensure our sustainability. In ancient times, physical activity was high with hard availability of food, contrary to the present scenario where food is abundant but expenditure is less, thus storing extra energy in different body tissues [129].

Pro-opiomelanocortin (POMC) secrets many anorexigenic peptides, including melanocyte stimulating hormone (MSH) controls food intake and influences hair color. Mutations in the synthesis and processing of human POMC gene alter the synthesis of MSH and ACTH. Insufficient production of MSH fails to regulate eating behavior as well as hair pigmentation [130] while hypocortisolemia developed by ACTH deficiency drives towards severe and early onset of obesity in response to hyperphagia [131]. Function of POMC in the central melanocortin pathways and energy regulatory processes has been confirmed by studying transgenic animals with loss of POMC gene [132].

Neuropeptide Y (NPY) is attributed as one of the effective orexigenic peptide. Fine and continuous abnormalities imposed by various environmental and genetic factors in complex NPY network stimulates hyperphagia and unusual rate of weight gain results obesity and other relevant

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 February 2023 doi:10.20944/preprints202302.0223.v1

metabolic disorders [133]. Even a single intracerebroventricular injection of NPY showed significantly increased feeding in rats [134]. Similarly repeated exposure of this injection for a many days resulted an over consumption of food, increased body weight and higher body fat deposition [135] by stimulating de novo synthesis of fatty acids and triglycerides. Chronic NPY administration has also been associated with abnormal production of glucocorticoids, which in turn induce hyper secretions of insulin and triglycerides. These effects enhance insulin dependent transport of glucose in adipocytes and inhibit transport to muscles, building up of fat stores consequently [136,137,138].

Leptin is one of the major regulators of metabolic pathways conveying information to brain about chronic energy reserves. Primary production site of leptin is adipose tissue and directly proportional to body fat stores. Leptin acts primarily on hypothalamus elicit a series of neuroendocrine reactions that inhibit orexigenic peptides and augment anorexigenic peptides activity [139]. Mutations in Leptin (LEP) and leptin receptor (LEPR) genes are linked with overeating, early-onset obesity and associated phenotypic traits. Additionally, also found responsible for compromised immune system and reproductive capabilities due to diminished production of immune cells and pituitary gonadotropins respectively [140]. Leptin receptors are exclusively found in both NPY and POMC neural populations regulating both in a reciprocal manner. Diminished synthesis of leptin has been linked with lower expression of POMC mRNA and higher expression of NPY mRNA [2]. A point mutation in mice LEP gene showed lack of leptin production and an early induction of obesity, insulin resistance, overeating, hypothermia and lower energy utilization [141]. Four year administration of human leptin via subcutaneous route resulted sustained benefits against multiple congenital human leptin deficiency associated phenotypic abnormalities [142].

Leptin mediate synthesis of POMC derived melanocortin peptides with lessen caloric consumption and body weight by acting on melanocortin-4 receptor (MC4R) [81,143]. MC4 receptors are linked with management of body weight as confirmed by experimental investigation [144]. Mutant MC4 receptor acts as causative site for severe form of obesity. Partial or complete loss of function of these receptors directly depends on nature and extent of mutation [145]. The idea was further supported by experiments on rats and humans using Setmelanotide, a strong MC4R agonist improved weight loss in diet induced obesity and in obese animals with absolute POMC deficiency [146].

The peroxisomal proliferator activated receptors (PPARs) are ligand-activated transcriptional factors played vital role in cell division, inflammation, energy metabolism [147] and adipocyte differentiation. These receptors belong to nuclear hormone receptor superfamily with highest expression in mammalian adipose tissue. Significantly higher expression of PPAR receptor was examine in- in vitro analysis of differentiation of preadipocytes to adipocytes [148]. Another gene, called as Fat mass and obesity-associated (FTO) is also thought to be responsible for regulation of body fat by regulating the satiety mechanism. Mutation in FTO gene is directly associated with increased BMI exhibited diminished responsiveness to satiety signals and enhanced desire of hyperphagia in a food abundant environment along with multiple eating opportunities [149].

Conclusions

Obesity has been studied extensively throughout the world due to high incidence and association with several metabolic disorders including cardiovascular disorders. The food addition has considered one of potential key factor of obesity and excessive weight gain. Sedentary life style and availability of food also induce obesity. Overconsumption of food intake has been associated with factors such as stress, emotions, dietary restrictions, sweetness, palatability, neural pathways, hormonal imbalances, hunger, satiety and genetics.

Stress mediated variation in hypothalamic–pituitary–adrenal (HPA) axis with cortisol as end product ultimately influence food intake behavior and energy metabolism homeostasis. Irregular negative emotions drive overeating prominently in obese rather than normal individuals and negative emotions-triggered hyperphagia coupled with an improvement of mood. Food restriction and dieting, food deprivation also encourages reinforcement of food. Carbohydrates, mainly disaccharides like table sugar are considered the most potent addictive dietary substances associated with food addiction. Some palatable and energy efficient foods such as snacks and desserts, contributed obesity development owing to continuous intake stimulated by their appetizing nature and ability to reduce sensitivity of

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 February 2023 doi:10.20944/preprints202302.0223.v1

satiety mechanism. Prolonged intake of certain high calorie diets induces molecular and behavioral changes in brain reward centers similar to drugs abuse and addiction. Leptin mediate synthesis of POMC derived melanocortin peptides with lessen caloric consumption and body weight by acting on melanocortin-4 receptor (MC4R).

Leptin receptor (LEPR) genes are linked with overeating, early-onset obesity and associated phenotypic traits. Fat mass and obesity-associated (FTO) is also thought to be responsible for regulation of body fat by regulating the satiety mechanism. Future studies are required for uncovering dysregulation in neural and molecular pathways, delineation of potential brain areas involved in regulated of food intake and dysregulation associated obesity.

Author Contributions: MAB wrote the manuscript, searched the literature and wrote the manuscript, MA reviewed and edited the manuscript. All authors have read and approved the final manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: Funding source was not available.

Ethical Statement: This article does not contain any studies with human participants or animals used by any of the authors.

Acknowledgments: All data generated or analyzed was obtained from original papers and review articles cited from Google scholar, Science direct and PubMed.

Conflicts of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Pandit R, de Jong JW, Vanderschuren LJMJ, et al., 2011. Neurobiology of overeating and obesity: The role of melanocortins and beyond. Eur J Pharmacol 660:28–42.
2. Schwartz MW, Woods SC, Porte D, *et al.*, 2000. Central nervous system control of food intake. Nature 404:661–671.
3. Gold MS, Byars JA and Frost-Pineda K, 2004. Occupational exposure and addictions for physicians: case studies and theoretical implications. Psychiatr Clin North Am 27:745–753.
4. Imperatori C, Fabbricatore M, Vumbaca V, *et al.*, Food Addiction: definition, measurement and prevalence in healthy subjects and in patients with eating disorders. Riv Psichiatr 6.
5. White MA, Whisenhunt BL, Williamson DA, *et al.*, 2002. Development and Validation of the Food-Craving Inventory. Obes Res 10:107–114.
6. Moeller FG, Barratt ES, Dougherty DM, *et al.*, 2001. Psychiatric Aspects of Impulsivity. Am J Psychiatry 158:1783–1793.
7. Corsica JA and Pelchat ML, 2010. Food addiction: true or false?: Curr Opin Gastroenterol 26:165–169.
8. Dalton M and Finlayson G, 2014. Psychobiological examination of liking and wanting for fat and sweet taste in trait binge eating females. Physiol Behav 136:128–134.
9. Jebb SA, Kopelman P and Butland B, 2007. Executive Summary: FORESIGHT ?Tackling Obesities: Future Choices? project. Obes Rev 8:vi–ix.
10. Finlayson G, 2017. Food addiction and obesity: unnecessary medicalization of hedonic overeating. Nat Rev Endocrinol 13:493–498.
11. Gearhardt AN, Corbin WR and Brownell KD, 2009a. Preliminary validation of the Yale Food Addiction Scale. Appetite 52:430–436.
12. Saunders, R., 1999. Binge eating in gastric bypass patients before surgery. *Obesity Surgery*, *9*(1), pp.72-76.
13. Hagan MM, Wauford PK, Chandler PC, *et al.*, 2002. A new animal model of binge eating: Key synergistic role of past caloric restriction and stress. 10.
14. Adam TC and Epel ES, 2007. Stress, eating and the reward system. Physiol Behav 91:449–458.
15. Mathes WF, Brownley KA, Mo X, *et al.*, 2009. The biology of binge eating. Appetite 52:545–553.
16. Tsigos C and Chrousos GP, 2002. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. J Psychosom Res 53:865–871.
17. Apple JK, Dikeman ME, Minton JE, *et al.*, 1995. Effects of restraint and isolation stress and epidural blockade on endocrine and blood metabolite status, muscle glycogen metabolism, and incidence of dark-cutting longissimus muscle of sheep1. J Anim Sci 73:2295–2307.
18. Silveira PP, Xavier MH, Souza FH, *et al.*, 2000. Interaction between repeated restraint stress and concomitant midazolam administration on sweet food ingestion in rats. Braz J Med Biol Res 33:1343–1350.
19. Kyrou I and Tsigos C, 2009. Stress hormones: physiological stress and regulation of metabolism. Curr Opin Pharmacol 9:787–793.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 February 2023 doi:10.20944/preprints202302.0223.v1

20. Nieuwenhuizen AG and Rutters F, 2008a. The hypothalamic-pituitary-adrenal-axis in the regulation of energy balance. Physiol Behav 94:169–177.
21. Björntorp P, 2001. Do stress reactions cause abdominal obesity and comorbidities? Obes Rev 2:73–86.
22. Chuang J-C and Zigman JM, 2010. Ghrelin's Roles in Stress, Mood, and Anxiety Regulation. Int J Pept 2010:1–5.
23. Maniam J and Morris MJ, 2012. The link between stress and feeding behaviour. Neuropharmacology 63:97–110.
24. Nieuwenhuizen AG and Rutters F, 2008b. The hypothalamic-pituitary-adrenal-axis in the regulation of energy balance. Physiol Behav 94:169–177.
25. Dedovic K, Duchesne A, Andrews J, *et al.*, 2009. The brain and the stress axis: The neural correlates of cortisol regulation in response to stress. NeuroImage 47:864–871.
26. Tataranni PA, Larson DE, Snitker S, *et al.*, 1996. Effects of glucocorticoids on energy metabolism and food intake in humans. Am J Physiol-Endocrinol Metab 271:E317–E325.
27. Leigh Gibson E, 2006. Emotional influences on food choice: Sensory, physiological and psychological pathways. Physiol Behav 89:53–61.
28. Macht M, 2008. How emotions affect eating: A five-way model. Appetite 50:1–11.
29. Köster EP, 2009. Diversity in the determinants of food choice: A psychological perspective. Food Qual Prefer 20:70–82.
30. Nolan LJ, Halperin LB and Geliebter A, 2010. Emotional Appetite Questionnaire. Construct validity and relationship with BMI. Appetite 54:314–319.
31. van Strien T, Peter Herman C and Verheijden MW, 2012. Eating style, overeating and weight gain. A prospective 2-year follow-up study in a representative Dutch sample. Appetite 59:782–789.
32. Sinha R, 2008. Chronic Stress, Drug Use, and Vulnerability to Addiction. Ann N Y Acad Sci 1141:105–130.
33. Moy J, Petrie TA, Dockendorff S, *et al.*, 2013. Dieting, exercise, and intuitive eating among early adolescents. Eat Behav 14:529–532.
34. Berridge K and Winkielman P, 2003. What is an unconscious emotion?(The case for unconscious "liking"). Cogn Emot 17:181–211.
35. Meiselman HL, 2013. The future in sensory/consumer research:evolving to a better science. Food Qual Prefer 27:208–214.
36. Gutjar S, de Graaf C, Kooijman V, *et al.*, 2015. The role of emotions in food choice and liking. Food Res Int 76:216–223.
37. Joyner MA, Schulte EM, Wilt AR, *et al.*, 2015. Addictive-like eating mediates the association between eating motivations and elevated body mass index. Transl Issues Psychol Sci 1:217–228.
38. Stice E, Fisher M and Lowe MR, 2004. Are Dietary Restraint Scales Valid Measures of Acute Dietary Restriction? Unobtrusive Observational Data Suggest Not. Psychol Assess 16:51–59.
39. Sultson H, Kukk K and Akkermann K, 2017. Positive and negative emotional eating have different associations with overeating and binge eating: Construction and validation of the Positive-Negative Emotional Eating Scale. Appetite 116:423–430.
40. Evers C, Marijn Stok F and de Ridder DTD, 2010. Feeding Your Feelings: Emotion Regulation Strategies and Emotional Eating. Pers Soc Psychol Bull 36:792–804.
41. Görlach MG, Kohlmann S, Shedden-Mora M, *et al.*, 2016. Expressive Suppression of Emotions and Overeating in Individuals with Overweight and Obesity: Expressive Suppression, Overeating and Obesity. Eur Eat Disord Rev 24:377–382.
42. Leehr EJ, Krohmer K, Schag K, *et al.*, 2015. Emotion regulation model in binge eating disorder and obesity - a systematic review. Neurosci Biobehav Rev 49:125–134.
43. Wurtman RJ and Wurtman JJ, 1996. CARBOHYDRATE-CRAVING, OBESITY AND. 2.
44. Masheb RM and Grilo CM, 2006. Emotional overeating and its associations with eating disorder psychopathology among overweight patients with Binge eating disorder. Int J Eat Disord 39:141–146.
45. van Strien T, Konttinen H, Homberg JR, *et al.*, 2016. Emotional eating as a mediator between depression and weight gain. Appetite 100:216–224.
46. Spoor STP, Bekker MHJ, Van Strien T, *et al.*, 2007. Relations between negative affect, coping, and emotional eating. Appetite 48:368–376.
47. Werthmann J, Renner F, Roefs A, *et al.*, 2014. Looking at food in sad mood: Do attention biases lead emotional eaters into overeating after a negative mood induction? Eat Behav 15:230–236.
48. Kröller K, Jahnke D and Warschburger P, 2013. Are maternal weight, eating and feeding practices associated with emotional eating in childhood? Appetite 65:25–30.
49. Blissett J, Haycraft E and Farrow C, 2010. Inducing preschool children's emotional eating: relations with parental feeding practices. Am J Clin Nutr 92:359–365.
50. Talbot LS, Maguen S, Epel ES, *et al.*, 2013. Posttraumatic Stress Disorder Is Associated With Emotional Eating: Emotional Eating in PTSD. J Trauma Stress 26:521–525.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 February 2023 doi:10.20944/preprints202302.0223.v1

51. Lazarevich I, Irigoyen Camacho ME, Velázquez-Alva M del C, *et al.*, 2016. Relationship among obesity, depression, and emotional eating in young adults. Appetite 107:639–644.
52. Beaver JD, 2006. Individual Differences in Reward Drive Predict Neural Responses to Images of Food. J Neurosci 26:5160–5166.
53. Breiter HC, Gollub RL, Weisskoff RM, *et al.*, 1997. Acute Effects of Cocaine on Human Brain Activity and Emotion. Neuron 19:591–611.
54. Volkow ND, Wang G-J, Tomasi D, *et al.*, 2013. Obesity and addiction: neurobiological overlaps: Overlaps between drug and food addiction. Obes Rev 14:2–18.
55. Gearhardt AN, Corbin WR and Brownell KD, 2009b. Food Addiction: An Examination of the Diagnostic Criteria for Dependence. J Addict Med 3:1–7.
56. Gordon E, Ariel-Donges A, Bauman V, *et al.*, 2018. What Is the Evidence for "Food Addiction?" A Systematic Review. Nutrients 10:477.
57. Volkow ND, Fowler JS, Wang GJ, *et al.*, 2009. Imaging dopamine's role in drug abuse and addiction. Neuropharmacology 56:3–8.
58. Volkow ND and Wise RA, 2005. How can drug addiction help us understand obesity? Nat Neurosci 8:555–560.
59. Volkow ND, Wang G-J, Fowler JS, *et al.*, 2008. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. Philos Trans R Soc B Biol Sci 363:3191–3200.
60. Stice E, Spoor S, Bohon C, *et al.*, 2008. Relation Between Obesity and Blunted Striatal Response to Food Is Moderated by TaqIA A1 Allele. Science 322:449–452.
61. Murphy KG and Bloom SR, 2006. Gut hormones and the regulation of energy homeostasis. Nature 444:854–859.
62. Berthoud H-R, 2012. The neurobiology of food intake in an obesogenic environment. Proc Nutr Soc 71:478–487.
63. Avena NM, Rada P and Hoebel BG, 2008. Evidence for sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav Rev 32:20–39.
64. Johnson PM and Kenny PJ, 2010. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nat Neurosci 13:635–641.
65. Rada P, Avena NM and Hoebel BG, 2005. Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. Neuroscience 134:737–744.
66. Stice E, Spoor S, Ng J, *et al.*, 2009. Relation of obesity to consummatory and anticipatory food reward. Physiol Behav 97:551–560.
67. Pandit R, Mercer JG, Overduin J, *et al.*, 2012. Dietary Factors Affect Food Reward and Motivation to Eat. Obes Facts 5:221–242.
68. Leibowitz SF and Wortley KE, 2004. Hypothalamic control of energy balance: different peptides, different functions&. 32.
69. Robinson TE and Berridge KC, 2008. The incentive sensitization theory of addiction: some current issues. Philos Trans R Soc B Biol Sci 363:3137–3146.
70. García-García I, Horstmann A, Jurado MA, *et al.*, 2014. Reward processing in obesity, substance addiction and non-substance addiction: Obesity, addictions and reward. Obes Rev 15:853–869.
71. Filbey FM, Myers US and DeWitt S, 2012. Reward circuit function in high BMI individuals with compulsive overeating: Similarities with addiction. NeuroImage 63:1800–1806.
72. Pessoa L and Adolphs R, 2010. Emotion processing and the amygdala: from a "low road" to "many roads" of evaluating biological significance. Nat Rev Neurosci 11:773–782.
73. Phelps EA and LeDoux JE, 2005. Contributions of the Amygdala to Emotion Processing: From Animal Models to Human Behavior. Neuron 48:175–187.
74. Lesscher HMB and Vanderschuren LJMJ, 2012. Compulsive drug use and its neural substrates. Rev Neurosci 23.
75. Imperatori C, Fabbricatore M, Innamorati M, *et al.*, 2015. Modification of EEG functional connectivity and EEG power spectra in overweight and obese patients with food addiction: An eLORETA study. Brain Imaging Behav 9:703–716.
76. Finlayson G, King N and Blundell J, 2008. The role of implicit wanting in relation to explicit liking and wanting for food: Implications for appetite control. Appetite 50:120–127.
77. Griffioen-Roose S, Finlayson G, Mars M, *et al.*, 2010. Measuring food reward and the transfer effect of sensory specific satiety. Appetite 55:648–655.
78. French SA, Mitchell NR, Finlayson G, *et al.*, 2014. Questionnaire and laboratory measures of eating behavior. Associations with energy intake and BMI in a community sample of working adults. Appetite 72:50–58.
79. Rolls ET, 2007. Understanding the mechanisms of food intake and obesity. Obes Rev 8:67–72.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 February 2023 doi:10.20944/preprints202302.0223.v1

80. Chang G-Q, Gaysinskaya V, Karatayev O, *et al.*, 2008. Maternal High-Fat Diet and Fetal Programming: Increased Proliferation of Hypothalamic Peptide-Producing Neurons That Increase Risk for Overeating and Obesity. J Neurosci 28:12107–12119.
81. Cone RD, 2005. Anatomy and regulation of the central melanocortin system. Nat Neurosci 8:571–578.
82. Huon GF, 1994. Dieting, binge eating, and some of their correlates among secondary school girls. 6.
83. Allen KL, Byrne SM and McLean NJ, 2012. The dual-pathway and cognitive-behavioural models of binge eating: prospective evaluation and comparison. Eur Child Adolesc Psychiatry 21:51–62.
84. Raynor HA and Epstein LH, 2003. The relative-reinforcing value of food under differing levels of food deprivation and restriction. Appetite 40:15–24.
85. Stice E, Akutagawa D, Gaggar A, *et al.*, 2000. Negative affect moderates the relation between dieting and binge eating. Int J Eat Disord 27:218–229.
86. Cottone P, Sabino V, Steardo L, *et al.*, 2008. Opioid-Dependent Anticipatory Negative Contrast and Binge-Like Eating in Rats with Limited Access to Highly Preferred Food. Neuropsychopharmacology 33:524–535.
87. Calderon LL, Yu CK and Jambazian P, 2004. Dieting practices in high school students. J Am Diet Assoc 104:1369–1374.
88. Birch LL, Fisher JO and Davison KK, 2003. Learning to overeat: maternal use of restrictive feeding practices promotes girls' eating in the absence of hunger. Am J Clin Nutr 78:215–220.
89. Coelho JS, Polivy J and Herman CP, 2006. Selective carbohydrate or protein restriction: Effects on subsequent food intake and cravings. Appetite 47:352–360.
90. Massey A and Hill AJ, 2012. Dieting and food craving. A descriptive, quasi-prospective study. Appetite 58:781–785.
91. Grimm JW, Fyall AM and Osincup DP, 2005. Incubation of sucrose craving: effects of reduced training and sucrose pre-loading. Physiol Behav 84:73–79.
92. Hagan MM, Chandler PC, Wauford PK, *et al.*, 2003. The role of palatable food and hunger as trigger factors in an animal model of stress induced binge eating. Int J Eat Disord 34:183–197.
93. O'Connor KL, Scisco JL, Smith TJ, *et al.*, 2016. Altered Appetite-Mediating Hormone Concentrations Precede Compensatory Overeating After Severe, Short-Term Energy Deprivation in Healthy Adults. J Nutr 146:209–217.
94. Ebneter D, Latner J, Rosewall J, *et al.*, 2012. Impulsivity in restrained eaters: Emotional and external eating are associated with attentional and motor impulsivity. Eat Weight Disord - Stud Anorex Bulim Obes 17:e62–e65.
95. Avena NM, Murray S and Gold MS, 2013. Comparing the effects of food restriction and overeating on brain reward systems. Exp Gerontol 48:1062–1067.
96. Sclafani A, 2007. Sweet taste signaling in the gut. Proc Natl Acad Sci 104:14887–14888.
97. Ludwig DS, Majzoub JA, Al-Zahrani A, *et al.*, 1999. High Glycemic Index Foods, Overeating, and Obesity. PEDIATRICS 103:e26–e26.
98. Kelley AE, Baldo BA and Pratt WE, 2005. A proposed hypothalamic-thalamic-striatal axis for the integration of energy balance, arousal, and food reward. J Comp Neurol 493:72–85.
99. Wadden TA and Foster GD, 2000. BEHAVIORAL TREATMENT OF OBESITY. 21.
100. Spring B, Schneider K, Smith M, *et al.*, 2008. Abuse potential of carbohydrates for overweight carbohydrate cravers. Psychopharmacology (Berl) 197:637–647.
101. Liu Y, von Deneen KM, Kobeissy FH, *et al.*, 2010. Food Addiction and Obesity: Evidence from Bench to Bedside. J Psychoactive Drugs 42:133–145.
102. Rada P and Hoebel BG, 2005. Acetylcholine in the accumbens is decreased by diazepam and increased by benzodiazepine withdrawal: a possible mechanism for dependency. Eur J Pharmacol 508:131–138.
103. Avena NM, Bocarsly ME, Rada P, *et al.*, 2008. After daily bingeing on a sucrose solution, food deprivation induces anxiety and accumbens dopamine/acetylcholine imbalance. Physiol Behav 94:309–315.
104. Duffey KJ, Gordon-Larsen P, Jacobs DR, *et al.*, 2007. Differential associations of fast food and restaurant food consumption with 3-y change in body mass index: the Coronary Artery Risk Development in Young Adults Study. Am J Clin Nutr 85:201–208.
105. N. Gearhardt A, Davis C, Kuschner R, *et al.*, 2011. The Addiction Potential of Hyperpalatable Foods. Curr Drug Abuse Rev 4:140–145.
106. Schulte EM, Avena NM and Gearhardt AN, 2015. Which Foods May Be Addictive? The Roles of Processing, Fat Content, and Glycemic Load. PLOS ONE 10:e0117959.
107. Waters A, Hill A and Waller G, 2001. Internal and external antecedents of binge eating episodes in a group of women with bulimia nervosa. Int J Eat Disord 29:17–22.
108. Avena NM, Rada P and Hoebel BG, 2009. Sugar and Fat Bingeing Have Notable Differences in Addictive-like Behavior. J Nutr 139:623–628.
109. Malik VS, Schulze MB and Hu FB, 2006. Intake of sugar-sweetened beverages and weight gain: a systematic review1–3. 15.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 February 2023 doi:10.20944/preprints202302.0223.v1

110. Block G, 2004. Foods contributing to energy intake in the US: data from NHANES III and NHANES 1999–2000. J Food Compos Anal 17:439–447.
111. Vartanian LR, Schwartz MB and Brownell KD, 2007. Effects of Soft Drink Consumption on Nutrition and Health: A Systematic Review and Meta-Analysis. Am J Public Health 97:667–675.
112. Bray GA, Nielsen SJ and Popkin BM, 2004. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. Am J Clin Nutr 79:537–543.
113. DiMeglio D and Mattes R, 2000. Liquid versus solid carbohydrate: effects on food intake and body weight. Int J Obes 24:794–800.
114. Buemann B, Toubro S and Astrup A, 2002. The effect of wine or beer versus a carbonated soft drink, served at a meal, on ad libitum energy intake. Int J Obes 26:1367–1372.
115. Drewnowski A, 2009. Energy Density, Palatability, and Satiety: Implications for Weight Control. Nutr Rev 56:347–353.
116. de Araujo IE, 2004. Representation in the Human Brain of Food Texture and Oral Fat. J Neurosci 24:3086–3093.
117. Rolls ET, Kringelbach ML and de Araujo IET, 2003. Different representations of pleasant and unpleasant odours in the human brain. Eur J Neurosci 18:695–703.
118. Liu Y, Gao J-H, Liu H-L, *et al.*, 2000. The temporal response of the brain after eating revealed by functional MRI. Nature 405:1058–1062.
119. Boggiano MM, Dorsey JR, Thomas JM, *et al.*, 2009. The Pavlovian power of palatable food: lessons for weight-loss adherence from a new rodent model of cue-induced overeating. Int J Obes 33:693–701.
120. Rogers PJ and Hill AJ, 1989. Breakdown of dietary restraint following mere exposure to food stimuli: Interrelationships between restraint, hunger, salivation, and food intake. Addict Behav 14:387–397.
121. Furudono Y, Ando C, Yamamoto C, *et al.*, 2006. Involvement of specific orexigenic neuropeptides in sweetener-induced overconsumption in rats. Behav Brain Res 175:241–248.
122. Alsiö J, Olszewski PK, Levine AS, *et al.*, 2012. Feed-forward mechanisms: Addiction-like behavioral and molecular adaptations in overeating. Front Neuroendocrinol 33:127–139.
123. Davis C and Carter JC, 2014. If Certain Foods are Addictive, How Might this Change the Treatment of Compulsive Overeating and Obesity? Curr Addict Rep 1:89–95.
124. Kelley AE, Will MJ, Steininger TL, *et al.*, 2003. Restricted daily consumption of a highly palatable food (chocolate EnsureR) alters striatal enkephalin gene expression. Eur J Neurosci 18:2592–2598.
125. Drewnowski, A., 1995. Metabolic determinants of binge eating. *Addictive behaviors*, *20*(6), pp.733-745.
126. Walley AJ, Blakemore AIF and Froguel P, 2006. Genetics of obesity and the prediction of risk for health. Hum Mol Genet 15:R124–R130.
127. Herrera BM and Lindgren CM, 2010. The Genetics of Obesity. Curr Diab Rep 10:498–505.
128. Hebebrand J, Sommerlad C, Geller F, *et al.*, 2001. The genetics of obesity: practical implications. Int J Obes 25:S10–S18.
129. Unger R and Orci L, 2000. Lipotoxic diseases of nonadipose tissues in obesity. Int J Obes 24:S28–S32.
130. Krude H, Biebermann H, Luck W, *et al.*, 1998. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. 19:3.
131. Krude H, Biebermann H, Schnabel D, *et al.*, 2003. Obesity Due to Proopiomelanocortin Deficiency: Three New Cases and Treatment Trials with Thyroid Hormone and ACTH4–10. J Clin Endocrinol Metab 88:4633–4640.
132. Wardlaw SL, 2001. Obesity as a Neuroendocrine Disease: Lessons to Be Learned from Proopiomelanocortin and Melanocortin Receptor Mutations in Mice and Men*. 86:5.
133. Kalra SP and Kalra PS, 2004. NPY and cohorts in regulating appetite, obesity and metabolic syndrome: beneficial effects of gene therapy. Neuropeptides 38:201–211.
134. Clark JT, Kalra PS, Crowley WR, *et al.*, 1984. NEUROPEPTIDE Y AND HUMAN PANCREATIC POLYPEPTIDE STIMULATE FEEDING BEHAVIOR IN RATS. Endocrinology 115:427–429.
135. Glenn Stanley B, Kyrkouli SE, Lampert S, *et al.*, 1986. Neuropeptide Y chronically injected into the hypothalamus: A powerful neurochemical inducer of hyperphagia and obesity. Peptides 7:1189–1192.
136. Zarjevski N, Cusin I, Vettor R, *et al.*, 1994. Intracerebroventricular Administration of Neuropeptide Y to Normal Rats Has Divergent Effects on Glucose Utilization by Adipose Tissue and Skeletal Muscle. 43:6.
137. Vettor R, Zarjevski N, Rohner-Jeanrenaud E, *et al.*, 1996. Induction and reversibility of an obesity syndrome by intracerebroventricular neuropeptide Y administration to normal rats. 7.
138. Sainsbury A, Rohner-Jeanrenaud F, Grouzmann E, *et al.*, 1996. Acute Intracerebroventricular Administration of Neuropeptide Y Stimulates Corticosterone Output and Feeding but Not Insulin Output in Normal Rats. Neuroendocrinology 63:318–326.
139. Margetic S, Gazzola C, Pegg G, *et al.*, 2002. Leptin: a review of its peripheral actions and interactions. Int J Obes 26:1407–1433.
140. Dubern B and Clement K, 2012. Leptin and leptin receptor-related monogenic obesity. Biochimie 94:2111–2115.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 February 2023 doi:10.20944/preprints202302.0223.v1

141. Zhang Y, Proenca R, Maffei M, *et al.*, 1994. Positional cloning of the mouse obese gene and its human homologue. Nature 372:425–432.
142. Farooqi IS, Matarese G, Lord GM, *et al.*, 2002. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. J Clin Invest 110:12.
143. Gautron L, Elmquist JK and Williams KW, 2015. Neural Control of Energy Balance: Translating Circuits to Therapies. Cell 161:133–145.
144. Huszar D, Lynch CA, Fairchild-Huntress V, *et al.*, 1997. Targeted Disruption of the Melanocortin-4 Receptor Results in Obesity in Mice. Cell 88:131–141.
145. MacKenzie RG, 2006. Obesity-associated mutations in the human melanocortin-4 receptor gene. Peptides 27:395–403.
146. Collet T-H, Dubern B, Mokrosinski J, *et al.*, 2017. Evaluation of a melanocortin-4 receptor (MC4R) agonist (Setmelanotide) in MC4R deficiency. Mol Metab 6:1321–1329.
147. Kersten S, 2002. Peroxisome proliferator activated receptors and obesity. Eur J Pharmacol 440:223–234.
148. Elbrecht A, Chen Y, Cullinan CA, *et al.*, 1996. Molecular Cloning, Expression and Characterization of Human Peroxisome Proliferator Activated Receptors g1 and g2. Biochem Biophys Res Commun 224:7.
149. Wardle J, Carnell S, Haworth CMA, *et al.*, 2008. Obesity Associated Genetic Variation in *FTO* Is Associated with Diminished Satiety. J Clin Endocrinol Metab 93:3640–3643.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.