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Therapeutic Utilization of Neuro Imaging Studies in Obesity for Optimal Utilization of Drugs used in Treatment for Obesity-Lessons Learnt from Bariatric Surgery

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ABSTRACT

Human obesity differs from that of rodents and animals which are usually utilized for studying both aetioathogenesis along with treatment of obesity. This is in view of hypothalamus generally considered to be the organ for homeostatic control is under control by various supra homeostatic control besides peripheral regulation. Hence the needs to understand how the higher centres regulate hyothalamus for a given response. Various functional neuroimaging studies have proved to be helpful in depicting these roles. Further it has helped in understanding how the most effective treatment like bariatric surgery (BS) alters these supra hypothalamic control in altering hippocampus, areas involved in executive function along with reducing ghrelin besides changing the cortical thickness with alterations of ratios of gray and white matter. These changes need to be translate to drugs utilized for anti-obesity therapy as has been done by lorcaserin, liraglutude and other natural food products like walnuts and other such natural products to help better get some safe options for anti-obesity therapies that prove to be clinically effective.

Keywords: Hypothalamus, Learning and memory, Hippocampus, Attention systems, Cognitive control, BS, Anti-obesity drugs

INTRODUCTION

Obesity has become a worldwide health epidemic as declared by World Health Organization (WHO) in 2003 especially in industrialized countries, where, >1/3rd population is obese and 1/3rd people are overweight [1]. Since, eating in humans not only controlled by hypothalamus, we tried to study the role of higher CNS centres involved in eating, to have a better understanding of aetioathogenesis of obesity.

MATERIAL AND METHODS

We did a PubMed study of MeSH Terms like hypothalamus, reward and memory in obesity, attention, cognitive control of eating, besides various neuroimaging studies pertaining to obesity from 1990-2018.

RESULTS

We found a total of 382 articles pertaining to this. Considering the duplicate nature of some articles we selected 51 articles for this mini-review. No meta-analysis was done.

Role of hypothalamus

Although most of our concentration has been focused on studying role of hypothalamus in obesity with the findings of orexigenic neuropeptide Y(NPY)/Agouti Related Protein (AgRP) neurons and anorexigenic proopio melanocortin (POMC)/Cocaine and Amphetamine Related Transcript (CART) neurons in the arcuate nucleus **(Figure 1)** [2-4] and further orexigenic neurons in Lateral Hypothalamus (LH), paradoxical stimulation results in rats and monkeys over

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stimulation of LH and Ventral Medial Hypothalamus (VMH), suggests there are concerns over human studies of hypothalamus in regulation of appetite and eating. Activation of hypothalamus along with that of thalamus, midbrain and striatum occurred in Functional Magnetic Resonance (fMRI) imaging study as predicted by milkshake presentation on weight gain in a year with these fMRI imaging study of humans [5]. Hypothalamus receives external signals and direct connections with reward along with emotional and memory systems and thus activation of the hypothalamus might be subject to control influence of these higher systems **(Figure 2)**. That is although hypothalamus is critical to homeostatic control of eating it gets influenced by different component systems which determine food intake. Role of studying Central Nervous Systems (CNS) by utilizing fMRI and other human imaging studies in obesity and eating [6]. Thus, translational research regarding how the hypothalamic mechanisms might get impacted in obesity is needed in view of supra homeostatic control.

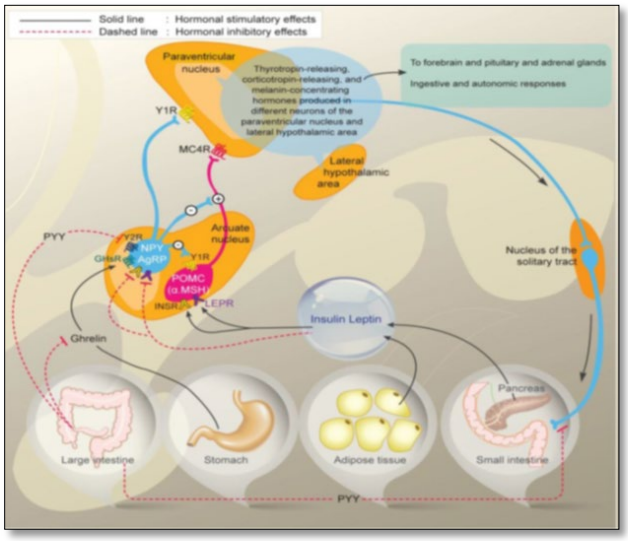

Figure 1. Diagram depicting Orexigenic Agouti related peptide (AgRP)/Neuropeptide Y neurons (Agrp/NPY) and anorexigenic proopiomelanocirtin neurons (POMC/CART) in arcuate nucleus of hypothalamus and their regulation by circulating signals like leptin produced by adipocytes and insulin from beta cells of pancreas in energy homeostasis, besides role of ghrelin and Peptide YY(PYY) on orexegenic control acting through their recep¬tors respectively. Also interconnection of arcuate nucleus with par ventricular nucleus and further with lateral hypothalamic areas is depicted and also over Nucleus Tract of Solitary nucleus (NTS) in hindbrain along with autonomic nervous system in regulation of energy homeostasis is depicted.

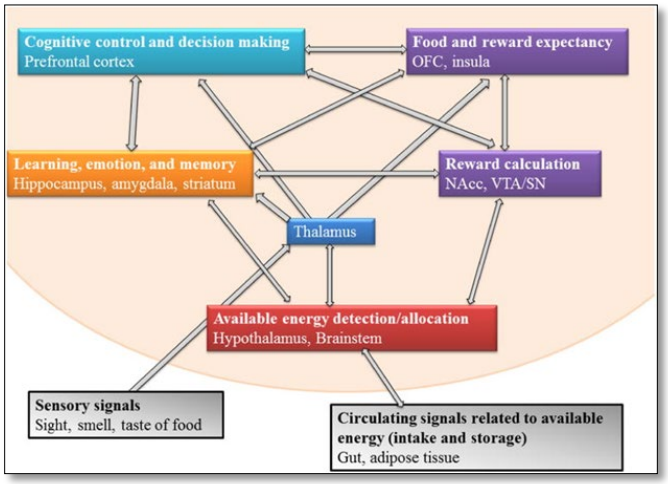

Figure 2. General map of connectivity of the hypothalamus to other CNS centers important for energy intake. These areas communicate with each other and the hypothalamus to control energy intake. Importantly, the hypothalamus also receives key inputs from the periphery regarding available energy (recent intake and storage).
NAcc: Nucleus Accumbens; OFC: Orbit Frontal Cortex; SN: Substantial Nigra; VTA: Ventral Tegmental Area

Role of reward systems (Figure 3)

Main theories regarding how these get changed in obesity is: i) Hyporesponsitivity to reward-as summarized by PET studies have shown lower availability of dopamine D2 receptors in striatum in obese as compared to normal weight rats along with same findings in humans as well. Thus suggestion is lower dopaminergic signal might => people to seek highly rewarding foods that in turn => obesity. An under responsive reward circuit and habitual food intake of high fat/calorie foods has been compared to drugs of addiction as reviewed earlier [2,6-12].

Other theory: ii) Hyper responsitivity to food cues => individuals to seek more and more in quantity. Increased exploration of these highly rewarding foods => larger disconnect between reward exposure to food cues and response to consuming foods which => them to eat more foods to achieve expected reward. This has been supported by activation of nucleus accumbens, midbrain and Orbitofrontal Cortex (OFC) in visual foods cues and to achieve the expected reward anticipation of milk shake [13].

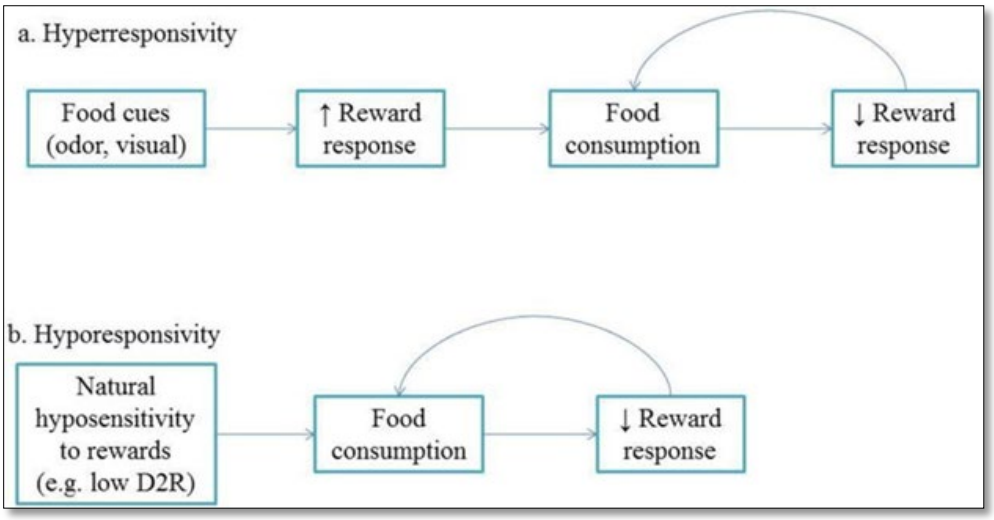

Figure 3. Theories of how reward responsivity is affected in obesity: hyper responsivity (a) and hyporesponsivity (b). The first theory suggests that obese individuals have a heightened reward response to food cues but after increased food consumption, this leads to a decreased response to reward to actual food consumption (but not food cues), and this disconnect leads to greater food intake over time. The second theory posits that individuals with a natural hyposensitivity for rewards consume more food because they require more food consumption and higher calorie or high fat foods to achieve the same level of reward [6].

Role of emotion and memory

The amygdala is the primary one that regulates appetite in response to emotions. Amygdala activates to food cues [14,15] and this response increases in childhood, adolescent and adult obesity [16-19]. Activation of amygdala also predicts consumption of high fat or high calorie foods [20]. Participants with responses of amygdala to food cues when not hungry had chances of gaining weight [21]. Higher levels of leptin in adolescents correlated with activation of amygdale to high calorie foods [19]. Stress relieving effects of sucrose gets mediated via amygdalar circuit communicating with hypothalamo-pituitary-Adrenal (H-P-A) axis [22].

Memory is mainly regulated by hippocampus and parahippocampal formation that might influence eating. Reduced functioning of hippocampus => increased food intake and poor diet quality [23,24]. Though typical timing of food gets controlled by circadian rhythms and suprachiasmatic nucleus, evidence supports this gets over ridden by memory along with experiences **(Figure 4)** [24]. Hippocampus gets inputs regarding food cues from many other areas that include insula, OFC, as well as arcuate nucleus of hypothalamus. Further hippocampus gets controlled by peripheral signals like leptin and ghrelin to regulate food intake. Obesity, possibly could comprise hippocampus functions via Blood Brain Barrier (BBB), although hippocampus is protected by BBB, cytokines associated with inflammation may not be able to reach hippocampus, yet there is evidence that inflammation in CNS might be carried out by microglia like in hypothalamus [4,25,26]. In obesity, microglial action has been shown to impair function of hippocampus are through CNS inflammatory processes. These effects on hippocampus have been seen more in rodents than human brain with more studies required in humans.

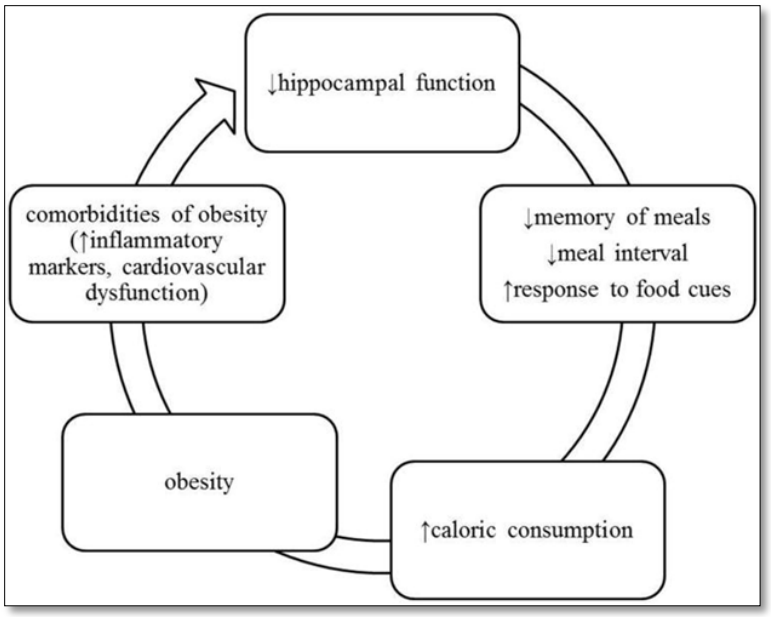

Figure 4. Memory influences eating behaviors in a cyclical manner. Decreased hippocampal activity leads to decreased memory of meals and increased response to food cues. This leads to increased caloric consumption and obesity, which in turn leads to increased inflammation and cardiometabolic dysfunction which in turn decreases hippocampal function [6].

Attention systems

Brain network of attention systems include parietal and visual cortices, along with some areas of frontal cortex [27,28]. Increased activation of occipetal cortex has been shown for high calorie/HFD images **(Figure 5)**.

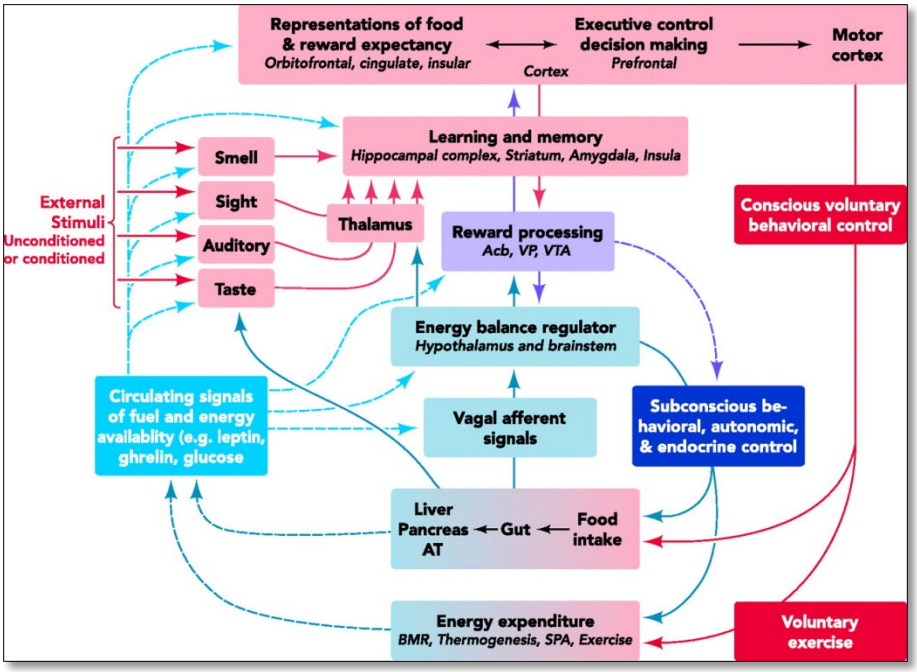

Figure 5. Major Systems and pathways responsible for the neural integration of internal and external information in the control of appetite and energy expenditure [52].
Blue areas and pathways are mainly involved in metabolic and energy balance regulation. Red areas and pathways are mainly involved in communication with the external world through cognitive and emotional processes such as learning and memory, reward, mood, stress, choice and decision making

ROLE OF COGNITIVE CONTROL SYSTEMS

Cognitive Control Systems have executive functions including inhibition of prepotent responses. Cognitive Control allows a person to refuse a piece of cake if not feeling hungry. Prefrontal Cortex (PFC) makes most part of Cognitive Control networks especially the cingulate cortex, inferior frontal cortex, pre-supplementary motor area and dorsolateral PFC (DLPFC) [29]. Impaired inhibitory control has been shown in obese humans. A proposal has been given that impaired Cognitive Control might affect increased reward responses to food cues and thus overeating [30,31]. Less metabolism has been seen in obese as measured by Positron Emission Tomography (PET) imaging or reduced activity in PFC that correlates with dopamine receptor availability and BMI [11,32]. Thus deficits in Cognitive Control have been seen both in general and food specific tasks in obese people though it is not clear whether poor cognitive or inhibitory control is caused by obesity or causes obesity **(Figure 6)**.

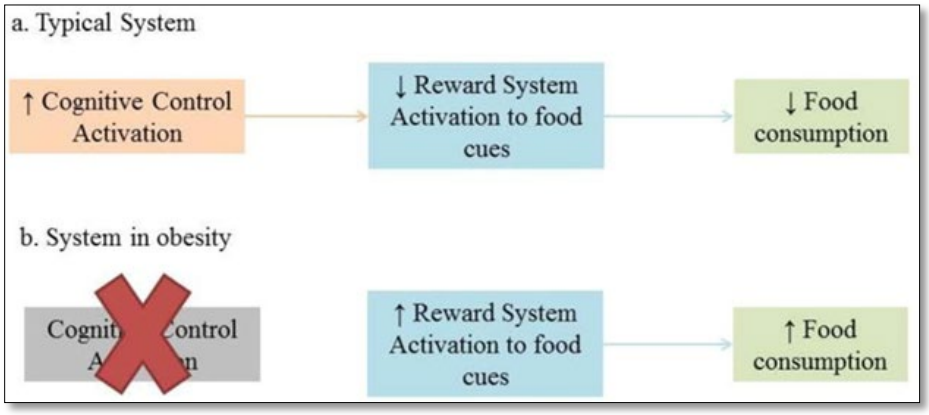

Figure 6. A theory of how cognitive control may interact with reward and food consumption is that in typical cases, heightened cognitive control may decrease the reward system's activation to food cues and thus decrease food consumption (**a**). This may be altered in obesity, where cognitive control is impaired, and the reward system may be heightened, leading to increased food consumption (**b**) [6].

PRACTICAL IMPLICATIONS IN THERAPEUTICS

Role of bariatric surgery (BS)

Li et al. [33] tested the hypothesis that Laparoscopic Sleeve Gastrectomy (LSG) induced reductions in appetite and total ghrelin levels were associated with reduced prefrontal reactivity to food cues. A fMRI cue related task with high calorie (HC) and low calorie (LC) food pictures were used to determine the brain connectivity in 22 obese participants tested before and 1 month after BS.19 other controls (Ctrl) without surgery were also tested at baseline and 1 month later. LSG significantly decreased: i) fasting plasma concentrations of total ghrelin, leptin and insulin ii) Craving for HC food and iii) brain activation in the right DLPFC in response to HC vs. LC food cues (PFWE<0.05). LSG-induced reduction in DLPFC activation to food cues were positively correlated with reduction in ghrelin levels and reduction in craving ratings for food. Psychophysiological interaction (PPI) connective analysis with the central anterior cingulated cortex (vACC) after LSG and changes in BMI were negatively correlated with changes in connectivity between the right DLPFC and vACC in the LSG group only. Thus these findings suggest that LSG induced weight loss may be related to reductions in ghrelin, possibly leading to decreased food cravings and hypothetically reducing DLPFC response in the HC food cues [33].

Zhang et al. [34] measured brain activity with Amplitude of Low Frequency Fluctuations (ALFF), captured with resting state fMRI in 30 obese participants both before and after 1month of LSG and in 26 obese controls without surgery that were studied at baseline and 1 month later. A 2 way analysis was performed to model the groups and time effects on ALFF and state functional connectivity. Significant decreases in appetite, BMI, fasting plasma ghrelin and leptin levels, anxiety and ALFF in hippocampus (HIPP) and ALFF increased in Posterior Cingulate Cortex (PCC, PFWE<0.05), 1 month post LSG. Decreases in HIPP ALFF correlated with decreases in anxiety and increases in PCC ALFF correlated positively with decreases in anxiety. Seed voxel correlation analysis showed stronger connectivity between HIPP and insula and between PCC and DLPFC post LSG. Thus, concluding that ghrelin effects in HIPP modulate connectivity with the insula which processes interoception and might be relevant to LSG induced reductions in appetite/anxiety. Role of LSG in PCC and its enhanced connectivity with DLPFC in improving self-regulation following LSG needs further investigation [34].

Obesity related brain gray (GM) and white matter (WM) abnormalities have been reported in regions associated with food intake and cognitive – emotional regulation. BS is the most effective way to treat obesity and induce structural recovery of GM/WM density and WM integrity. Structural MRI and surface based morphometry analyses were used to

investigate BS induced alterations of cortical morphometry in 22 obese participants who were tested before and one month post BS and in 21 obese controls (Ctrl) without surgery who were tested twice (baseline and one month). Results showed that fasting plasma ghrelin, insulin and leptin levels were significantly reduced post BS (P<0.001). Post BS significant decreases in cortical thickness in the precuneus (PFDR<0.05) that were associated with decreases in BMI. There were also significant increases post-BS in cortical thickness in middle (MFG) and superior frontal gyri (SFG) superior temporal gyrus (STG), insula and vACC; and n cortical volume in left post central gyrus (Post Cen) and vACC (PFDR<0.05). Post BS changes in SFG were associated with decrease in BMI. These findings suggest that structural changes in brain regions implicated in executive control and self-referential processing are associated with BS-induced weight loss [35].

Further Li et al. [36] tried to understand the brain alterations of Resting State Functional Connectivity (RSFC) of Resting State Networks (RSNs) related to food intake and influence of BS on these. They used Functional Connectivity Density (FCD) mapping to calculate local ((FCD/Global (gFCD) voxel wise connectivity matrices in 22 obese participants who underwent fMRI before and 1 month after sleeve gastrectomy (SG) and in 19 obese controls (Ctrl) without surgery but tested twice (baseline and 1 month later). Two factors (group time) repeated measures ANOVA was used to assess main and interaction effects in IFCD/gFCD regions of interest were identified for subsequent seed to voxel connectivity analysis to assess RSFC and to examine association with weight loss. BS significantly reduced IFCD in VMPFC, PCC/precuneus and dorsal Anterior Cingulate Cortex (dACC)/Dorsomedial Prefrontal Cortex (DMPFC) and decreased gFCD in VMPFC, right dorsolateral PFC (DLPFC) and right insula (PFWE<0.05). IFCD decreased in VMPFC, PCC and precuneus correlated with reduction in BMI after surgery. Seed to voxel connectivity analysis showed that the VMPFC had stronger connectivity with left DLPFC and weaker connectivity with hippocampus/parahippocampus and PCC/precuneus had stronger connectivity with right caudate and left DLPFC after surgery. BS significantly decreased FCD in region as involved in self-referential processing (VMPFC, DMPFC, dACC and precuneus) and interoception (insula) and changes in VMPFC/precuneus were associated with reduction in BMI suggesting a role in improving control of eating behaviors following surgery [36].

Role of anti-obesity drugs

Furthermore Lor caserin, a 5T 2c receptor agonist has been found to be effective in treating obesity in humans. 5T 2c receptors are located almost only in the CNS, which includes thalamus and hypothalamus, areas known to be involved in feeding regulation but also in more cortical areas involved in higher though and top down processes [37-39]. Thus Farr et al. [40] conducted a randomized, placebo controlled blind trial with 48 obese participants using fMRI to study the effects of lorcaserin on the brain. Subjects taking lorcaserin had decreased brain activations in the attention related parietal and visual cortices in response to highly palatable foods cues at one week in fasting state and in the parietal cortex, 4 weeks in response to any cues in the fed state. Decreases in calorie intake, weight and BMI correlated with activations of the amygdala, parietal and visual cortices at baseline. Thus indicating that lorcaserin exerts its weight reducing effects by decreasing attention related brain activations to food cues (parietal and visual cortices) and emotional and limbic activity (insula, amygdala). This indicates that baseline activation of amygdala relates to increased efficacy that suggests that Lorcaserin would be of particular benefit in obesity associated with emotional states [40].

Similarly Liraglutide a glucagon like peptide 1 (GLP1) analogue has been approved both for treatment of both T2DM and obesity [2,3]. Farr et al. [41] investigated if receptors are expressed in human brains and if Liraglutide administration affects neural responses to food cues in diabetic individuals which were the primary outcome. Thus they studied consecutively 22 human brains, examined expression of GLP1 receptors in the hypothalamus, medulla oblongata and parietal cortex using immunohistochemistry. In a randomized (assigned by pharmacy using a randomization enrollment table), placebo controlled double blinded cross over trial, 21 individuals with T2DM (18 included in analysis due to lack of poor quality of data) were treated with placebo and Liraglutide for a total of 17 days each (0.6 mg for 7 days, 1.2 mg for 7 days and 1.8 mg for 3 days). Participants were eligible if they had T2DM and were currently on lifestyle changes or metformin for treatment. Participants, caregivers, people doing measurement and/or examinations and people assessing the outcomes were blinded to the medication assignment. Both metabolic changes along with neurocognitive and neuroimaging (fMRI) of responses to food cues were studied by them. Immunohistochemical analysis showed the presence of GLP1 receptors on neurons in the human hypothalamus, medulla and parietal cortex. Liraglutide decreased activation of the parietal cortex in response to highly desirable (vs. less desirable) food images (p<0.001: effecr size: placebo 0.53+-0.24, luraglutide-0.47+-0.18). No significant side effects were noted. In a secondary analysis, they found reduced activation of insula and putamen, areas involved in the reward system. Further, they showed increased ratings of hunger and appetite correlated with increased brain activation in response to highly desirable food cues while on liraglutide, while ratings of nausea correlated with decreased brain activation. Thus they interpreted that presence of GLP1 receptors was reported for 1st time in human brains. They also saw that liraglutide alters brain activity related to highly desirable food cues. Thus their data pointed to a

central mechanism contributing to or underlying the effects of liraglutide on metabolism and weight loss. More studies would be required to confirm and extend these findings in larger samples of diabetic individuals and or with the higher doses of liraglutide (3 mg) that had been recently approved for obesity treatment [41].

To study if obese individuals with more components of metabolic syndrome (MetS) and/or prediabetes showed activation of brain centres in response to food cues, Farr et al. [42] examined prediabetes (n=26) vs. obese non-diabetics (n=11), using fMRI. They also did regression analysis on the basis of the number of MetS components/subject. Obese individuals with prediabetes had reduced activation of the reward related putamen in the fasting state and reduced activation of the salience and reward-related insula after eating. Obese individuals with components of MetS showed reduced activation of putamen in the fasting state. All these activations remain significant when correlated with BMI, Waist Circumference (WC), HbA1c and gender. Decreased activation in reward related brain areas between obese individuals is more pronounced in subjects with prediabetes and MetS. Greater prospective studies are required to quantify their contribution to the development of prediabetes/MetS and to study if these conditions might predispose to exacerbation of obesity along with development of comorbidities over time [42]. Similarly in another study Farr et al. [43] showed that obese individuals having type2 diabetes mellitus (T2DM) showed less activation of the salience and reward related insula while fasting and increased activation of amygdala to highly desirable foods after a meal. Thus these findings in T2DM suggested a persistence of difference between obese versus non-obese individuals. Future larger studies can confirm the differential activation between lean and obese individuals with and without DM [43].

Walnuts have specific properties like high alpha-linoleic acid (ALA) content that might add to the obesity and T2DM reducing properties of walnuts [44,45]. The group of Mantzoros, Farr et al. [46] showed walnuts increased satiety and fullness [45]. Previously walnuts were shown to improve memory and increase hippocampal N-methyl-D-aspartate (NMDA) receptors in rats which suggested they might have effects on the brain [46]. Thus Farr et al. [47] performed a randomized, placebo controlled trial of 10patients who received living in a controlled environment either walnuts as smoothie or placebo for 5 days each, separated by a wash out period of one month using fMRI. Walnut consumption reduced feelings of hunger and appetite assessed using visual analog scales and increased activation of the right insula to highly desirable foods. Thus concluding that walnut consumption might increase salience and cognitive control processing of highly desirable food cues, the beneficial metabolic effects observed [47].

CONCLUSION

Thus trying to study higher brain centres communicating with the hypothalamus further helps besides studying the alteration in hormones interacting with hypothalamus for homeostatic states helps us in further understanding how BS, the most effective treatment till date for human obesity works. We have been trying to study how anti-obesity drugs orally can be utilized in better getting treatment without BS [48], which is not only costly and not without risks besides limited indications for BMI>35 kg/m^2 with comorbidities or >=40 kg/m^2 [49,50]. Further studying these interactions with other drugs that have been approved for obesity like lorcaserin, GLP1 Analogues like liraglutide and other drugs give us a better insight besides changes in this connectivity in obese and diabetic patients has helped to understand how some naturally occurring products like walnuts might be utilized for better control of T2DM. Further doing these studies in thulakoids will better help in understanding how these naturally occurring alkaloids found in spinach can get utilized for obesity therapy [51].

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