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REVIEW

Bariatric Surgery and the Central Nervous System

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Abstract Bariatric procedures are now known to have an effect on hunger as well as on metabolism. The role of central nervous pathways in causing these effects after bariatric surgery is now being elucidated. A brief overview of these pathways has been presented for the sake of bariatric surgeons. A PubMed search was made using various search phrases to retrieve all original articles concerning the effect of bariatric surgery on the neural pathways. The mechanisms regulating the food intake and energy expenditure can be broadly divided into homeostatic and hedonic systems. The effect of bariatric surgery on the homeostatic system in animal models is not clear. A decrease in preference for sweet taste and high calorie foods has been demonstrated in animal models. The effect of bariatric surgery on the hedonic system in humans has been consistent with decreased activation of the hedonic system being demonstrated by functional MRI and decreased preference for intake of high energy foods also being observed post-surgery. The effect of bariatric surgery on dopamine signaling, which is involved in the hedonic system, is however not clear. Functional MRI studies have also demonstrated increased activation of the hypothalamus after surgery. Various studies utilizing questionnaires have demonstrated increased satiety and decreased hunger after bariatric surgery.

Keywords CNS · Arcuate nucleus · Hedonic system · fMRI · Homeostatic system · NPY · POMC · AGRP · Dopamine

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Introduction

Bariatric surgery has emerged as the most effective way of combating morbid obesity and its associated comorbidities. Bariatric surgery is also well known to decrease appetite and hunger and promote satiety. It also is suspected to increase the energy expenditure. These actions are partly mediated through actions on the central nervous system. Since weight loss by other means leads to increased appetite and calorie conservation, the reduced appetite seen after bariatric surgery has been attributed to changes in gut hormones (like peptide YY (PYY), ghrelin, and glucagon-like peptide-1 (GLP-1). Bariatric surgery also has an effect on the reward system of the brain and this was suspected from the changes in the food preferences seen in post-bariatric patients. This article reviews the neural pathways regulating food intake and energy expenditure. This article also reviews the animal and the human data available so far, which have elucidated the role of bariatric surgery in causing changes in neural pathways. Though these neural pathways are well known to the basic science community, there is a need for informing the bariatric surgeon of these topics due to increasing recognition of bariatric surgery as a tool to reverse pathophysiological changes in these pathways and thus reverse obesity and associated metabolic diseases. Understanding of these pathways through bariatric surgery research could also pave the way for the design of newer drugs (knifeless surgery) to combat the epidemic of obesity.

The Homeostatic Pathway Regulating Food Intake and Energy Expenditure

The homeostatic pathways of food intake and energy expenditure can be divided into sensory, afferent, integrative,

and efferent pathways. The efferent pathways can be further subdivided into those affecting food intake or energy expenditure. The peripheral nerves and the humoral substances form a part of the afferent pathway. The various nuclei in the brain which are described below form the integrative pathway, while the nuclei in the distal part of this pathway and the peripheral nerves form the efferent pathway.

The hypothalamus has since long been known to be involved in the regulation of food intake and energy expenditure. Nearly 70 years ago, Hetherington and Ranson [1] produced hypothalamic lesions in rat which caused obesity in these animals. The role of the hypothalamic nuclei has been further confirmed with the use of spontaneously obese rat models like ob/ob mouse which have highlighted the importance of leptin signaling in the hypothalamus.

The neural pathways regulating food intake and energy homeostasis have traditionally been thought to constitute a hierarchy of neurons—the first order neurons originating from the arcuate nucleus which end on the second order neurons in the paraventricular nucleus of the hypothalamus. The neurons in the arcuate nucleus have receptors for gastrointestinal hormones and adipokines like leptin, ghrelin, PYY, and GLP-1. The arcuate nucleus consists of two types of neurons involved in the regulation of energy homeostasis—the neuropeptide Y (NPY)/agouti gene-related peptide (AGRP) co-secreting neurons and the proopiomelanocortin (POMC) secreting neurons which also co-express catecholamine and amphetamine-regulated transcript (CART). NPY/AGRP are anabolic and orexigenic in nature whereas POMC and CART are catabolic and anorexigenic. Melanocyte-stimulating hormone (α-MSH) is a proteolytic product of POMC.

The first order neurons project to the second order neurons in the lateral hypothalamic area (LHA), the paraventricular nucleus (PVN) and the ventromedial hypothalamus (VMN). α-MSH and AGRP act on the melanocortin (MC4R) receptors on these second order neurons to stimulate and inhibit them, respectively. The orexigenic effects of NPY are mediated through Y1 and Y5 receptors which are present in various parts of the hypothalamus including the paraventricular nucleus. The receptors for CART and its downstream signaling pathways have not yet been elucidated. The LHA is regarded as the feeding center and the VMN as the satiety center. The paraventricular nucleus is the site of regulation of pituitary function, and these neurons regulate the secretion of thyrotropin-releasing hormone, corticotrophin-releasing hormone, etc. The paraventricular nucleus is also the site of autonomic nervous system regulation, and these neurons project to the dorsal motor nucleus of the vagus (and other brainstem nuclei) and the intermediolateral spinal columns to regulate parasympathetic and sympathetic outflow, respectively.

This traditional view of the pathways regulating energy homeostasis though is accepted even today needs important modifications in view of recently available data. Accordingly, first order neurons are also suspected to be present in other regions of the hypothalamus [2] and probably in other regions of the brain. Secondly, the role of PVN as a region regulating energy expenditure has been questioned by some authorities [3]. It is also not certain whether there are second order neurons present in other parts of the brain which express MC4R and regulate food intake/energy expenditure. The homeostatic system has been depicted in Fig. 1.

The Reward System and Obesity

The reward system is constituted mostly by the mesolimbic pathway which extends from the ventral tegmental area to the nucleus accumbens (or ventral striatum). It also includes structures like the amygdala and the hippocampus. The pathway involves dopamine acting on the D2 receptors. The prefrontal cortex is involved in actually initiating behavioral responses based on hedonic appraisals of food cues. In addition to being implicated in obesity, the reward system is widely implicated in drug addiction.

Presentation of highly palatable foods induces increased release of dopamine from the nucleus accumbens, though the mechanism behind this is unclear [4]. Exposure to highly palatable foods produces similar neurochemical and molecular changes in the ventral striatum as is produced by drugs of abuse [5].

Obesity is a state of decreased dopamine signaling. Obese patients have been shown to have a decreased D2 receptor level in the striatum by PET imaging [6]. Obesity has been described as a reward deficiency syndrome, where deficiency of dopamine signaling results in compensatory overeating [6]. These dopamine receptor levels are hypothesized to provide a *negative feedback* for a defended set point for reward. Hence, dopamine signaling does not constitute reward itself; it is just a sensing mechanism. This decreased dopamine signaling is believed to increase "wanting" for food. The down-regulation of the reward system has also been hypothesized to increase the response to cues for high vs. low palatability foods since the high palatability foods promise to overcome the blunted reward response in a better manner [7].

Defects in the reward system in obese subjects have also been documented in functional MRI studies involving food intake or presentation of images of food. Stoeckel et al. [7] in a functional MRI study showed that presentation of pictures of high energy foods produced greater activation of several reward system regions in obese women when compared to healthy weight women. Stimulation by pictures of high calorie foods was greater when compared to that by

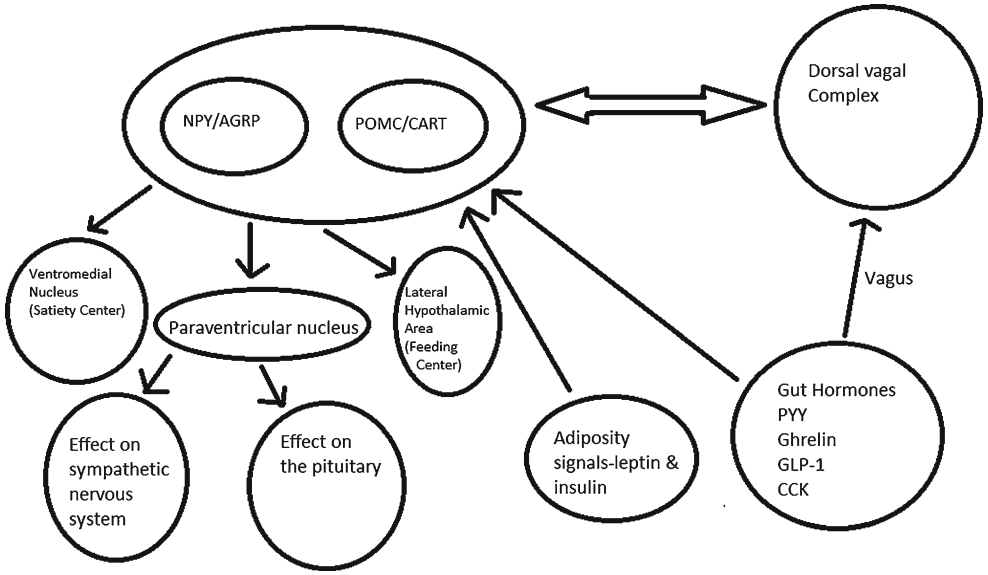

Fig. 1 Humoral regulation of homeostatic system. Humoral regulation of the homeostatic system occurs through ghrelin, PYY, GLP-1, leptin, and insulin. The gastrointestinal peptides have a direct action on the hypothalamus as well as act via the vagus nerve. Ghrelin acts mainly via the various nerves. NYP/AGRP are orexigenic and anabolic while POMC/CART are anorexigenic and catabolic. Ghrelin increases NPY and AGRP release. PYY decreases NPY release. GLP-1 activates the POMC neurons. Leptin increases POMC and decreases NPY/AGRP release. Insulin has also been shown to decrease release of NPY and AGRP. NPY, AGRP, and α-MSH (proteolytic cleavage product of POMC) act on the second order neurons in the paraventricular nucleus (PVN), lateral hypothalamic area (LHA), and ventromedial hypothalamus (VMN). Neurons in the PVN regulate the sympathetic and parasympathetic nervous systems in addition to thyroid function. VMN and LHA are satiety and feeding centers, respectively

low calorie foods in obese women. Another study found greater activation of dorsal striatum and certain other brain areas in response to pictures of high calorie foods in overweight women using functional MRI when compared to normal weight women [9]. In contrast, actual intake of food is associated with lesser activation of striatal regions in obese when compared to lean patients [8]. Hence, while obese patients have an increased "motivation" or "wanting" for food intake, actual food intake is associated with decreased "liking". However, whether these changes are responsible for obesity or if a reversal of these changes produces weight loss is not clear.

Increased activation of the mesolimbic areas has been observed in response to calorie restriction [10]. It would be interesting to know if bariatric surgery avoids this activation in a calorie-restricted patient. As explained below, the changes in the levels of the gut hormones may be responsible for modulation of activity of the reward system by bariatric surgery. The reward system has been depicted in Fig. 2.

Humoral Regulation of the Homeostatic and Hedonic Systems

The changes in gastrointestinal peptides that occur during a meal have an effect on the brain centers to decrease feeding and promote satiety. In contrast, the adipokine leptin signals to the CNS the energy stores that have accumulated in the body over a long term. As described below, bariatric surgery could have an effect on the central nervous system by altering the levels of these gastrointestinal hormones in the fasted state and by altering their response to food. Understanding the actions of these gastrointestinal hormones on the central nervous system is crucial to comprehend the effects of bariatric surgery on the central nervous system.

Ghrelin

Ghrelin, the only known gastrointestinal orexigenic peptide, has the highest levels before a meal and is decreased postprandially. This pattern is absent in obesity. The basis of this variation in ghrelin is not yet elucidated, but is likely related to changes in blood glucose concentrations rather than a physical effect of the food on the stomach [11–13]. Peripheral ghrelin does not penetrate the blood–brain barrier to a great extent and probably acts through vagal afferents to stimulate appetite, and this is currently believed to account mostly for the actions of ghrelin as an orexigenic peptide [14]. Nevertheless, ghrelin-secreting neurons are also present in the hypothalamus and in the arcuate nucleus neurons [15]. Ghrelin causes arcuate nucleus neurons to increase the release of NPY and AGRP. Ghrelin mimics the action of NPY on the paraventricular nucleus [16]. Sleeve

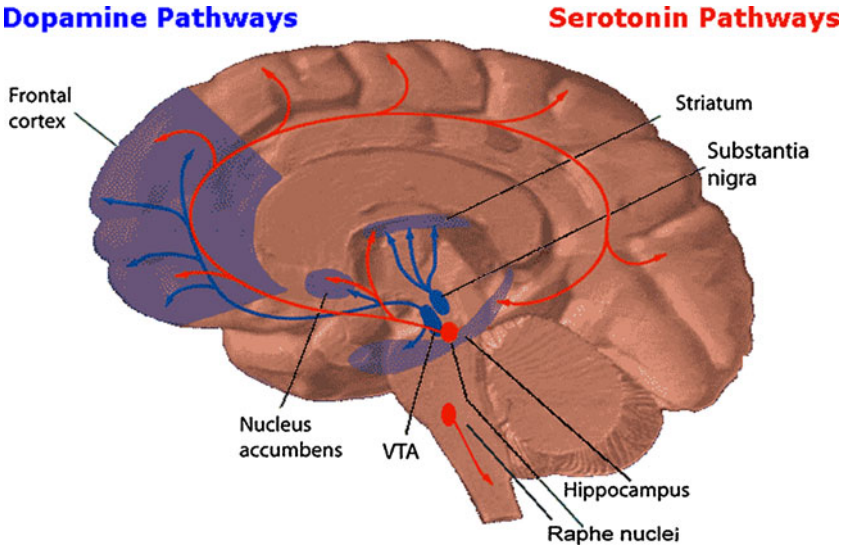

Fig. 2 The reward pathway (image is in public domain at http://en.wikipedia.org/wiki/File:Dopamineseratonin.png)

gastrectomy studies have consistently demonstrated a decrease in fasting ghrelin whereas the change in ghrelin levels after other types of bariatric surgery has been controversial. Sleeve gastrectomy patients also have a greater postprandial suppression of ghrelin postoperatively. In the randomized trial of gastric bypass versus sleeve gastrectomy, laparoscopic sleeve gastrectomy (LSG) was found to produce a greater decrease in appetite which could be attributed to decrease in ghrelin, not consistently seen with Roux-en-Y gastric bypass (RYGB) [17].

Peptide YY

Peptide YY is released from the distal small intestine and the colon and its release is considered to be proportional to the ratio of calorie content to body weight, and as such, its release is decreased in obese patients [18]. It is an important factor for long-lasting appetite suppression after a meal [19]. PYY(3–36) which is the active form binds to Y2 receptors and causes inhibition of NPY release by activating these inhibitory presynaptic receptors [20]. PYY administration has been shown to increase c-fos expression in the arcuate nucleus, certain parts of nucleus of solitary tract, and area postrema. Though PYY also increases POMC release, decrease in NPY is currently believed to mostly account for its appetite-suppressing effect. Using functional MRI studies in humans, PYY infusion in (healthy) humans to attain levels similar to the postprandial state has been shown to cause modulation of activity in the hypothalamus, brain stem, and the reward processing centers [76]. PYY is known to cross the blood–brain barrier. PYY may also act via the vagus nerve as the effect of PYY is attenuated in vagotomized rats [21]. Post-bariatric surgery (RYGB, LSG, and biliopancreatic diversion (BPD)) patients have shown a greater increase in postprandial PYY [22]. Sleeve gastrectomy and RYGB have been shown to produce equal increases in postprandial PYY [23, 24]. The change in fasting PYY has not been consistent across studies [22, 24, 25].

PYY is also suspected to play a crucial role in the decrease in food intake after bariatric surgery with associated maintenance of weight loss. In an animal experiment by Chandarana et al. [26], PYY knockout mice did not have acute weight loss after gastric bypass unlike their wild-type counterparts. This was also seen in the animal experiment by le Roux et al. [27] where administration of PYY antagonist after jejunointestinal bypass (JIB) in rats resulted in increased food intake. Moreover, PYY-treated sham-operated rats had a similar food intake compared to JIB rats. Inhibition of PYY and GLP-1 secretion by octreotide also resulted in increased food intake in human patients after RYGB [28].

Adipokines

Leptin is an indicator of long-term energy stores and its levels are increased in obesity. It acts on the CNS through neurons expressing long form of leptin receptor (LepRb). Leptin is transported across the blood–brain barrier via receptor-mediated endocytosis, which is a saturable mechanism. Leptin acts on the arcuate nucleus to upregulate the appetite decreasing neuropeptides namely POMC and CART and decrease the appetite-enhancing neuropeptides namely NPY and AGRP [29–31]. Leptin also increases expression of anorexigenic brain-derived neurotropic factor in the ventromedial hypothalamus. Its action on the nucleus of solitary tract also contributes to satiety [32]. This response in the arcuate nucleus projects to the LHA to decrease appetite and to PVN to increase sympathetic activity and increase thyrotropin-releasing hormone secretion both of which increase energy expenditure. Leptin also inhibits

the production of endocannabinoids [33], which are well known to induce hunger. Leptin also acts on the ventromedial hypothalamus to increase glucose uptake, though the exact mechanism of this is uncertain [34]. In addition, leptin also promotes synaptic plasticity which may potentiate its anorectic effect [35]. Bariatric surgery causes a decrease (not an increase in leptin) and this should cause increased appetite and decreased energy expenditure (in addition to increased activation of hedonic system in fed state). However, obese individuals have a lesser increase in CSF leptin, and hence, the ratio of CSF leptin to serum leptin is higher in lean when compared to obese individuals [36], and this may contribute to leptin resistance in obese patients. However, studies on the effect of bariatric surgery on CSF leptin are lacking and the effect of bariatric surgery on central appetite regulation through leptin remains uncertain at this time. However, weight regain due to decreased leptin can be prevented by other humoral changes accompanying surgery, and increase in PYY relative to decrease in leptin has been suggested to be responsible for sustained weight loss after bariatric surgery [37].

Adiponectin does not cross the blood–brain barrier. However, it does affect secretion of centrally acting substances from the brain endothelial cells and hence can indirectly increase energy expenditure by acting at the level of the CNS [38]. Increase in adiponectin after bariatric surgery has been well established.

Glucagon-like Peptide-1

GLP-1, in addition to its anti-diabetic effect, also has anorexic properties and is well known to produce weight loss in diabetic patients. Intraventricular administration of GLP-1 has been shown to decrease food intake in lean and obese rats [39]. Though the exact mechanisms have not been elucidated, GLP-1 has been shown to stimulate neurons in the hypothalamic and brainstem regions as measured by *c-fos* expression, though the data regarding this have not been consistent [40]. GLP-1 in the brain is also suspected to be closely connected to the enteral glucose sensing mechanism. In a mouse model, the muscle glycogenesis and glycolysis was found to be increased by enteric glucose infusion and this increase was no longer evident after infusion of GLP-1 receptor antagonist into the brain. The same experiment found that enteric glucose (and thus GLP-1) activated only NPY but not the POMC neurons [41]. However, more definitive animal studies detecting the presence of GLP-1 receptors in the arcuate nucleus have localized these receptors to the POMC neurons and have concluded that GLP-1 action on the arcuate nucleus increases glucose-induced insulin secretion and reduces hepatic glucose production [42]. GLP-1 is also known to activate POMC neurons, thus accounting for its anorectic action [43]. There is also some evidence that GLP-1 is involved in activation of the sympathetic nervous system and GLP-1 may be a downstream signal for leptin [44, 45]. The change in the levels of fasting GLP-1 after bariatric surgery is not clear [22, 25]. However, increase in postprandial GLP-1 has been demonstrated after RYGB, sleeve gastrectomy, and BPD [22, 23, 46].

Humoral Regulation of the Reward System

The gastrointestinal hormones and adipokines also have an influence on the reward pathway. Leptin receptors have also been demonstrated in the ventral tegmental area [47]. Farooqi et al. [48] in a landmark report showed that in patients with congenital leptin deficiency, "wanting" of food correlated with striatal activation in both fasting and the fed states, whereas this correlation was found only in the fasted state after leptin treatment, reflecting the condition in normal controls. Preclinical studies have shown ghrelin to effect signaling in the mesolimbic system [49–51]. Ghrelin receptors are expressed in the ventral tegmental area and administration of ghrelin into this area (and to a lesser extent nucleus accumbens) has been shown to elicit a feeding response [52]. In addition, ghrelin infusion has been shown to increase activity in several regions of the hedonic system as shown by functional MRI studies in humans [53]. The alteration of the levels of these hormones by bariatric surgery and the consequent effects on the CNS have been presented in Fig. 3.

Animal Studies in Bariatric Surgery

Decrease in food intake induced by bariatric surgery has been well documented in animal models [54, 55]. Rat models of gastric bypass, gastric banding, sleeve gastrectomy, and biliopancreatic diversion have been used to demonstrate a decrease in food intake after bariatric surgery and this has been dealt in a previous review [55]. The importance of PYY in causing this decrease in food intake has been mentioned in the previous section. The change in energy expenditure after bariatric surgery is not clear from animal models [57].

A few rat and mouse experimental models have tried to elucidate the changes that occur after bariatric surgery in the brain centers that are responsible for food intake and energy homeostasis. These experiments have been largely inconclusive.

In an experiment involving Sprague–Dawley rats, Romanova et al. [56] did not find any differences in the decrease of NPY in the arcuate and paraventricular nuclei between the RYGB rats and pair fed rats, although there was a significant decrease in NPY in both the above rats when compared to obese controls. Similarly, an increase in α-

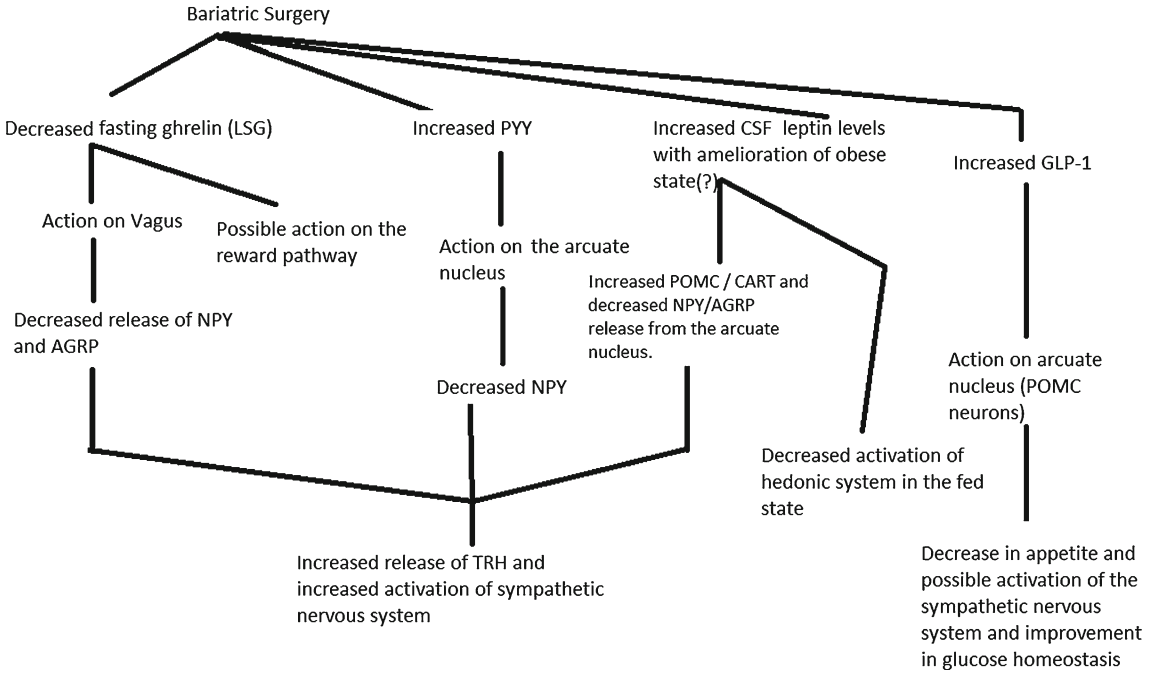

Fig. 3 Possible mechanisms of action of bariatric surgery on the CNS

MSH was noted in the same nuclei of the two types of rats when compared to obese controls, although the increase in RYGB vs. PF rats was significant only for the magnocellular PVN. The RYGB rats also had a greater increase in serotonin receptors in the PVN when compared to PF rats. Thus, only the last two changes could be attributed to the surgery alone and other changes are likely to have occurred due to the calorie restriction.

Nadreau et al. [57] found that NPY and AGRP mRNA expression in the ARC were higher in biliopancreatic diversion-operated rats when compared to control rats. The tissues were obtained 50 days after the surgical procedure. There was an initial decrease in energy expenditure which did not persist throughout the study. These results are contradictory to the expected changes.

Wang and Liu [58] reported that hypothalamic growth hormone secretagogue receptor 1a (GHSR1a) levels in the hypothalamus were lower after gastric banding while they were higher after sleeve gastrectomy. GHSR1a are receptors for ghrelin and their higher levels after sleeve gastrectomy may be due to a compensation for decreased ghrelin levels. Another study found an increased excretion of γ-aminobutyric acid and glutamate in stool of rats that have undergone RYGB, thus strengthening the evidence for alteration of levels of central neuropeptides by bariatric surgery [59].

Meguid et al. [37] elucidated the mechanisms involving weight regain after gastric bypass surgery in a rat model. They found that rats which had failure of sustained weight loss had low plasma PYY/leptin ratio and had reversal of post-surgical changes in the central nervous system and metabolism. Decreased orexigenic and increased anorexigenic activity in the arcuate nucleus and paraventricular nucleus of hypothalamus were reversed in rats with weight regain. Sonoda et al. [60] found that parvalbumin hippocampal interneurons were increased in rats subjected to gastric restriction, which is the first available evidence for hippocampal plasticity after gastric restriction.

In an experiment in rats involving testing of changes in reward mechanisms, RYGB rats were found to exhibit decreased liking for higher concentrations of sucrose and corn oil when compared to sham-operated obese and lean rats. The reduced 'wanting' of a palatable reward in the incentive runway seen in sham-operated obese SD rats was fully restored after RYGB to the level found in lean control rats. Thus, though wanting of palatable foods was increased overall, liking was reduced only for the high concentration foods while the opposite was true for “liking” of low concentration foods after RYGB. These discordant results between “liking” and “wanting” need further investigation as different food materials were used for the two test paradigms in the experiment [61]. These findings are also contradictory to the findings in human studies utilizing imaging techniques described below, which have consistently indicated that obese patients have a greater “wanting” for food and this is reduced after bariatric surgery.

Various experiments have assessed food preference of rats after RYGB. A decrease in preference for sucrose [82], especially for the higher concentration solutions, has been found in these animals after gastric bypass [83]. In

addition, Otsuka Long–Evans Tokushima Fatty rats which had undergone gastric bypass showed similar extracellular recordings from taste response neurons in the pontine and parabrachial nuclei when compared to lean rats. The obese rats, however, had a rightward shift in the concentration responses to oral sucrose when compared to lean rats [84]. However, contradictory results have been obtained in some studies [85]. Using two bottle preference tests, le Roux et al. demonstrated decreased preference for higher lipid concentrations [86]. Thus, most of the above experiments demonstrate a decrease preference for sweet taste and for high calorie food after gastric bypass.

The mechanisms underlying these changes in food preferences after RYGB need to be elucidated and the role of gut peptides and adipokines in this process should be ascertained. However, some initial studies were unable to show a role for GLP-1 in such changes in rat models of gastric bypass [85]. The animal studies have been summarized in Table 1.

Human Studies in Bariatric Surgery

Studies Utilizing Imaging Techniques to Study Changes in Neural Pathways

A few human studies are available which have shed light on the changes in the neural pathways after bariatric surgery. These studies have utilized PET and MRI techniques and have shed some light on changes occurring in both the homeostatic and hedonic pathways.

Dunn et al. [62] reported a decrease in dopamine D2 receptors in the caudate, putamen, ventral thalamus, hypothalamus, substantia nigra, medial hypothalamus, and amygdala after RYGB and sleeve gastrectomy using PET studies. They used a DA D2 radioligand whose binding is sensitive to competition with endogenous dopamine. In contrast, Steele et al. [63] reported an increase in dopamine receptors in the ventral striatum, caudate, and putamen and found that this increase was proportional to the weight lost. Such discordant results could be attributed to the presence of comorbid conditions which can alter dopamine signaling.

Using functional MRI, Bruce et al. [64] detected activation of various brain regions to pictures of food vs. non-food in patients before after gastric banding. They found that brain activation was decreased in the parahippocampus, medial prefrontal cortex, insula, and inferior frontal gyrus (involved in food motivation and reward) and increased in pre-frontal cortex (involved in cognitive control and inhibition).

Ochner et al. [65] in a study of women undergoing gastric bypass found decreased activation of the mesolimbic areas in response to auditory and visual food cues, for the high energy density (and less pronounced for low density) food 1 month after surgery when compared to before surgery. This was accompanied by a decreased desire to eat after surgery, which was again more pronounced for high energy foods. The above two studies have thus assessed motivation to obtain food before and after bariatric surgery by using food cues.

van de Sand-Lee et al. [66] in a study of lean and obese subjects (before and after RYGB) utilizing functional MRI studies found changes in fMRI patterns particularly in the hypothalamus in obese patients with ingestion of glucose. They utilized temporal clustering analysis (TCA) and functional connectivity MRI (fcMRI) studies. The TCA studies showed distinct patterns in obese patients before surgery and lean patients especially in the hypothalamus and somatosensory cortices. The TCA was performed at three time points after ingestion of glucose. Both analytic methods showed patterns resembling lean patients in obese subjects after surgery. Of note, the TCA demonstrated increased activation of the hypothalamus, somatosensory, and orbitofrontal cortex after when compared to before surgery. The same study also found an increase in CSF levels of IL-6 and IL-10, cytokines implicated in causing reduction of hypothalamic leptin resistance. The study, however, did not measure activities in the regions involved in the reward pathway.

Studies Measuring Changes in Appetite

Various studies have attempted to measure appetite and satiety after bariatric surgery by using questionnaires. While decrease in appetite and increase in satiety may be due to reduction in the size of the stomach, humoral mediators altered by bariatric surgery may also play a role by having an effect on the central nervous system. Morrow et al. [80] reported a significant decrease in hunger 5 months after gastric bypass using a visual analogue scale.

Schultes et al. [75] measured hedonic hunger using Power of Food Scale (PFS) in gastric bypass patients and compared them to obese patients and lean patients. PFS is a questionnaire used to measure appetite and is not designed to measure actual food consumption. It has three domains—food available, food present, and food tasted. A score for each domain and an aggregate score are calculated. Obese patients were found to have greater domain scores (except in the food tasted domain where the scores were found to be equal) and aggregated score when compared to non-obese patients. Post-gastric bypass patients had reduced scores in all domains and had a reduced aggregated score when compared to obese patients, thus indicating that hedonic hunger is reduced post-gastric bypass. Further, the aggregated score and the "food available" and "food present" scores did not differ between post-gastric bypass patients and non-obese control subjects. They, however, noted that

Table 1 Animal experiments on the effects of bariatric surgery on CNS

Author	Year	Type of animal model	Controls	Surgery	Result
Romanova	2004	Sprague–Dawley rats	Sham-operated pair fed and lean	RYGB	Increase in α-MSH in the magnocellular PVN
Nadreau	2006	Male Wistar	Sham-operated and lean	BPD	Increased AGRP and NPY mRNA expression in arcuate nucleus
Meguid	2008	Sprague–Dawley	Sham-operated	RYGB	Reversal of increase in anorexigenic activity and decrease in orexigenic activity in the hypothalamus with weight regain
Wang	2009	Male Wistar	Sham-operated	Gastric banding and SG	Decreased hypothalamic GHSR1a expression seen after gastric banding and increased GHSr1a receptor expression seen after SG
Hajnal	2010	OLETF	Sham-operated and lean	RYGB	Decreased 24-h two-bottle preference for sucrose and 10-s lick responses for sucrose after surgery. Neural responses of taste neurons similar in surgical and lean rats
Li	2011	Male Wistar	Sham-operated	RYGB	Increased excretion of GABA and glutamate in stool
Sonoda	2011	Male Wistar	Sham-operated	Gastric restriction with phytobezoar	Increase in the expression of the parvalbumin interneurons in the hippocampal CA1 and CA3 subfields
Shin	2011	Sprague–Dawley	Sham-operated obese and lean control	RYGB	Decreased liking for high calorie food in RYGB-operated rats. Improved wanting in incentive runway in RYGB-operated rats which became similar to lean rats
Bueter	2011	Wistar	Sham-operated	RYGB	Reduced the sucrose intake relative to water. Preoperative sucrose exposure reduced this effect
Tichansky	2011	Sprague–Dawley	Sham-operated	RYGB	The RYGB rats showed a significant decrease in mean licks for the highest concentration of sucrose
Mathes	2011	Sprague–Dawley	Sham-operated	RYGB	Increased appetitive behavior after RYGB which was not affected by GLP-1 receptor modulation
Le Roux	2011	Wistar	Sham-operated	RYGB	Decreased preference for higher lipid concentrations

OLETF Otsuka Long–Evans Tokushima Fatty

such a reduction in hedonic hunger could be partly attributed to dumping symptoms.

Thirlby et al. [77] measured changes in appetite and satiety before and after RYGB using a visual analogue scale "Snickers" test. Patients were stratified based on familial risk of obesity (high vs. low obesity risk index—ORI). Hunger was suppressed after RYGB. Patients with higher ORI were found to have a greater reduction in hunger and increase in satiety 3 h after a standardized meal.

Kalarchian et al. [78] administered the Three Factor Eating Questionnaire (TFEQ) and the Eating Disorder Examination (EDE) before and after gastric bypass. They found a decrease in disinhibition and hunger scores and increase in restraint score of TFEQ. EDE restraint scores increased in binge eaters and decreased in non-binge eaters. Another study utilizing TFEQ found similar results [81].

Laurenius et al. [79] reported a transient increase in cognitive restraint using the TEFQ 6 weeks after gastric bypass. They also reported a decrease in meal size and eating rate (amount of food consumed per minute) after surgery.

Studies Measuring Changes in Taste and in Food Preferences

Data available on the taste changes/food preferences after bariatric surgery also serve as indicators for changes that

occur in the reward pathways. Nevertheless, these changes could also be due to non-central nervous system mechanisms like dumping syndrome.

Halmi et al. [67] found a statistically significant decrease in intake of high fat meats and high calorie carbohydrates 6 months after gastric bypass. Patients found these foods no longer enjoyable. Thomas and Marcus [68] found that post-gastric bypass patients avoided high fat food. Brown et al. [69] reported that patients were not interested in sweets or desserts after surgery. Kenler et al. [70] in a comparative trial using diet interviews showed that gastric bypass patients consumed 45 % less solid sweets/sweet high calorie beverages and 37 % less milk or ice cream compared with gastroplasty patients. Similar results were reported by Olbers et al. [71]. Thirlby et al. also reported a decreased preference for high fat foods which was more pronounced in high ORI patients [77].

Decrease in taste thresholds for foods has been reported after bariatric surgery. While Scruggs et al. [72] reported a decrease in bitter recognition threshold, Burge et al. [73] and Bueter et al. [82] reported a decrease in sweet recognition threshold. The stage in the taste pathway, where bariatric surgery acts to produce these changes, remains to be established and the reward pathway is a well-known component of the taste pathway [74]. The human studies have been summarized in Table 2.

Summary

The regulation of food intake by the central nervous system is by the homeostatic and the hedonic systems. The arcuate nucleus is the major player in the homeostatic system. The mesolimbic pathway is the major player in the reward system. Obese patients are known to have a reward deficiency syndrome, owing to decreased dopamine signaling. This is believed to increase wanting for food. Gastrointestinal hormones and adipokines have an influence on the homeostatic and hedonic systems. These peptides are also altered by bariatric surgery thus paving way for the potential effect of

Table 2 Human studies on the effects of bariatric surgery on CNS

Author	Year	Surgery	Investigational method	Result
Dunn	2010	RYGB and sleeve gastrectomy	PET	Decrease in D2 receptors in the hypothalamus, striatal regions, and amygdala
Steele	2010	RYGB	PET	Increase in D2 receptors in the ventral striatum, caudate, and putamen
Bruce	2011	LAGB	fMRI	Decreased activation of parahippocampus and insula (reward system) and increased activation of pre-frontal cortex (inhibition)
Ochner	2011	RYGB	fMRI	Decreased activation of key mesolimbic areas which was more pronounced for high (vs. low) calorie food cues
Van de sand lee	2011	RYGB	fMRI	TCA and fcMRI patterns in obese patients after surgery resembled those of lean patients
Halmi	1981	RYGB	Clinical	Decrease in intake of high calorie carbohydrate foods
Brown	1982	RYGB	Clinical	Patients not interested in sweets
Kenler	1990	RYGB	Clinical	Gastric bypass patients consumed less high calorie beverages/sweets and milk when compared to gastroplasty patients
Scruggs	1994	RYGB	Modified Henkin forced choice 3 stimulus technique	Decrease in bitter taste recognition threshold
Burge	1995	RYGB	Taste acuity	Decrease in sweet taste recognition threshold
Kalarchian	1999	RYGB	TFEQ	Decrease in hunger and disinhibition scores. Increase in restraint scores
Thirlby	2006	RYGB	Visual analogue scale "Snickers" test	Decreased hunger and increased satiety
Olbers	2006	RYGB	Clinical	Decreased intake of fats and sweets in RYGB when compared to vertical banded gastroplasty
Thomas	2008	RYGB	Clinical	Decreased selection of high fat vs. low fat food
Morrow	2008	RYGB	Visual analogue scale	Decrease in hunger
Schultes	2010	RYGB	Power of Food Scale	Reduced "hedonic hunger"
Laurenius	2011	RYGB	TFEQ	Increase in cognitive restraint

TFEQ Three Factor Eating Questionnaire

bariatric surgery on the central nervous system. Animal studies to assess the changes in the homeostatic system have been unable to draw useful conclusions. A significant increase in α-MSH in the PVN has however been demonstrated in a rat model of gastric bypass. Human studies have utilized PET to measured dopamine receptor levels and functional MRI to study activation of various regions of the brain before and after surgery. Two studies have reported divergent results on dopamine receptor levels. Studies regarding the reward pathway have demonstrated decreased activation of the reward centers after surgery and this can also be interpreted from decreased preference for high calorie foods after surgery. Increased activation of the hypothalamus in humans has been demonstrated in another study utilizing functional MRI techniques, thus showing the effect of bariatric surgery on the homeostatic system. A decrease in threshold for sweet taste has been reported which may be due to an effect on the reward system. In addition, several studies have reported decrease in appetite and increase in satiety after bariatric surgery.

Future Directions

The changes in the levels of the neurotransmitters in the hypothalamus and in the reward pathway after bariatric surgery need to be confirmed from animal models. These experiments could also utilize alteration of the effects of the humoral mediators so that their role in causing CNS changes can be elucidated. Changes in liking and wanting should be elucidated in animal models using well-designed studies. Human studies should further elucidate the changes in dopamine signaling after bariatric surgery after controlling for comorbid psychiatric conditions. It would also be interesting to know if different bariatric surgeries have differing effects on the central nervous system.

Conflict of Interest Dr. Raghavendra Rao declares no conflict of interest.

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