Trends in Endocrinology & Metabolism

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Review

Brain Feeding Circuits after Roux-en-Y Gastric Bypass

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Metabolic surgical procedures, such as Roux-en-Y gastric bypass (RYGB), uniquely reprogram feeding behavior and body weight in obese subjects. Clinical neuroimaging and animal studies are only now beginning to shed light on some of the underlying central mechanisms. We present here the roles of key brain neurotransmitter/neuromodulator systems in food choice, value, and intake at various stages after RYGB. In doing so, we elaborate on how known signals emanating from the reorganized gut, including peptide hormones and microbiota products, impinge on newly mapped homeostatic and hedonic brain feeding circuits. Continued progress in the rapidly evolving field of metabolic surgery will inform the design of more effective weight-loss compounds.

Highlights

Weight loss after RYGB is attributable to multifaceted changes in feeding behavior in humans and animal models.

Several feeding-regulatory neurotransmitter/neuromodulator systems have consistently been shown to be targeted by RYGB surgery in humans and animal models.

The melanocortin 4 receptor (MC4R) and 5-hydroxytryptamine 2A (5-HT_{2A}) receptor both positively modulate postoperative weight loss, indicating that appetite-suppressing, hypothalamic proopiomelanocortin (POMC) and dorsal raphe serotonergic pathways, respectively, are enhanced.

Striatal function and brain μ-opioid receptor (MOR) signaling are lowered postoperatively, indicating that mesolimbic dopaminergic and brain opioidergic pathways, which promote palatable food intake, are suppressed.

Gut hormones, microbiota products, and leptin likely generate this post-RYGB brain state.

The Superiority of Metabolic Surgery over Conservative Weight-Loss Treatments

In attempts to tackle the continuously growing **obesity** (see Glossary) problem, several centrally acting, appetite-suppressing compounds have recently been approved, including the long-lasting glucagon-like peptide 1 (GLP-1) analog liraglutide and the selective 5 hydroxytryptamine 2C (5-HT_{2C}) receptor agonist lorcaserin [1]. These, however, still pale in comparison to **metabolic surgical procedures** such as RYGB and vertical sleeve gastrectomy (VSG) in the magnitude of weight loss they produce (in the order of 5–7% vs 36–38% in the first year for medicinal vs surgical interventions, respectively) [1]. Given that intensive medical therapy for diabetes fares equally less well in similar head-to-head comparisons [2], RYGB and VSG remain the gold-standard treatment option for severe obesity and some of its associated comorbidities. It therefore stands to reason that further understanding the mechanisms by which these metabolic surgical procedures work will contribute significantly to the development of better noninvasive alternatives, and this has ushered in a fertile field of metabolic research bringing together basic, clinical, and surgical scientists. It should also be added that such rationally designed pharmacotherapies used as an adjunct to lifestyle changes will also be of benefit to individuals with mild to moderate obesity, and who are otherwise ineligible to receive either RYGB or VSG because of the associated risks and their irreversible nature.

The first full gastric bypass procedure was devised with a view to induce weight loss by physically restricting caloric intake [3]. It entailed transection of the upper part of the stomach, forming a small gastric pouch, which was then adjoined to a loop of mid-jejunum through a side incision, and this proved to be remarkably effective [3]. Largely owing to technical reasons for the surgeon, and severe vomiting for the patient, the Roux-en-Y configuration was subsequently adopted (involving actual transection of the mid-jejunum) [4], and the procedure subsequently underwent a series of adjustments in limb lengths with the intention to promote malabsorption for maximal effects on body weight [5]. It is now well established that, over and

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above the mechanical processes, a host of complex physiological alterations take place postoperatively, contrasting with metabolic surgical procedures that do not involve gastrointestinal reconfiguration such as gastric banding [6]. Despite the gain in popularity of VSG, which unlike RYGB entails removal of only the greater curvature of the stomach but confers comparable physiological effects and metabolic benefits [6], most brain studies conducted so far have been on the latter procedure, which will therefore be the main focus of this Review.

A major part of the success of RYGB stems from multifaceted improvements in feeding behavior [7]. While the consensus is that in humans this engenders sustainably lowered caloric intake [7], in most rodent models the initial reduction in meal size is eventually counterbalanced by an increase in meal frequency such that, at later stages postoperatively, RYGB-operated animals consume as much as obese **sham-operated controls** [8]. Nevertheless, the lack of a powerful rebound behavioral response to weight loss characteristic of RYGB is reproducibly captured, allowing the role of altered gut–brain communication in adjusting the whole-body energy balance set-point back to lower levels to be studied in greater detail [7]. Indeed, it has been shown in rats that, for complete weight loss and diminished fat preference postoperatively, sensory information from the gut must reach hindbrain nucleus tractus solitarius (NTS) neurons through the celiac branch of the vagus nerve [9]. Surprisingly, it remains largely unclear precisely which gut-generated signals are responsible for the modified brain structure/function after RYGB. Augmented GLP-1 release from enteroendocrine L cells acting on peripheral and/or central GLP-1 receptors was initially widely considered to be a major contributor, but has been difficult to prove experimentally [10–13] (Table 1). However, as will be presented throughout this text, central GLP-1 receptor signaling consistently manages to explain some of the functional changes imparted by RYGB on brain feeding circuits.

Aided for the most part by the use of *in vivo* neuroimaging techniques such as **positron emission tomography** (PET), a distinct post-RYGB neurochemical profile is steadily beginning to emerge from human and animal studies. This comprises neurotransmitters/neuromodulators that are traditionally implicated in the homeostatic aspects of feeding, such as the **melanocortinergic** and **serotonergic systems**, as well as those in the hedonic aspects of feeding, such as the **dopaminergic** and **opioidergic systems**. How these are affected in obesity and at different stages after RYGB, particularly in animal models, will be the subject of discussion here, as well as their causal roles in modifying various aspects of feeding behavior and body weight postoperatively. In addition, potential mediating peripheral factors, including gut hormones, adipokines, and microbiota products, which are profoundly changed postoperatively [14–18], will be speculated upon with reference to newly identified molecularly, anatomically, and functionally distinct brain feeding circuits. The use of appropriate controls in studies will be emphasized throughout, as will species differences. Finally, future directions will be given.

The Brain Melanocortinergic System

Over the past 20 years, pharmacologic, genetic, and contemporary neuroscience approaches have firmly established opposing roles for proopiomelanocortin (POMC) and agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons of the hypothalamic arcuate nucleus (ARC) on whole-body energy-balance regulation. While their projections are widespread and overlapping, it is now clear that AgRP/NPY neurons functionally cancel POMC neuron output specifically at the level of melanocortin 4 receptors (MC4Rs) situated in the hypothalamic paraventricular nucleus (PVN), to stimulate food intake [19] (Figure 1A). MC4Rs also play an underappreciated role in macronutrient selection, and animal and humans studies show that their activation favors reduced fat intake [20,21].

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For the reasons mentioned above, the hypothalamic melanocortinergic system is an obvious starting point to probe the effects of RYGB on brain feeding circuits. Puzzlingly, at the gene expression level at least, results obtained from analyses performed on mice and rats after RYGB compared to obese sham-operated counterparts have been highly inconsistent [22–24]. However, when compared to formerly obese controls forced to lose the equivalent amount of body weight through chronic caloric restriction, RYGB-operated mice do exhibit the expected anorectic neuropeptide profile, namely relatively higher hypothalamic *Pomc* and lower *Agrp*/*Npy* mRNA expression [23]. These findings serve to illustrate how RYGB prevents the brain starvation response to shrinkage of adipose tissue stores [7]. One way this could be achieved is through enhanced sensitivity to the adiposity signal leptin as a result of a decrease in hypothalamic protein tyrosine phosphatase 1B (PTP1B) activity, a major negative regulator of leptin receptor signaling in obesity, through local GLP-1 receptors [25]. Indeed, RYGB-operated rats have been shown to have lower hypothalamic PTP1B protein levels compared to obese sham-operated controls, accompanied by increased basal levels of phosphorylated signal transducer and activator of transcription 3 (pSTAT3) at serine 727 [24], a well-established downstream readout of leptin receptor activation. Furthermore, RYGB occludes the appetite-suppressing effects of the weight-loss drug topiramate in mice [26], which itself lowers hypothalamic PTP1B protein levels to enhance central leptin anorectic action [27]. Despite the lack of a major effect of chronic GLP-1 receptor antagonism on feeding and body weight in rodents at early [12] and late [11,13] stages after RYGB, data obtained from leptin-deficient *ob*/*ob* mice do leave room for a scenario in which hypothalamic GLP-1 receptors initially serve to restore local leptin receptor signaling capacity, enabling the lower levels of circulating leptin to then defend lesser adiposity [28,29], particularly in the face of a high-fat diet [29] (Table 1).

The actual causative role of the central melanocortinergic system in the negative whole-body energy balance induced by RYGB has been directly addressed in pharmacological and genetic experiments performed on animals by independent groups [30–32] (Table 1). Chronic (2 week) antagonism of brain MC4Rs in rats reversibly increased body weight by ~30% and almost tripled food intake, although comparable changes were also seen in obese sham-operated animals undergoing the same treatment [32]. Nevertheless, these findings are in line with those from hyperphagic obese MC4R-deficient mice that do not lose as much body weight as wild-type mice postoperatively [30,31]. Furthermore, through the use of elaborate genetic mouse models, MC4Rs in cholinergic preganglionic sympathetic neurons were systematically deduced to be required for the well-documented increase in energy expenditure postoperatively [8,32]. It remains unclear, however, precisely which chemically defined MC4R-containing brain neurons limit energy intake after RYGB, particularly in the form of fat [31]. To address this issue, hyperphagic obese mice lacking MC4R specifically in single-minded 1 (Sim1)-expressing neurons of the PVN [33] could prove to be useful (Figure 2A). Interestingly, hypophagia and weight loss after VSG are completely spared in global MC4R-deficient rats [34], implying that RYGB and VSG target different brain pathways to deliver their effects on feeding and body weight.

Substantiating the results from animal models, there are compelling clinical findings which suggest that RYGB targets the hypothalamic melanocortinergic system to influence feeding responses and body weight. Specifically, in a recent ^{18}F-fluorodeoxyglucose PET imaging study, hypothalamic metabolic activity 90 minutes following a fixed meal was found to reach supraphysiological levels (approximately double that of normal-weight controls) in patients postoperatively [35]. Because this was largely independent of gut hormone release [35], potential mediating peripheral factors could derive from gut microbiota, namely *Escherichia coli,* whose abundance has been shown to markedly increase in humans and animals after RYGB [16–18] (Figure 2A). Work performed on rats first suggested that these bacteria

Glossary

Dopaminergic system: in the brain, this comprises neurons which express tyrosine hydroxylase and that synthesize dopamine as well as their downstream target neurons that express dopamine receptors (D1R–D5R). The nigrostriatal system contains neurons whose cell bodies originate in the midbrain substantia nigra pars compacta and which project rostrally to the dorsal striatum (caudate nucleus and putamen). The mesolimbic system contains neurons whose cell bodies originate in the midbrain ventral tegmental area and which project rostrally to the ventral striatum (nucleus accumbens shell and core).

Functional magnetic resonance imaging (fMRI): an *in vivo* neuroimaging technique that requires placing subjects in a strong external magnetic field which provides indirect information about brain function. The technique is based on a signal received from water protons which is sensitive to neuronal activity-dependent changes in regional deoxyhemoglobin levels caused by sensory stimuli, pharmacological agents, or engaging in a particular behavior.

Melanocortinergic system: this comprises functionally opposing, non-overlapping neuronal populations in the arcuate nucleus of the hypothalamus (ARC) that synthesize the neuropeptides α-melanocyte stimulating hormone (derived from proopiomelanocortin, POMC) and agouti-related peptide (AgRP), as well as their downstream target neurons which express the melanocortin 4 receptor (MC4R).

Metabolic surgical procedures: a collection of bariatric surgical procedures that produce overall improvements in various metabolic indices by weight loss-dependent and -independent mechanisms.

Obesity: the condition of being in the unhealthy range on the body mass index (BMI) scale. Overweight, obese, severely obese, and morbidly obese individuals have a BMI of or greater than 25, 30, 35, and 40 kg/m^2, respectively.

Opioidergic system: comprises neurons that synthesize the neuropeptides POMC, preproenkephalin (PPE),

contribute to satiation at the later stages during food digestion by releasing peptides into the circulation which stimulate ARC POMC neurons [36,37]. The rerouting of chyme to the distal gut after RYGB could serve not only to expedite but also to potentiate this process, thereby converting it into one that promotes meal termination (satiety) [37]. Importantly, postoperative reductions in body weight, body mass index (BMI), and adiposity in patients correlate positively with fecal *E. coli* levels [16], suggesting conserved roles for this particular gut microbiota species in regulating host whole-body energy balance.

Further implicating the brain melanocortinergic system in the positive clinical outcome of RYGB, patients with a rare gain of function allele in *MC4R* (I125L) exhibit exaggerated and protracted weight loss postoperatively, with body-weight curves plateauing at 18 months compared to the usual 12 months [38]. An obvious but often overlooked question that arises concerning these individuals is how their obesity arose in the first place, given the preponderance of genetic evidence that would suggest the opposite. One plausible explanation for this conundrum could be that RYGB causes the increased trafficking of mutated MC4R to the somatodendritic membrane of PVN neurons (where it would exert its effects) through regulating the expression and/or function of melanocortin 2 receptor accessory protein 2 (MRAP2) [39]. Overall, the animal and human data lend strong support to the notion that RYGB exploits homeostatic feeding circuitry to promote satiety (Figure 1).

The Brain Serotonergic System

The raphe nuclei of the brainstem send widespread descending and ascending serotonergic projections throughout the central nervous system, including the hypothalamus, striatum, and cerebral cortex [40]. Drugs that recruit brain serotonergic circuits, such as the aforementioned lorcaserin and selective serotonin-reuptake inhibitors (SSRIs) such as sibutramine, are effective appetite-suppressants and weight-loss compounds, although the latter have been withdrawn from the market owing to their negative side effects [40]. Evidence from animal and human studies generally points to the hypothalamus as an important physiologic site of action of the brain serotonergic system as well as of these drugs in regulating whole-body energy balance [41–43].

Because pharmacologic and genetic studies have both implicated brain 5-HT_{1B} receptors in suppressing feeding [40], their hypothalamic levels were evaluated in one of the earlier investigations performed on rats subjected to RYGB [44]. Significantly higher 5-HT_{1B} receptor protein was found in the PVN compared to obese sham-operated animals, independently of weight loss [44]. Because the 5-HT_{1B} receptor is thought to act as an inhibitory presynaptic heteroreceptor in AgRP/NPY neuronal terminals [40], this provides another mechanism for how satiety-promoting MC4R-containing PVN neurons projecting to the central aspect of the brainstem lateral parabrachial nucleus (clPBN) [19] become more active postoperatively (Figure 1A). Notably, at early (10 day) but not late (20 day) stages after RYGB in mice, calcitonin gene regulated peptide (CGRP)-containing neurons in the external aspect of the lPBN (elPBN) are strongly stimulated by consumption of a high-fat meal [45], and this could also be mediated by membrane proteins released by gut *E. coli* [36]. These neurons form part of a well-mapped and separate satiating brain feeding circuit with inhibitory neurons in the lateral aspect of the central amygdaloid nucleus (CeAl) in 'fifth-order' [46–49] (Figure 1B).

Brain 5-HT_{2A} receptors are not typically associated with the serotonergic control of feeding [40], but well-powered clinical PET imaging experiments have reproducibly demonstrated strong positive correlations between their availability in the cerebral cortex and BMI [50]. The counterintuitive increase in cortical 5-HT_{2A} receptor availability in obesity is thought to be compensatory in nature to make up for chronically lowered brain serotonin levels [50]. These findings are

preprodynorphin (PPD), and orphanins, and their downstream target neurons which express the μ (MOR), δ (DOR), and κ (KOR) opioid receptors, and orphanin receptors. Endomorphins and endorphins derive from POMC and bind to the MOR, enkephalins derive from PPE and bind to the DOR and MOR, dynorphins derive from PPD and bind to the KOR, and orphanins bind to the orphanin receptors.

Positron emission tomography (PET): an *in vivo* imaging technique that requires the administration of radioisotopes; provides indirect information about brain function and neurochemistry based on the molecules the radioisotopes are conjugated to.

Serotonergic system: comprises neurons in the brainstem raphe nuclei which express tryptophan hydroxylase and that synthesize 5-hydroxytryptamine (5-HT), as well as their downstream target neurons that express 5-HT receptors (5-HT_1 to 5-HT_7).

Sham-operated controls: employed in animal studies of metabolic surgical procedures to control for surgical stress; usually entails midline laparotomy and manipulation of the gastrointestinal tract but with no anatomical reconfiguration.

Table 1. Studies Employing Genetic Loss-of-Function Approaches in Mouse Models of RYGB and VSG[a]

Affected pathway	Publication	Procedure	Anatomical rearrangement	Pre-, peri-, and post-operative diet	Genetic model	Body weight (% reduction compared to the sham-operated control group)	Food intake compared to the sham-operated control group	Food choice compared to the sham-operated control group
Gut nutrient-sensing	Mokadem *et al.* 2013 [10]	RYGB	Big gastric pouch, AL 12.5%, BP 12.5%, CC 75%	Two-choice diet (HFD vs NC) preoperatively, liquid diet for 1 week perioperatively, HFD postoperatively	WT (C57BL/6) α-gustducin$^{-/-}$	WT: 29% KO: 40% Postoperative week 5	WT ↔ KO ↓ Cumulative food intake postoperative weeks 1–5	No food-choice data provided
Gut nutrient-sensing	Steensels *et al.* 2017 [106]	RYGB	Small gastric pouch, AL 5 cm, BP 5 cm, CC 12–15 cm	Western diet preoperatively, crushed chow and liquid diet for 3 days perioperatively, Western diet postoperatively	WT (C57BL/6) α-gustducin$^{-/-}$	WT: 35% KO: 20% Postoperative week 7	WT ↓ KO ↔ Cumulative food intake postoperative weeks 1–7	No food-choice data provided
Gut hormone	Mokadem *et al.* 2013 [10]	RYGB	Big gastric pouch, AL 12.5%, BP 12.5%, CC 75%	Two-choice diet (HFD vs NC) preoperatively, liquid diet for 1 week perioperatively, HFD postoperatively	WT (C57BL/6) GLP-1R$^{-/-}$	WT: 29% KO: 25% Postoperative week 5	WT ↔ KO ↓ Cumulative food intake postoperative weeks 1–5	No food-choice data provided
Gut hormone	Ye *et al.* 2014 [11]	RYGB	Small gastric pouch, AL 5–6 cm, BP 6–7 cm, CC 16 cm	HFD preoperatively, no perioperative limitation, NC postoperatively	WT (C57BL/6) GLP-1R$^{-/-}$	WT: 28.5% KO: 30% Postoperative week 10	WT ↑ KO ↔ Average daily food intake postoperative weeks 0–10	WT HFD preference ↓ KO HFD preference ↓ Test details: two-choice diet preference test (HFD vs NC) postoperative weeks 10–16
Adipokine	Hao *et al.* 2015 [29]	RYGB	Small gastric pouch, AL 5–6 cm, BP 6–7 cm, CC 16 cm	HFD preoperatively, no perioperative limitation, NC postoperatively	WT (C57BL/6) *ob/ob*	WT: 33% *ob/ob*: 22% Postoperative week 15	WT ↔ *ob/ob* ↔ Average daily food intake for 3 days at postoperative week 6–7	No food-choice data provided
Adipokine	Mokadem *et al.* 2015 [28]	RYGB	Big gastric pouch, AL 12.5%, BP 12.5%, CC 75%	WT: HFD preoperatively, liquid diet for 1 week perioperatively, HFD postoperatively *ob/ob*: NC preoperatively, liquid diet for 1 week perioperatively, NC postoperatively	*ob/ob*	*ob/ob*: 32% Postoperative week 6	*ob/ob* ↓ Average daily food intake postoperative weeks 2–5	No food-choice data provided When challenged with HFD at postoperative weeks 7–8, compared to NC RYGB-operated mice, average food intake in RYGB-operated mice ↑
Hepatokine	Morrison *et al.* 2016 [107]	RYGB	Small gastric pouch, AL 5–6 cm, BP 6–7 cm, CC 16 cm	Two-choice diet (HFD vs NC) preoperatively, no perioperative limitation, two-choice diet (HFD vs NC) postoperatively	WT (C57BL/6) FGF21$^{-/-}$	WT: 38% KO: 31% Postoperative week 10	WT ↓, ↔, ↔ KO ↓, ↔, ↔ Average daily food intake postoperative weeks 0–1, 2–6, 7–11	WT NC preference ↓ KO NC preference ↓ Test details: two-choice diet preference test (HFD vs NC) postoperative weeks 7–8
		RYGB						

Table 1. (continued)

Affected pathway	Publication	Procedure	Anatomical rearrangement	Pre-, peri-, and post-operative diet	Genetic model	Body weight (% reduction compared to the sham-operated control group)	Food intake compared to the sham-operated control group	Food choice compared to the sham-operated control group
Brain neurotransmitter receptor	Hatoum *et al*. 2012 [30]		Big gastric pouch, AL 12.5%, BP 12.5%, CC 75%	WT: HFD preoperatively, liquid diet for 2 weeks perioperatively, HFD postoperatively $MC4R^{-/-}$: NC preoperatively, liquid diet for 2 weeks perioperatively, NC postoperatively	WT (C57BL/6) $MC4R^{-/-}$	WT: 30% KO: 21% Postoperative week 9	No food intake data provided	No food choice data provided
Brain neurotransmitter receptor	Zechner *et al*. 2013 [31]	RYGB	Big gastric pouch, AL 12.5%, BP 12.5%, CC 75%	WT: HFD preoperatively, liquid diet for 1 week perioperatively, with 0.25 g HFD thereafter until entirely consumed, HFD postoperatively $MC4R^{-/-}$: NC preoperatively, liquid diet for 1 week perioperatively, with 0.25 g HFD thereafter until entirely consumed, NC postoperatively	WT (C57BL/6) $MC4R^{-/-}$ $MC4R^{-/+}$ ChAT-$MC4R^{-/-}$ Phox-$MC4R^{-/-}$	WT: 27% $MC4R^{-/-}$: 10% $MC4R^{-/+}$: 25% ChAT-$MC4R^{-/-}$: 27% Phox-$MC4R^{-/-}$: 8% Postoperative week 6	WT ↔ $MC4R^{-/-}$ ↔ $MC4R^{-/+}$ ↓ ChAT-$MC4R^{-/-}$ ↓ Phox-$MC4R^{-/-}$ ↔ Average daily food intake postoperative weeks 2–6	No food-choice data provided When challenged with HFD at postoperative weeks 8–9, compared to $MC4R^{-/+}$ RYGB-operated mice, food intake in $MC4R^{-/-}$ RYGB-operated mice ↑
Brain neurotransmitter receptor	Carmody *et al*. 2015 [13]	RYGB	Big gastric pouch, AL 12.5%, BP 12.5%, CC 75%	HFD preoperatively, liquid diet for 2 weeks perioperatively, HFD postoperatively	WT (C57BL/6) 5-$HT2CR^{-/-}$	WT: 33% KO: 30% Postoperative week 8	WT ↔ KO ↔ Average daily food intake postoperative weeks 2–6	No food-choice data provided
Gut nutrient-sensing	Mul *et al*. 2014 [108]	VSG	Resection of 80% of the stomach	HFD preoperatively, liquid diet for 3 days postoperatively, HFD postoperatively	WT (C57BL/6) $Mogat2^{-/-}$	WT: 26% KO: 28% Postoperative week 16	No food intake data provided	No food choice data provided
Gut nutrient-sensing	Pressler *et al*. 2015 [109]	VSG	Resection of 80% of the stomach	HFD preoperatively, liquid diet for 3 days postoperatively, HFD postoperatively	WT (C57BL/6) ApoA-$IV^{-/-}$	WT: 8% KO: 13% Postoperative week 10	WT ↔ KO ↔ Average daily food intake for 4 days at postoperative week 8–9	WT fat preference ↓ KO fat preference ↔ WT carbohydrate preference ↔ KO carbohydrate preference ↑ WT protein preference ↑ KO protein preference ↔ Test details: three-choice diet preference test (fat vs carbohydrate vs protein) for 4 days on postoperative week 8–9
Gut hormone		VSG						

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Table 1. (continued)

Affected pathway	Publication	Procedure	Anatomical rearrangement	Pre-, peri-, and post-operative diet	Genetic model	Body weight (% reduction compared to the sham-operated control group)	Food intake compared to the sham-operated control group	Food choice compared to the sham-operated control group
	Wilson-Pérez *et al*. 2013 [110]		Resection of 80% of the stomach	HFD preoperatively, liquid diet for 3 days postoperatively, HFD postoperatively	WT (C57BL/6) GLP-1r$^{-/-}$ (homozygous floxed GLP-1r; CMV–cre)	WT: 13% KO: 15% Postoperative week 7	WT ↓, ↔ KO ↓, ↔ Average daily food intake for 3 days postoperative weeks 0–1 and 5–6	WT fat preference ↓ KO fat preference ↓ WT carbohydrate preference↑ KO carbohydrate preference ↑ WT protein preference ↑ KO protein preference ↔ Test details: three-choice diet preference test (fat vs carbohydrate vs protein) for 4 days on postoperative weeks 2–4
Gut hormone	Garibay *et al*. 2016 [111]	VSG	Resection of 70% of the stomach	HFD preoperatively with last 4 days liquid diet, liquid diet 14 days perioperatively, HFD postoperatively	WT (C57BL/6) GLP-1r$^{\beta-cell-/-}$	WT: 10% KO: 10% Postoperative week 6	WT ↓ KO ↓ Cumulative food intake postoperative weeks 2–6	No food choice data provided
Gut hormone	Chambers *et al*. 2013 [112]	VSG	Resection of 80% of the stomach	HFD preoperatively, liquid diet for 3 days perioperatively, HFD postoperatively	WT (C57BL/6) ghrelin$^{-/-}$	WT: 18% KO: 15% Postoperative week 10	WT ↓ KO ↓ Cumulative food intake postoperative weeks 1–6	WT fat preference ↓ KO fat preference ↓ WT carbohydrate preference ↑ KO carbohydrate preference ↑ WT protein preference ↔ KO protein preference ↔ Test details: three-choice diet preference test (fat vs carbohydrate vs protein) for 6 days on postoperative week 4–5
Bile acid signaling	Ryan *et al*. 2014 [113]	VSG	Resection of 80% of the stomach	HFD preoperatively, liquid diet for 3 days perioperatively, HFD postoperatively	WT (C57BL/6) FXR$^{-/-}$	WT: 23% KO: 0% Postoperative week 14	WT ↓, ↔ KO ↓, ↑ Cumulative food intake postoperative weeks 0–3 and 4–8	WT Fat preference ↓ KO fat preference ↔ WT carbohydrate preference ↔ KO carbohydrate preference ↔ WT protein preference ↔ KO protein preference ↔ Test details: three-choice diet preference test (fat vs carbohydrate vs protein) for 6 days on postoperative week 10–11

Table 1. (continued)

Affected pathway	Publication	Procedure	Anatomical rearrangement	Pre-, peri-, and post-operative diet	Genetic model	Body weight (% reduction compared to the sham-operated control group)	Food intake compared to the sham-operated control group	Food choice compared to the sham-operated control group
Bile acid signaling	Myronovych *et al*. 2014 [114]	VSG	Resection of 80% of the stomach	HFD preoperatively, liquid diet for 1 week perioperatively, HFD postoperatively	WT (C57BL/6) $SHP^{-/-}$	WT: 25% KO: 25% Postoperative week 8	WT ↓, ↓, ↔ KO ↓, ↓, ↔ Average daily food intake postoperative weeks 0–1, 1–2, 2–8	No food choice data provided
Bile acid signaling	Ding *et al*. 2016 [115]	VSG	Resection of 80% of the stomach	HFD preoperatively, liquid diet for 3 days perioperatively, HFD postoperatively	WT (C57BL/6) $Tgr5^{-/-}$	WT: 27% KO: 8% Postoperative week 14	WT ↓, ↓, ↔ KO ↓, ↓, ↔ Average daily food intake postoperative weeks 0–1, 1–2, 2–14	No food choice data provided
Bile acid signaling	McGavigan *et al*. 2017 [116]	VSG	Resection of 70% of the stomach	HFD preoperatively with last 4 days liquid diet, liquid diet 14 days perioperatively, HFD postoperatively	WT (C57BL/6) $Tgr5^{-/-}$	WT: 29% KO: 29% Postoperative week 25	WT ↓ KO ↓ Cumulative food intake postoperative weeks 2–25	No food choice data provided
Central circadian rhythm	Arble *et al*. 2015 [117]	VSG	Resection of 80% of the stomach	HFD preoperatively, liquid diet for 3 days perioperatively, HFD postoperatively	WT (C57BL/6) $Clock\Delta^{19}$	WT: 10% KO: 10% Postoperative week 7	WT ↓ KO ↓ Cumulative food intake postoperative weeks 1–7	No food choice data provided
Central circadian rhythm	Arble *et al*. 2016 [118]	VSG	Resection of 80% of the stomach	HFD preoperatively, liquid diet for 3 days perioperatively, HFD postoperatively	WT (C57BL/6) $Magel2^{-/-}$	WT: 22% KO: 22% Postoperative week 10	WT ↔ KO ↔ Cumulative food intake postoperative weeks 1–10	WT Fat preference ↓ KO fat preference ↓ WT carbohydrate preference↑ KO carbohydrate preference ↑ WT protein preference ↔ KO protein preference ↔ Test details: three-choice diet preference test (fat vs carbohydrate vs protein) for 5 days on postoperative week 13–14

[a]Symbols and abbreviations: ↑, increased; ↔, no change; ↓, reduced; AL, alimentary limb; BP, biliopancreatic limb; CC, common channel; HFD, high-fat diet; NC, normal chow; KO, knockout; RYBG, Roux-en-Y gastric bypass; VSG, vertical sleeve gastrectomy; WT, wild-type.

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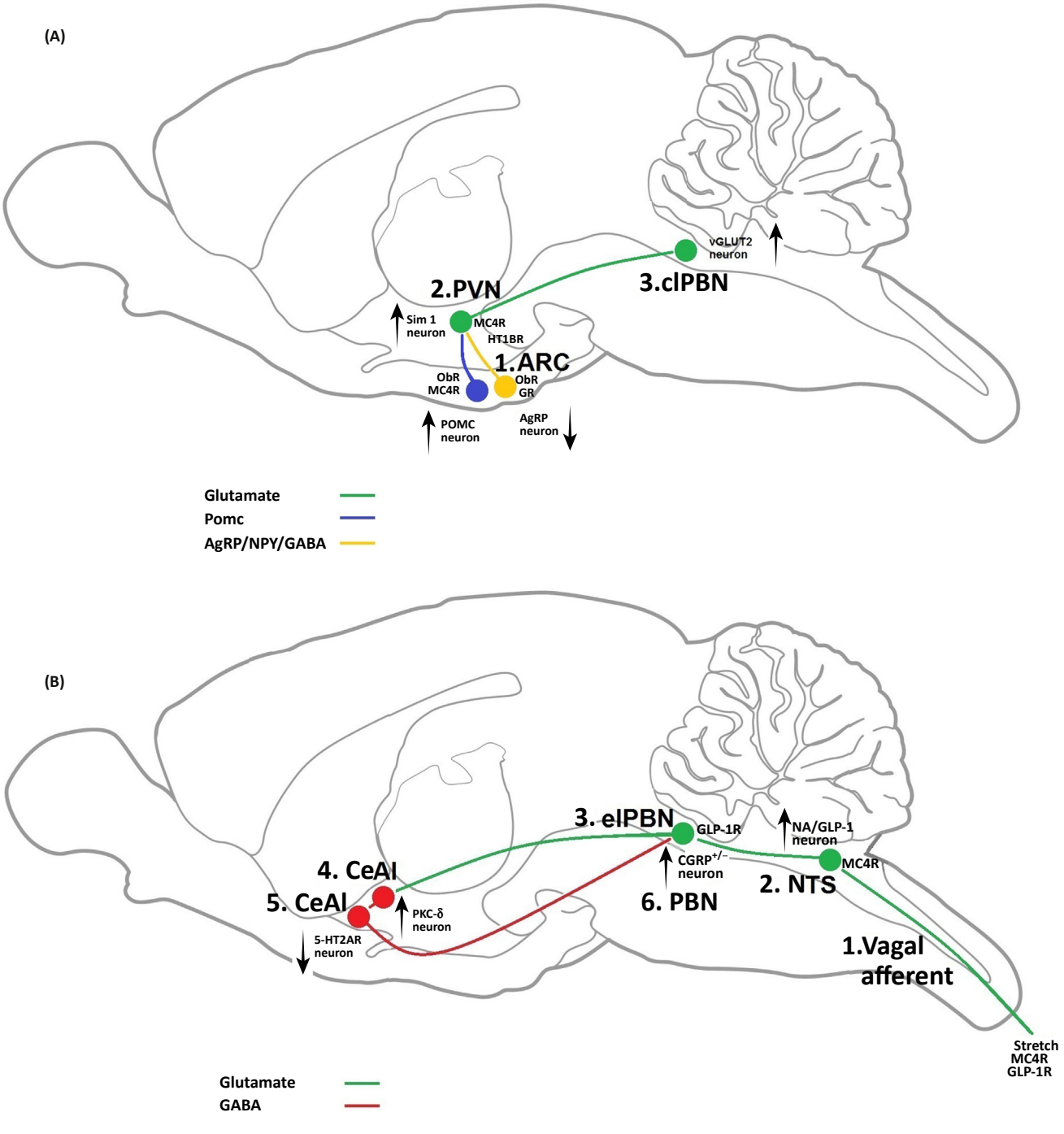


Figure 1. Exaggerated Activation of Homeostatic Feeding Circuits after Roux-en-Y Gastric Bypass (RYGB). (A) (1) The expansion of gut *E. coli* after RYGB [16–18] may result in greater circulating levels of peptide agonists of the MC4R expressed in arcuate nucleus of the hypothalamus (ARC) POMC neurons [36,37]. In ARC AgRP neurons projecting to the hypothalamic paraventricular nucleus (PVN), the increased 5-HT_{1B} receptor levels [44] could inhibit AgRP release [40], as could the decreased levels of circulating ghrelin [15,66,119] and increased levels of circulating $PYY_{3–36}$ [15,120]. Enhanced hypothalamic leptin receptor signaling would serve to both tonically stimulate POMC and inhibit AgRP [24,120]. (2) PVN MC4R-containing neurons projecting to (3) vesicular glutamate transporter 2 (vGLUT2)-expressing neurons in the brainstem lateral parabrachial nucleus (clPBN) would in turn become more active, contributing to increased satiety [19]. (B) In parallel, at least during the

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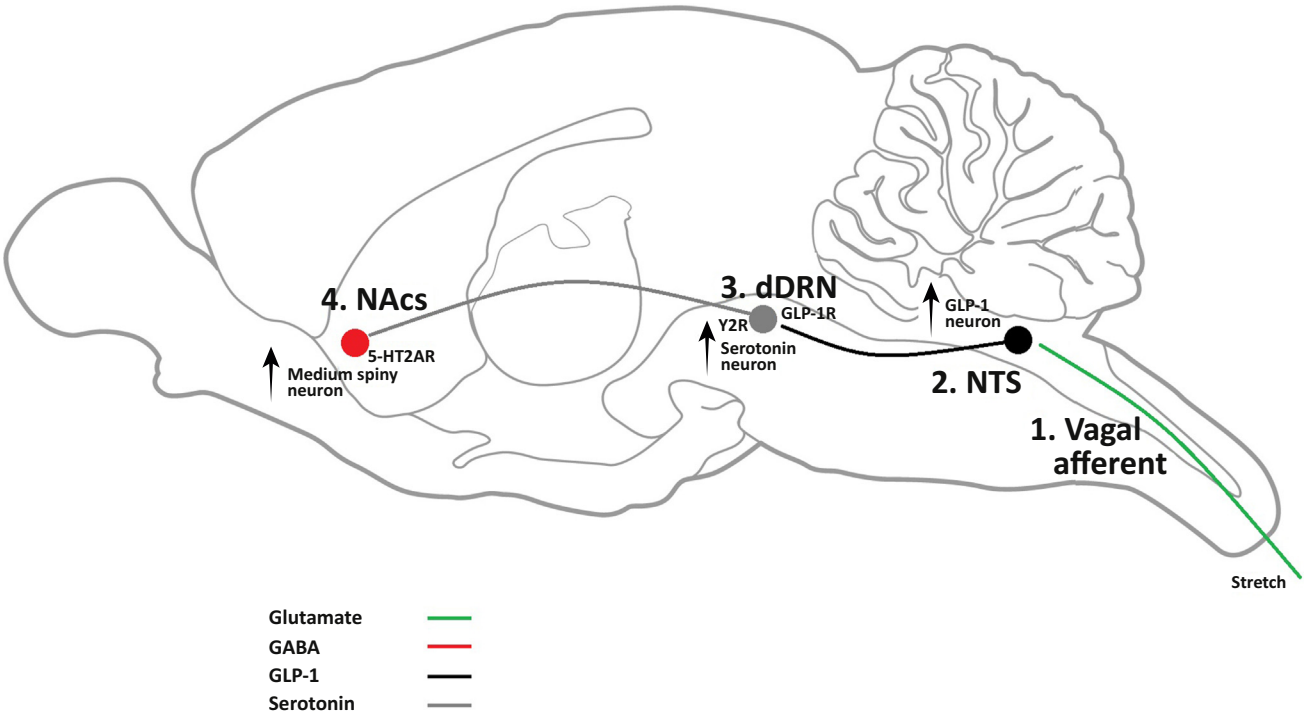


Figure 2. Enhanced Brain Serotonergic Signaling after Roux-en-Y Gastric Bypass (RYGB). Serotonergic neurons in the dorsal aspect of the dorsal raphe nucleus (dDRN) could be more active after RYGB either by (1) vagal afferents stimulated by gastric stretch which (2) excite GLP-1-containing neurons in the nucleus tractus solitarius (NTS) which project to the dDRN, and/or by the exaggerated levels of circulating GLP-1 and $PYY_{3–36}$ that signal via GLP-1Rs and Y2Rs, respectively [15,52,53,123]. (3) Serotonergic dDRN neurons projecting to the nucleus accumbens shell (NAcs) would then cause (4) increased 5-HT_{2A} receptor signaling in medium spiny GABAergic neurons, their depolarization, and suppression of feeding. GLP-1 receptor agonists and $PYY_{3–36}$ both markedly depolarize serotonergic DRN neurons, although the mechanisms have not been described [52,53].

what first prompted investigations into the effects of RYGB on brain 5-HT_{2A} receptors. In rats, RYGB selectively reduced 5-HT_{2A} receptor binding in the ventral striatum during weight-loss maintenance [51] which, contrary to obesity, may be due to chronically elevated serotonin levels in this brain region. Again, this could be mediated by enhanced GLP-1 receptor signaling in serotonergic neurons of the dorsal/dorsolateral aspect of the dorsal raphe nucleus (DRN) [52], and/or by another important anorexigenic L cell product enhanced after RYGB, peptide tyrosine-tyrosine 3–36 ($PYY_{3–36}$), acting on Y2 receptors expressed in the same serotonergic cells (Figure 2) [53]. Indeed, direct administration of GLP-1 receptor agonists or $PYY_{3–36}$ into the DRN has been shown to potently suppress food intake in rats and mice, respectively, and to stimulate serotonergic DRN neurons in patch-clamp electrophysiological experiments on brain slices [52,53].

stage of active weight loss [45], (1) vagal afferents and (2) noradrenalin (NA)-(co)containing glutamatergic NTS neurons projecting to (3) CGRP-containing neurons in the elPBN become more active in response food ingestion [45]. These neurons then sequentially recruit (4) protein kinase C-δ (PKC-δ) and (5) 5-HT_{2A} receptor-containing neurons in the central amygdaloid nucleus (CeAl) which could also contribute to increased satiety [46–49]. (6) The majority of anorexigenic parabrachial nucleus (PBN) neurons receiving input from 5-HT_{2A} receptor-containing neurons in the CaAl are negative for CGRP [49]. GLP-1-containing NTS neurons projecting to PBN CGRP neurons and circulating GLP-1 could also feed into this circuit [121–123]. *E. coli* proteins also activate neurons in the CeAl that are innervated by CGRP fibers [36], possibly via presynaptic MC4Rs in the nucleus tractus solitarius (NTS) or indeed on the same glutamatergic vagal afferent nerve endings in the gut [124].

In a subsequent clinical PET imaging study performed by the same group of researchers who originally evaluated the brain serotonergic system in obese subjects, cortical 5-HT_{2A} receptor availability was found not to be significantly modulated by RYGB [54]. However, it did have predictive value, in that those patients with higher cortical 5-HT_{2A} receptor availability preoperatively lost more weight postoperatively [54]. This suggests that those obese individuals with the lowest brain serotonergic tone benefit most from the potentially restorative effects of RYGB, with cortical 5-HT_{2A} receptors playing an active role. Interestingly, the weight loss-maintaining but not the weight loss-inducing effects of chronic central GLP-1 receptor agonist treatment in rats requires brain 5-HT_{2A} receptor signaling [52], which could similarly be the case for RYGB. Because, as with RYGB [26], brain 5-HT_{2C} receptors are dispensable for the effects of peripheral liraglutide treatment on feeding and body weight [52] (Table 1), circulating GLP-1 is further implicated in the outcome of the former on whole-body energy balance.

The Brain Dopaminergic System

In starvation-prone mice with ablated ARC AgRP neurons, chemogenetic activation of brain dopaminergic neurons can sufficiently sustain consumption of a palatable but not regular diet [55], highlighting their role in the control of hedonic feeding. Indeed, it has been widely reasoned that obesity could result from heightened incentivizing/invigorating properties of high-calorie food cues as a result of over-reactivity of mesolimbic dopaminergic circuits (the reward surfeit hypothesis) [56], which in clinical studies is most often assessed by **functional magnetic resonance imaging** (fMRI). An important consideration to make when attempting to understand the burgeoning literature on this subject is that changes in dorsal striatal blood oxygenation-level dependent (BOLD) signal detected by fMRI appear to more sensitively track phasic mesolimbic dopaminergic neuronal activity than that of ventral striatal BOLD signal, as revealed by optogenetic experiments performed on rats [57]. With this in mind, and despite species differences in neuroanatomy, greater dorsal striatal function is generally found in obese human subjects when viewing images of high-calorie foods in cross-sectional fMRI studies [56].

Using similar fMRI study paradigms on patients after RYGB, investigators have reported both reduced ventral tegmental area (VTA) [58] and dorsal striatal [59] function, the latter correlating with the desire to eat high-calorie foods [59]. This could be mediated in part by increased colonic production of the short-chain fatty acid propionate by gut microbiota [60] (specifically *Akkermansia muciniphila*) [17], and is reversed by blocking GLP-1 and $PYY_{3–36}$ release from L cells with octreotide [61] as well as by a GLP-1 receptor antagonist [62]. Furthermore, patients exhibit a lower breakpoint to obtain a food reward in a progressive ratio task postoperatively, which is also reversed by acute octreotide treatment [63]. Thus, RYGB could lower overall caloric intake in part by reducing the incentivizing/invigorating effects of high-calorie food cues through dampening mesolimbic dopaminergic signaling by a combination of different mechanisms (Figure 3A) during both the active weight-loss [58,59,61,62] and weight loss-maintenance [63] phases. Notably, this may not be the case for VSG because patients do not show attenuation in VTA function in response to viewing high-calorie food images [58].

It should be mentioned that the human behavioral findings described above have not been replicated in animals using tests of similar construct validity. Specifically, rats after RYGB have been found to traverse through a runway task to obtain a sweet-tasting food reward with fewer distractions compared to obese sham-operated controls in one study [64], and to show no changes in motivation in-progressive ratio 'dry-lick' tasks for sucrose or lipid rewards [65] in another. The species differences reiterate how animal models of RYGB can fall short of fully recapitulating the complex neural and behavioral effects of the procedure [7,8]. Nevertheless, future studies implementing an appropriate weight-loss control group could potentially reveal

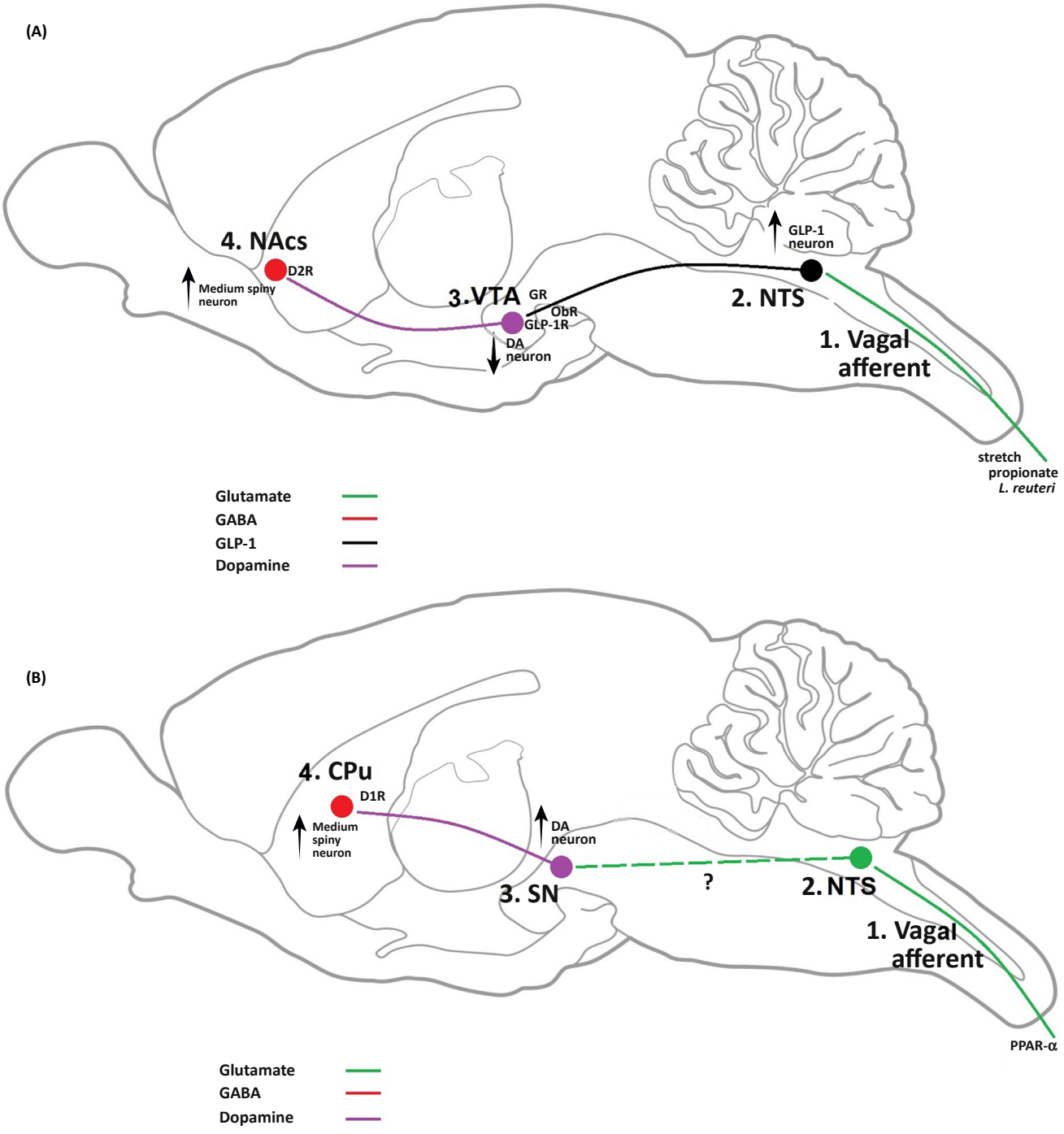


Figure 3. Dampened Mesolimbic but Augmented Nigostriatal Dopaminergic (DA) Signaling after Roux-en-Y Gastric Bypass (RYGB). (A) DA neurons in the ventral tegmental area (VTA) could be inhibited after RYGB either by (1) vagal afferents stimulated by gastric stretch which (2) excite GLP-1-containing neurons in the nucleus tractus solitarius (NTS) which project to the VTA, by the exaggerated levels of circulating GLP-1, restored leptin receptor signaling, and/or by the reduced circulating ghrelin levels [15,66–69,123]. Reduced *L. reuteri* products and increased A. *muciniphila* products (propionate) in the gut would also negatively modulate this pathway [17,18,60,70]. (3) This would in turn lead to reduced dopamine release in the nucleus accumbens shell (NAcs). The inhibition of VTA DA neurons by GLP-1 could be mediated by presynaptic GLP-1 receptors which suppress and potentiate glutamate and GABA release from afferent terminals, respectively [67]. Similarly, the

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whether RYGB prevents the increased motivational value of high-calorie food cues that forms another part of the starvation response of the brain. Interestingly, complementing the reduced VTA tyrosine hydroxylase expression found in rats after RYGB [22], patch-clamp electrophysiological analysis of VTA dopaminergic neuronal activity in rat brain slices revealed that, in contrast to chronic caloric restriction, RYGB occludes the inhibitory effect of a ghrelin receptor antagonist on action potential frequency [66]. These latter results suggest that the reduction of circulating ghrelin levels after RYGB [15,66] serves to tone down the function of the mesolimbic dopaminergic pathway, which could work in concert with increased GLP-1 receptor [67] and restored leptin receptor signaling in the VTA [68,69], as well as with reduced gut *Lactobacillus reuteri* abundance [18,70] (Figure 3A).

A complex quadratic relationship between striatal dopamine 2 receptor (D2R) availability and BMI has been shown to exist from numerous clinical PET and single photon emission computed tomography (SPECT) imaging studies implementing a variety of D2R radioligands [71]. Consequently, it was widely predicted that RYGB may alter striatal D2R availability to impact on the hedonic aspects of feeding and body weight. Although preliminary studies hinted at such during a very early stage of active weight loss (6 weeks postoperatively) [72,73], this was later shown not to be the case in better powered studies performed on patients at 6 months postoperatively [74,75]. However, in a follow-up study performed on patients at a stage of weight-loss maintenance after RYGB (at least 2 years postoperatively), striatal D2R availability was indeed found to increase, approaching the levels in lean controls [76]. Although no correlation was noted between changes in striatal D2R availability and BMI [76], future larger-scale studies could reveal if there is a correlation. This would shed some light on the reasons for weight regain in a significant number of individuals who undergo RYGB (as many as 50% historically) [77]. Notably, the lack of a change in striatal D2R availability in patients early after RYGB is more in line with more recent genetic findings in mice on their traditional role in controlling physical activity (and not susceptibility to hedonic feeding and developing obesity) [78] which, correspondingly, is unaffected in patients at the early 9 month stage postoperatively [79].

An alternative/complementary perspective to the reward surfeit model is that diminished striatal dopaminergic signaling in response to food receipt leads to compensatory overeating and weight gain (the reward deficit hypothesis) [56]. Such a change of direction in striatal dopaminergic signaling in obesity actually aligns well with the potentiating and weight loss-independent effects of RYGB on dorsal striatal dopamine concentrations reported in animal investigations [80,81]. Dopamine release measured by *in vivo* cerebral microdialysis was found to be most pronounced after consumption of a high-fat meal in rats, and to be mediated by the vagus nerve [81]. Moreover, the markedly suppressed high-fat emulsion intake postoperatively was fully reversed by blocking intestinal peroxisome proliferator associated receptor α (PPAR-α) and vagus nerve signaling at one end, and dorsal striatal D1R signaling at the other [81]. These effects were not seen in obese or body weight-matched sham-operated animals, suggesting that intestinal reconfiguration itself causes the more efficient metabolism of ingested fat into endogenous PPAR-α agonists in enterocytes, which in turn is transmitted to the nigrostriatal dopaminergic pathway by sensory vagal afferent neurons. Dorsal striatal D1Rs then contribute to limit further high-fat emulsion intake as part of a negative feedback loop first

inhibition of VTA DA neurons by leptin could be mediated by presynaptic leptin receptor and Janus kinase–STAT3 signaling which suppress glutamate release from afferent terminals [69]. (B) Dopaminergic neurons of the substantia nigra pars compacta (SN) are stimulated by fat ingestion after RYGB by (1) activation of vagal afferents through PPAR-α [81]. Via as yet uncharacterized projections from the (2) NTS, (3) dopaminergic SN neurons are recruited. Ultimately, (4) D1R-containing neurons in the caudate putamen (CPu) suppress further fat intake [81].

discovered in mice (Figure 3B) [81,82]. Remarkably, additional experiments revealed that this same gut–striatal D1R pathway promotes the intake of low-fat emulsion postoperatively [81], which is again in line with the original findings obtained from obese mice supplemented with the natural PPAR-α agonist oleoylethamide (OEA) [82]. This might explain the shift in preference from high- to low-fat foods consistently observed after RYGB in animal studies [15,17,64–66,81]. A learned aversion to [83] or avoidance of [84] fatty foods, which involve separate brain pathways, could also play a role in the altered food choice.

The Brain Opioidergic System

A rich heritage of pharmacological and molecular studies has, perhaps more than any other system, implicated brain opioid receptors in the control of hedonic feeding, although the underyling brain circuits have not yet been as precisely mapped using modern neuroscientific techniques as the others mentioned in this Review. Nevertheless, striatal/prefrontal μ-opioid receptors (MORs) in particular have consistently been demonstrated to positively regulate fat and sugar intakes [85,86], the 'appetitive-driver' arm of top-down executive control [86], the sensory pleasantness or so-called 'liking' of sucrose solutions [87], as well as the incentive salience or so-called 'wanting' of food [87] in rats. Genetic deletion of β-endorphin and the more widely distributed enkephalins, both of which are endogenous MOR agonists, has further been shown to lower 'liking' and 'wanting' of sucrose solutions based on detailed microstructural intake analysis in mice [88]. It therefore comes as no surprise that the effects of RYGB on brain MOR signaling has received attention in recent human and animal PET imaging investigations with the selective MOR radioligand [^{11}C]-carfentanil.

Providing the foundation for the human study were the initial [^{11}C]-carfentanil PET imaging findings that brain MOR availability is markedly decreased in various limbic and cortical regions in obesity, such as the thalamus, striatum, amygdala, and insular, orbitofrontal, and cingulate cortices [89]. This was proposed to be an adaptive change caused by a chronic increase in brain opioid (presumably enkephalin) release from overconsumption of palatable, calorically dense foods as part of a positive feedback loop first characterized in rats [90]. The strong negative correlations registered between MOR availability and BMI in both the ventral and dorsal parts of the striatum certainly validate the idea that weight gain is proportional to the amount of opioid release and resultant MOR downregulation in these brain regions [89]. In a subsequent study by the same group of researchers, metabolic surgery (RYGB and VSG) was found to cause a striking widespread normalization of brain MOR availability to the levels in lean participants [75]. According to the logic described above, this would suggest chronically lowered brain opioid release postoperatively and, fittingly, is a pattern of change opposite to that described earlier for the brain serotonergic system. Such changes were not found in obese individuals who experienced a comparable degree of weight loss from 4 months of dieting in a separate study [91]. Together, these results are significant because they provide a pertinent example of a faulty brain feeding system in human obesity that, for all intents and purposes, is essentially 'fixed' specifically by RYGB.

Contrasting with the clinical findings, small-animal [^{11}C]-carfentanil PET imaging revealed a marked weight loss-independent reduction in striatal/frontal cortical MOR availability in rats after RYGB, which was perfectly matched by MOR protein expression and oral high-fat emulsion intake [92]. While not formally tested, the reduced MOR levels postoperatively could possibly be a result of reduced circulating ghrelin levels [15,66,93]. Downstream circuits affected by these changes would converge at the level of orexigenic neuronal populations in the lateral hypothalamus [85,86], a major brain feeding hub which has previously been shown to be another site where RYGB counteracts the starvation response of the brain [22] (Figure 4).

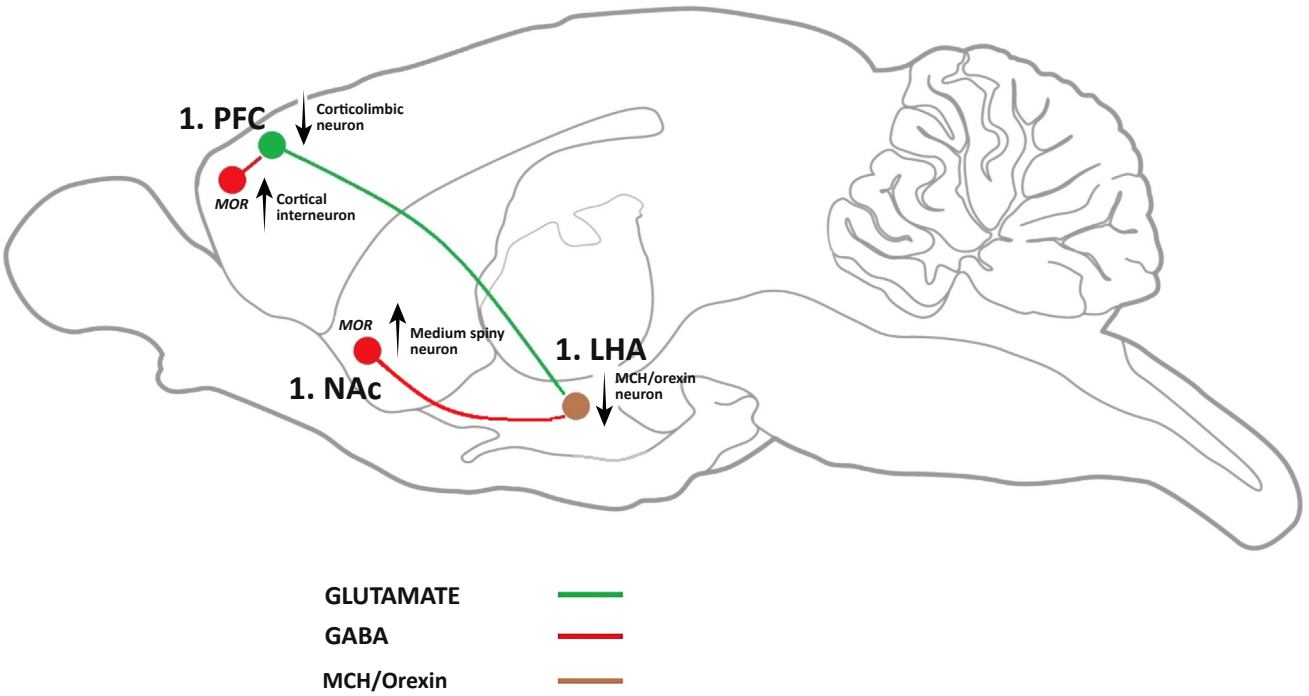


Figure 4. Suppressed Prefrontal Cortical and Ventral Striatal μ-Opioid Receptor (MOR) Signaling after Roux-en-Y Gastric Bypass (RYGB): Potential Effects on Lateral Hypothalamic Area Orexigenic Neurons. Reduced MOR signaling after RYGB [92] in (1) prefrontal cortex (PFC) GABAergic interneurons would lead to their increased excitability [86]. Subsequently, the activity of local projection neurons to the lateral hypothalamic area (LHA) decreases [86]. (2) This would then cause the decreased function of orexigenic melanocortin concentrating hormone (MCH) and/or orexin-containing neurons [22,86]. In parallel, reduced MOR signaling in (1) GABAergic medium spiny neurons of the nucleus accumbens (NAc) would lead to their increased activity, and then (2) decreased function of orexigenic neurons in the LHA [85].

The discrepancies between the clinical and animal [^{11}C]-carfentanil PET imaging findings may be attributable to the different stages after surgery at which they were performed (active weight loss for the human study [75] vs weight-loss stability for the rat study) [92], or could simply be due to species differences in the magnitude of feeding-induced brain opioid release [94], which would conceivably differentially impact on brain MOR dynamics. These issues notwithstanding, as a whole, the human and animal data do consistently suggest that RYGB inhibits striatal/frontal cortical MOR signaling to suppress fat intake [95,96], to negatively modulate local functional responses to viewing high-calorie visual food cues [97], to lower the sensory pleasantness and possibly also to limit the incentive salience of such foods [96–99], as well as to influence executive control functions such as external eating [75], although further mechanistic studies will clearly be necessary to substantiate this. Along these lines, it would be interesting to relate changes in MOR signaling to the enhanced dorsolateral prefrontal cortical function reported specifically in patients with greater weight loss after RYGB [100]. Because this occurred when subjects were asked to actively resist craving for high-calorie food images [100], it suggests increased inhibitory control postoperatively.

Concluding Remarks and Future Perspectives

We have summarized animal and human data showing that pronounced changes in various brain feeding circuits take place after RYGB, and have related this to improvements in feeding behavior. More work will be necessary to determine if these changes are static or dynamic, especially across active weight-loss, weight-stability, and weight-regain phases. Additional

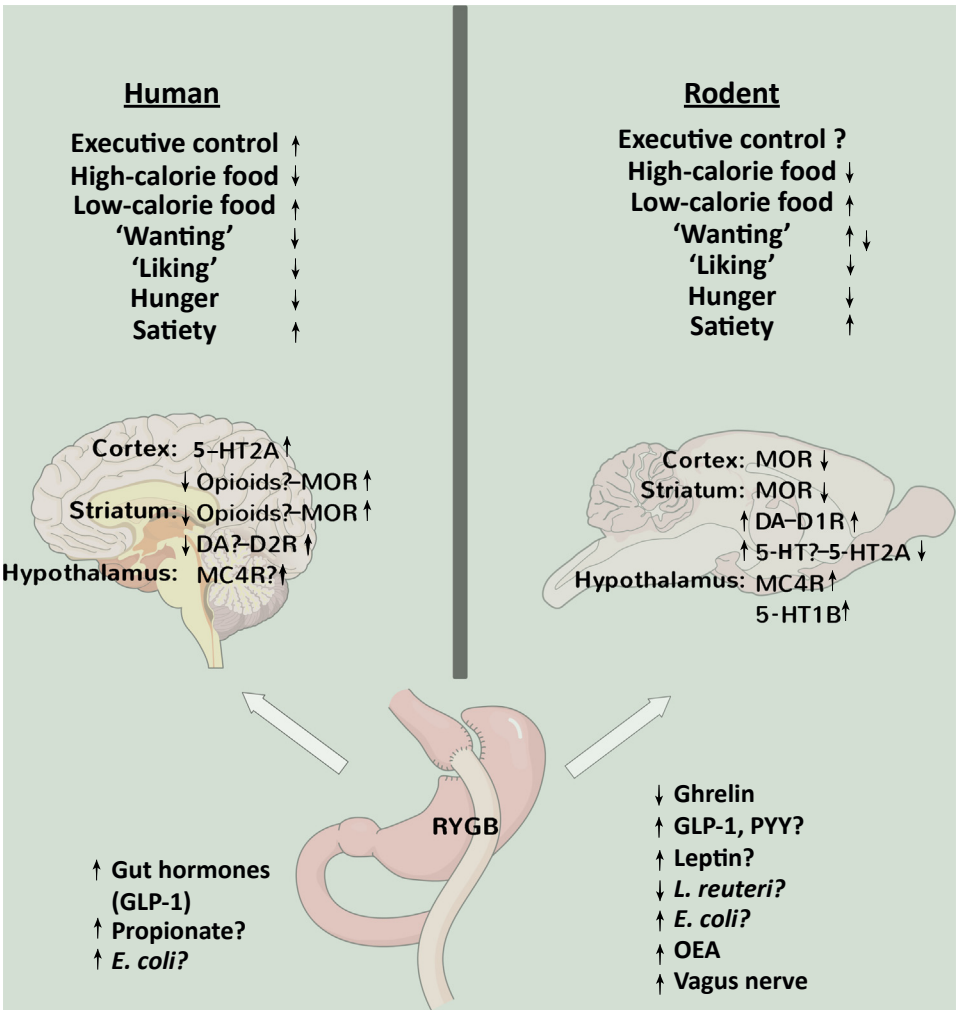


Figure 5. An Altered Central Neurochemical Profile Underlying Changes in Feeding Behavior after Roux-en-Y Gastric Bypass (RYGB). Associative and causative evidence from animals and humans indicate that numerous brain feeding circuits work together to lastingly improve various aspects of feeding behavior after RYGB. The gut factors that could be responsible for this are shown. For the human dopaminergic and opioidergic systems, a chronic decrease in dopamine and endogenous opioid release may account for the upregulated D2R [76] and μ-opioid receptor (MOR) [75] levels found after RYGB, respectively. Conversely, for the rodent serotonergic system, a chronic increase in 5-HT release may account for the downregulated 5-HT_{2A} receptor levels [51] found after RYGB. An exception to this rule appears to exist for the rodent dopaminergic system, in which increases in feeding-induced dopamine release are associated with upregulated D1R levels [81] for reasons that remain unclear. Symbols and abbreviations: ↑, increased; ↔, no change; ↓, reduced; OEA, PPAR-α agonist oleoylethamide.

brain feeding circuits, such as those recruited by endocannabinoids (ECs), deserve future consideration. This is especially because a convincing progressive reduction in hypothalamic EC signaling has previously been shown in rats after VSG [101], and because chronic (1 week) treatment with the selective cannabinoid 1 receptor (CB1R) antagonist rimonabant has been shown to lower striatal BOLD signal in response to viewing images of chocolate in a human fMRI study [102], again analogous to the effects of RYGB. Furthermore, a good CB1R radioligand has already been developed and effectively tested in a clinical pharmacological

weight-loss trial [103], and which could potentially be used in future PET imaging investigations on obese patients before and after surgery.

Despite tremendous progress in the field in recent years, to date no single long-term interventional study has definitively characterized a central molecular determinant of the negative whole-body energy balance induced by RYGB (Table 1). Work on neuron-specific knockout/knockdown and ablation models in animals can bridge this gap in knowledge. Chemogenetic and optogenetic techniques that allow fine temporospatial control of neuronal activity *in vivo* will also prove to be valuable in determining causative roles of specific brain feeding circuits. This has already been applied to good effect in a duodenal–jejunal bypass mouse model in the context of maladaptive habitual sugar consumption [104]. Given the general lack of success with targeting individual pathways (Table 1), targeting multiple pathways may be necessary to yield further insight.

It is hoped that a more complete description of brain feeding circuits affected by RYGB will aid in the development of noninvasive alternatives. Given that studies to date suggest that RYGB promotes hypothalamic MC4R, ventral striatal/cortical 5-HT_{2A} receptor, and dorsal striatal D1R signaling, and to generally suppress brain MOR signaling (Figure 5), a combinatorial pharmacological treatment to that effect may cause marked and lasting weight loss through modified feeding behaviors that ultimately amount to reduced caloric intake. Key to the success of this approach would be the timing and tailoring of specific drug combinations. It is noteworthy that the slow-release bupropion and naltrexone hybrid compound, which has recently been approved for the treatment of obesity, may at least partially mimic RYGB (through MOR antagonism and dopamine transporter blockade, with concomitant enhancement in ARC POMC neuron function) [105]. That only comparably modest weight loss is caused by this drug attests to the fact that additional brain feeding circuits are targeted by RYGB. Considering that the delivery of compounds to discrete brain regions remains technically demanding, further characterization of changes in gut–brain communication after metabolic surgery may more readily facilitate attainment of a healthier neurochemical profile in obese subjects (see Outstanding Questions).

Outstanding Questions

To what extent is the retained efficacy of RYGB in lowering body weight in germline GLP-1 receptor-deficient mice due to developmental compensation/redundancy in the system? Would postoperative tissue-specific deletion of the GLP-1 receptor yield any insight?

Can techniques such as deep brain imaging reveal the activation status of ARC POMC/AgRP neurons in mice after RYGB under various feeding conditions? What would be the effect of inhibiting or ablating ARC POMC neurons? Conversely, what would be the effect of stimulating ARC AgRP neurons?

Would blocking brain 5-HT_{2A} receptor signaling reverse the effects of RYGB on feeding and body weight? Does RYGB increase brain serotonergic tone, and is this due to enhanced GLP-1 receptor and/or Y2 receptor signaling within dorsal raphe neurons? What would be the effect of inhibiting/ablating serotonergic dorsal raphe neurons? Similarly, what would be the effect of inhibiting/ablating CGRP neurons of the PBN at specific stages postoperatively?

Does RYGB reduce endogenous brain opioid release in response to the intake of a palatable meal? What would be the underlying mechanisms? Would acute MOR agonist injections into the striatum reverse the suppressed sucrose/lipid intake? Would chronic treatment cause weight regain by increasing palatable food intake?

What would be the metabolic phenotype of germ-free animals subjected to RYGB? How would brain feeding circuits be affected in these animals? Similarly, what would be the metabolic effects of antibiotic treatment on previously RYGB-operated subjects?

How are more recently identified brain feeding circuits, such as those containing anorexigenic cholinergic neurons of the basal forebrain, and ghrelin-responsive, fat intake-promoting GABAergic neurons of the zona incerta, affected by RYGB? Can RYGB be used as an experimental tool to discover new brain feeding circuits?

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