

**Review Article**

# Gastric Bypass Surgery Regulates Glucose Homeostasis Through the Hypothalamus

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**Abstract:** To explore the role of blood glucose regulation in gastric bypass surgery is a hot point in the treatment of diabetes in recent years. Current evidence is very clear that the gastric bypass surgery is one of the most promising therapy to cure type 2 diabetes. However, the mechanisms are not yet understood. Studying the mechanism of surgical treatment can not only understand the pathogenesis of diabetes, but also have important scientific and practical significance for clinically and safely carrying out this therapy. As is known to all, the body's energy metabolism and glucose homeostasis are regulated by the hypothalamus. Thus, we summarize the process mechanism of central regulation of glucose homeostasis in post-surgery and find that the hypothalamus after gastric bypass surgery showed enhanced expression of peripheral signal receptors, enhancement of leptin signal and insulin signal, and expression changes of certain related genes, then issued neuroendocrine signals to control peripheral insulin sensitivity and glucose metabolism. Then, we prove that the improvement of peripheral metabolic status is caused by the decisive role of central regulation in post-surgery. These findings provide scientific basis to improve the understanding of the neuroendocrine mechanism of diabetes and the development of clinical implication of gastric bypass surgery.

**Keywords:** Gastric Bypass Surgery, Hypothalamus, Glucose Homeostasis, Neuroendocrine, Diabetes

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## 1. Introduction

So far, the role of blood glucose regulation in gastric bypass surgery is unquestionable. RYGB has been the gold standard for bariatric surgery for many years, furthermore, its long-term beneficial results in T2DM are far superior to those obtained by other bariatric surgery [1], and no major late surgical complications have been reported for at least 5 years [2]. A 12-year observational prospective follow-up study of Roux-en-Y gastric bypass surgery in the United States show that Surgery can effectively alleviate and prevent type 2 diabetes in the long term [3]. The benefits of metabolic surgery should be considered as the improvement of the entire "metabolic state". For many years, most of the researches on the treatment mechanism have searched for answers in the periphery, and there is a lot of evidence for improving peripheral metabolism. However, they are not able

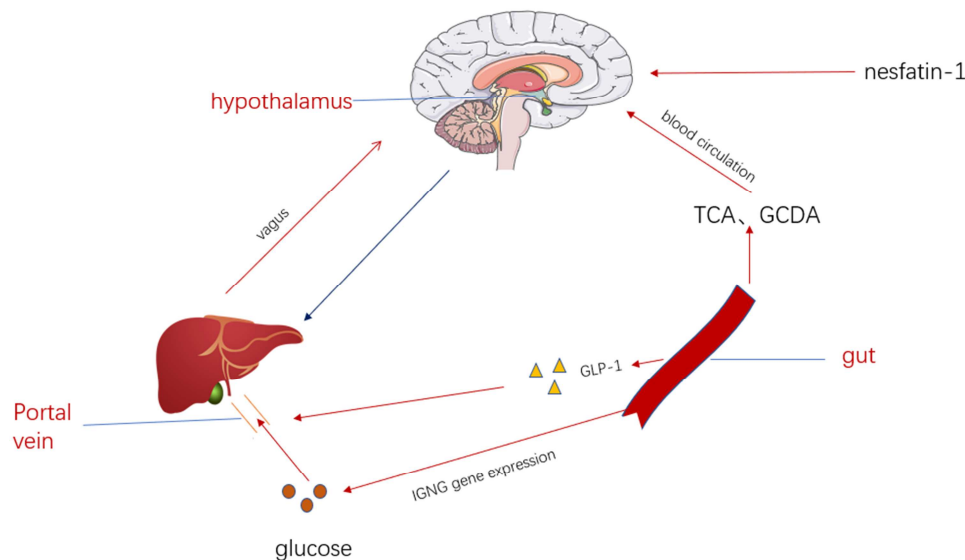
to clarify the mechanism of these changes. It is regrettable that there are few studies in the brain. Most people don't realize the "decisive role" of the central nervous system after surgery. For example, in rats with hypothalamic Ventromedial nucleus (VMH) knockdown of IR, the improvement in peripheral metabolism caused by surgery is not obvious [4]. Leptin, a hormone involved in food intake and energy metabolism control of the body and the signal regulation of glucose and insulin, its receptors are expressed in the brain, and there are almost no targets in the periphery. Therefore, we hypothesized that the brain, especially the hypothalamus, acts as a receiving station that integrates a series of peripheral signals and then responds accordingly to maintain the glucose homeostasis [5].

## 2. Central Receptor Expression and Insulin Signal Enhancement

### 2.1. GLP-1—Hindbrain—Hypothalamus

One week after surgery, the post-prandial glucagon-like peptide 1 (GLP-1) response was increased [6], and four weeks after surgery, the level of GLP-1 in the body was significantly higher than that before surgery [7]. Some studies have shown that food directly stimulates the distal intestine to increase the secretion of GLP-1 (see figure 1) after RYGB [8]. Meanwhile, It has also been observed that intestinal putrescine transport increases 2 weeks after RYGB [9]. Microbial treatment of putrescine can produce gamma-aminobutyric acid (GABA), this is an inhibitory neurotransmitter founded in the mammalian central nervous system and is thought to stimulate intestinal cells to release GLP-1 [10]. A 6-week postoperative study demonstrated that deoxycholate-TGR5-mTORC1 signal enhancement contributes to up-regulation of GLP-1 production [11]. An increase in the density of cell population producing incretin (GLP-1 cells, GIP cells, and peptide YY immunoreactive cells) in the jejunum was observed 12 months after RYGB, which provide an anatomical explanation for the increase in

GLP-1 plasma levels observed after surgery [12]. GLP-1 was also found to be produced by a small fraction of nerve cells in the brain stem nucleus tractus solitarius (NTS), which is released as a neuroregulatory in the brainstem and hypothalamus [13]. Local injection of GLP-1 into the arcuate nucleus of the hypothalamus reduces hepatic glucose production, and local injection of hypothalamic paraventricular nucleus inhibits food intake [14]. At the same time, it has been proved that the expression of GLP-1 receptor is up-regulated after gastric bypass (see figure 3), and the expression of GLP-1R mRNA in hypothalamus is negatively correlated with blood glucose level [15]. Peripheral glucose balance may be regulated by activation of the hypothalamic GLP-1R receptor after gastric bypass surgery. Infusion of GLP-1 in the portal vein induces neuronal-mediated insulin secretion by promoting the introduction of hepatic vagus nerve into the central [16]. The afferent nerve signal reaches the brain through the NTS and the area postrema (AP) [17]. The NTS receives input from the afferent nerve of the vagus nerve, while the AP is the target of circulating factors such as islet amyloid polypeptide (IAPP) and GLP-1 [18]. A series of effects of GLP-1 are ultimately achieved through conduction to the central receptor.



**Figure 1.** Peripheral signal transmission to the central nervous system after RYGB.

### 2.2. Central Bile Acid Signal

Human and animal studies have confirmed an increase in total bile acid concentration after fasting or postprandial one or two weeks after RYGB surgery [19], and expression of the G protein-coupled bile acid receptor (GPARB, TGR5) in the intestine increased 3 months after RYGB [20]. In the liver and intestine, most of the bile acids are transmitted mainly through the farnesoid X receptor (FXR) and TGR5. Peripheral activation of bile acid signaling can inhibit hepatic glycogen breakdown [21], reduce inflammation [22], activate macrophage [23], and improve pancreatic function [24]. For example, bile acid TUDCA enhances insulin secretion via the

cAMP / PKA pathway [25]. Male mice have impaired insulin sensitivity in TGR5 knockout mice [26]. TGR5 is expressed in the central nervous system [27], but its signaling role in the central nervous system is still unclear. Bile acids enter the hypothalamic neurons, especially taurocholic acid (TCA) and glycochenodeoxycholic acid (GCDA), which are transported into neurons (see figure 1) via ASBT to activate the glucocorticoid receptor (GR) to bring about the HPA axis Suppression [28]. It is important that the expression of GR in pre-diabetes and marked diabetes is decreasing [29]. It is concluded that the role of bile acid signaling in the hypothalamus may prevent or alleviate diabetes, and bile acids have long been found to be synthesized in the brain

[30], suggesting that bile acids should play a metabolic role in the brain.

### 2.3. Hypothalamic Neuropeptide Nesfatin-1 Expression

The expression of nesfatin-1 in plasma and hypothalamus of T2DM rats was elevated 2 months after RYGB, and the pancreas was reversed [31]. Negative correlation was observed between nesfatin-1 and the assessment of HOMA insulin resistance and hemoglobin A1c homeostasis model [32]. The nesfatin-1 receptor has been shown to be present in the hypothalamic paraventricular nucleus (PVN), the cerebellum, the posterior region, and the dorsal motor nucleus of the vagus nerve (DMN) [33]. In addition, studies have indicated that central hypoglycemia induces intense neuronal activation in the nucleus of the vagus nerve, including arcuate nucleus (ARC), PVN, Lateral hypothalamic area (LHA), dorsal motor nucleus of the vagus (DMNX), and NTS, and found that a significant proportion of c-Fos-positive neurons express NUCB2 / nesfatin-1 [34]. Therefore, changes in nesfatin-1 in the hypothalamus after RYGB may indicate a state of hypoglycemia in the central nervous system. As a peptide substance produced by the hypothalamus, nesfatin-1 acts to regulate insulin secretion, glucose homeostasis and systemic energy balance [35]. Nesfatin-1 can cross the blood-brain barrier (see figure 1) and is not saturated [36]. Its role in the central can significantly increase insulin's ability to inhibit hepatic glucose production and inhibit liver PEPCK mRNA and protein levels (see figure 3). Besides, it enhances hepatic insulin signaling by increasing hepatic phosphorylation of AMPK (Thr172) and Akt (Ser473), TORC2 (Thr171) and mTOR (Ser2448) [37]. Furthermore, studies have shown that the hypoglycemic effect of nesfatin-1 is insulin-dependent and is associated with PPAR $\gamma$  and AMPK pathways [38]. Although its receptor is also distributed in the periphery, most of the literature can be seen that its regulation of glucose homeostasis mainly through the role of the central

nervous system.

### 2.4. Central Regulation of DVC Pathway

The regulation of gastrointestinal function in the hypothalamus is mainly achieved by the dorsal vagal complex (DVC) pathway, which includes the NTS and the dorsal motor nucleus of vagus, DMV) (see figure 2). One of the gut-brain connections is that the vagus nerve transmits sensory information to the hindbrain feeding center, which affects food preferences and then changes the dietary pattern, thus maintaining energy balance [17]. Nutrients that are not digested after RYGB enter the jejunum directly, and are likely to over-stimulate the vagus nerve and send a stronger signal to the brain. RYGB surgery significantly activates microglia in NTS and DMV. This activation of microglia may affect the vagus nerve structure through cytokine release. The role of cytokines in the anti-obesity effect of bariatric surgery requires further study [39]. DVC neurons expressing NMDA are required for hypothalamic peripheral nutrient signalling to activate the forebrain-hindbrain circuit to reduce glucose production [40]. Increased extracellular glycine levels in DVC can enhance N-methyl D-aspartate (NMDA) receptors and activate brain-hepatic axis to reduce glucose production [41]. NMDA ion channels and receptors have been localized to the vagal afferent terminals in the hindbrain NTS [42, 43]. NTS can be used as a key part of neural circuit fusion, integrating nutrient sensing signals in the body to negatively regulate glucose production [44]. The DMV neurons expressing MC4R can participate in the regulation of glucose/ insulin homeostasis through their projection of the ganglia in the pancreas [45]. In addition, circulating high glucagon activates the glucagon receptor Gcgr-PKA-Erk1 / 2-K ATP channel signal in DVC to inhibit glucose production and reduce plasma glucose levels [46]. This further elaborates the important role of DVC in the regulation of the hypothalamus, and finally achieves the regulation of peripheral homeostasis.

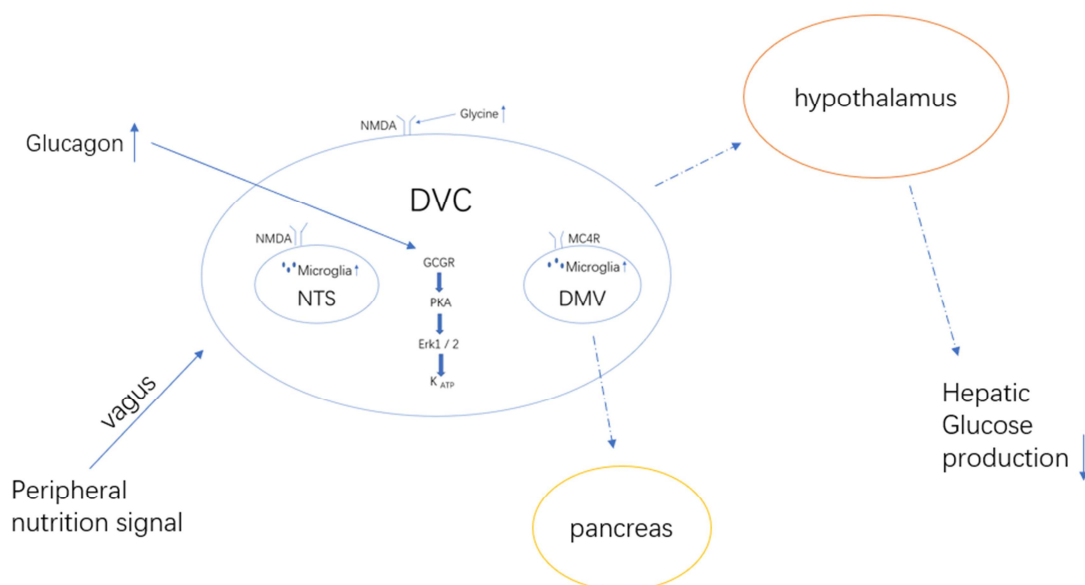


Figure 2. Hypothalamic-DVC pathway perception after RYGB.

### 3. Hypothalamic Leptin Signal Enhancement

#### 3.1. Intestinal Gluconeogenesis and Hypothalamic Regulation

Eight weeks after surgery, intestinal gluconeogenesis increased significantly [47]. It has been reported that the role of the intestinal gluconeogenesis gene (IGNG) in the rapid control of blood glucose is due to the fact that after RYGB, the derivation of food in the distal small intestine induces the gene expression of IGNG in this part (see figure 1) and causes glucose to be released into the portal blood, which stimulating the hepatic portal vein's blood glucose receptors and transmit peripheral blood glucose signals to the hypothalamus by stimulating vagal reflexes. Then the hypothalamus sends a signal through the liver vagus nerve into the liver to Feedback inhibit the gluconeogenesis of the liver, thereby regulating glucose homeostasis [8]. What's more, in the rat lacking the key enzyme of intestinal gluconeogenesis, Phosphorylation of STAT3 decrease, which is a key intermediate in the hypothalamic leptin signal cascade. This change is restored after intestinal infusion of glucose [48]. This also indicates that intestinal gluconeogenesis also improves the sensitivity of the hypothalamic leptin signaling pathway, and the hypothalamic leptin action plays a very important role in the regulation of

the body's glucose homeostasis.

#### 3.2. Hypothalamic PTP1B-leptin Signaling

Eight weeks after RYGB, hepatic glucose metabolism was improved in obese rats, and PTP1B expression was down-regulated. PTP1B expression was correlated with plasma GLP-1 levels [49]. At the same time, in another 8-week study of obese rats, RYGB also effectively reduced the expression of PTP1B in the hypothalamus of obese rats and enhanced the activity of leptin signalling [50]. In hypothalamic PTP1B knockout mice, increased phosphorylation of stat3 in the hypothalamus, enhanced leptin signaling pathway, increased peripheral insulin sensitivity, and improved glucose metabolism were observed [51]. Further, in the hypothalamic PTP1B and leptin receptor knockout mice, glucose homeostasis is severely impaired, indicating that the observed improvement in hypothalamic PTP1B deficiency is dependent on leptin receptor signaling and PTP1B is a negative regulator of leptin signalling [52]. PTP1B expression is regulated by androgen receptor (AR)-mediated transcriptional repression, and AR-deficient male mice exhibit insulin resistance [53]. RYGB may improve hypothalamic leptin signaling sensitivity through activation of hypothalamic AR and then inhibition of PTP1B expression.

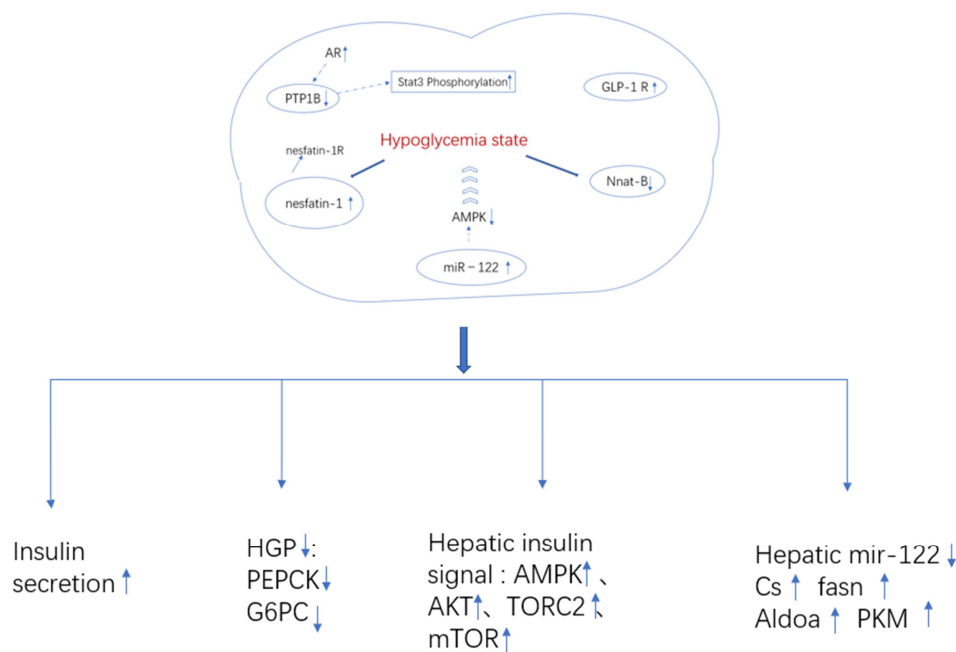


Figure 3. Changes of the hypothalamus after RYGB and the regulation of the periphery.

### 4. Related Gene Expression

#### 4.1. Hypothalamic miRNA and AMPK Regulation

25 days after RYGB, miR-122 expression in rat hypothalamus increased significantly, and AMPK phosphorylation level in hypothalamus decreased. MiR-122

was negatively correlated with AMPK activation. It is speculated that miR-122 directly or indirectly regulates AMPK activity [54]. MiR-122 is mainly expressed in the liver, and most studies are in the liver. Plasma and liver miR-122 expression was decreased 53 days after SD rats Roux-en-Y gastric bypass surgery. Metabolic surgery has been shown to significantly alter circulating miRNAs in

patients, especially miR-122. MiR-122 directly regulates hepatocyte citrate synthase (Cs), Glut1, fatty acid synthase (Fasn), aldolase A (Aldoa) and glucose-6-phosphate dehydrogenase (G6pd), uncoupling protein 2 (Ucp2) and AMP-activated kinase  $\beta$ 1 (Prkab1) [55]. MiR-122 also inhibits glucose metabolism, including the brain by down-regulating pyruvate kinase (PKM) and GLUT1 [56]. The increase in miR-122 expression in the hypothalamus after metabolic surgery is a new finding. The hypothalamic miR-122 may regulate AMPK changes through some kind of signal, and this change in AMPK also indicates that the hypothalamus is in a “low energy” state (see figure 3). Corresponding to the previous hypoglycemia state, this state may be an important factor in the input of hypothalamic information and a series of adjustments to the periphery.

#### 4.2. Hypothalamic Nnat-B and Glucose Metabolism

Nnat-B expression in hypothalamus was significantly reduced 10 days after gastric bypass [57]. NNAT mRNA expression is regulated by miRNA708 in islet cells [58]. Under normal conditions, glucose stimulation leads to the inhibition of MiR-708 [59], promotes the expression of Nnat, and stimulates the secretion of proinsulin by activating the signal peptidase complex (SPC) in islet beta cells to process proinsulin [60]. In pancreatic beta cells transfected with the Nnat gene, the ratio of Nnat- $\beta$  to Nnat- $\alpha$  increases in proportion to glucose concentration and glucose exposure time [60]. Overexpression of Nnat-B at high glucose concentrations induced ER stress and decreased gene expression of  $\beta$ -cell function, glucokinase (GCK), pancreatic duodenal homeobox-1 (PDX1) and insulin [60]. It can be seen that Nnat-B expression is related to its perceived glucose concentration. It is important to know that Nnat is mainly expressed in the hypothalamus, followed by brain stem and white adipose tissue (WAT) [57]. Therefore, the role of Nnat in the hypothalamus should be given enough attention. In pig placenta, Nnat is an important protein that regulates glucose transport, which is accomplished by the PI3K/ AKT pathway [61]. After RYGB surgery, a decrease in Nnat-B (see figure 3) may also indicate a decrease in glucose metabolism in the hypothalamus. In the hypothalamic nucleus, including DMH, PVN, VMH and ARC, and the lateral hypothalamic area LHA, Nnat mRNA expression was regulated by fasting, and Nnat mRNA expression in hypothalamus was decreased in fasting state [62]. The decrease in Nnat-B expression may be related to a “fasting state” of the hypothalamus after surgery.

## 5. Conclusion

In summary, gastric bypass surgery affects central leptin and insulin signaling pathways by the interaction of peripheral signals and central receptors, as well as activation or inhibition of certain central receptors. The brain, especially the hypothalamus, plays a decisive role in regulating glucose homeostasis after gastric bypass surgery. It is worth noting that after RYGB, the hypothalamus

presents a state of “low energy consumption”, which is similar to the “fasting state”, which proves that RYGB is a change in the whole metabolic state. In this state, the hypothalamus, as a signal hub, sends signals to regulate glucose homeostasis by regulating peripheral insulin secretion, insulin signaling pathway, leptin signaling pathway, and expression of glucose metabolism-related enzymes, factors and hormones.

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