Nutrición Hospitalaria

Nutr Hosp 2013;28(Supl. 2):109-114
ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198
CODEN NUHOEQ
S.V.R. 318

Influence of diabetes surgery on a gut-brain-liver axis regulating food intake and internal glucose production

G. Mithieux[1-3]

[1]Institut National de la Santé et de la Recherche Médicale. U855. Lyon. F-69732. France. [2]Université de Lyon. Lyon. F-69008. France. [3]Université Lyon I. Villeurbanne. F-69622. France.

Abstract

It has long been known that the brain, especially the hypothalamus, can modulate both insulin secretion and hepatic glucose fluxes, via the modulation of the sympathetic system (promoting glycogen breakdown) and the parasympathetic system (stimulating glycogen deposition). Central insulin signalling or hypothalamic long-chain fatty acid oxidation can also control insulin's suppression of endogenous glucose production. Interestingly, intestinal gluconeogenesis can initiate a portal glucose signal, transmitted to the hypothalamus via the gastrointestinal nervous system. This signal may modulate the sensation of hunger and satiety and insulin sensitivity of hepatic glucose fluxes as well. The rapid improvements of glucose control taking place after gastric bypass surgery in obese diabetics has long been mysterious. Actually, the specificity of gastric bypass in obese diabetic mice relates to major changes in the sensations of hunger and to rapid improvement in insulin sensitivity of endogenous glucose production. We have shown that an induction of intestinal gluconeogenesis plays a major role in these phenomena. In addition, the restoration of the secretion of glucagon like peptide 1 and consequently of insulin plays a key additional role to improve postprandial glucose tolerance. Therefore, a synergy between incretin effects and intestinal gluconeogenesis might be a key feature explaining the rapid improvement of glucose control in obese diabetics after bypass surgery.

(Nutr Hosp 2013; 28 (Supl. 2):109-114)

Key words: *Gastric bypass. Brain. Liver. Intestinal gluconeogenesis. Insulin sensitivity. Glucagon-like peptide 1.*

INFLUENCIA DE LA CIRUGÍA DE DIABETES SOBRE EL EJE INTESTINO-CEREBRO-HÍGADO QUE REGULA INGESTA ALIMENTARIA Y PRODUCCIÓN INTERNA DE GLUCOSA

Resumen

Se sabe desde hace tiempo que el cerebro, especialmente el hipotálamo, puede modular la secreción de insulina y los flujos hepáticos de glucosa mediante la modulación del sistema simpático (promoviendo la degradación del glucógeno) y el sistema parasimpático (estimulando el depósito de glucógeno). La señalización central de la insulina o la oxidación hipotalámica de los ácidos grasos de cadena larga también pueden controlar la producción de la glucosa endógena por la supresión de la insulina. De forma interesante, la gluconeogénesis intestinal puede iniciar una señal de glucosa portal, que se transmite al hipotálamo a través del sistema nervioso gastrointestinal. Esta señal puede modular la sensación de hambre y la saciedad, así como la sensibilidad a la insulina de los flujos hepáticos de glucosa. Las mejorías rápidas del control de la glucosa que ocurren tras la cirugía de derivación gástrica en los diabéticos obesos siguen siendo un misterio. En realidad, la especificidad de la derivación gástrica en ratones obesos diabéticos se relaciona con cambios importantes en las sensaciones de hambre y con una mejoría rápida de la sensibilidad a la insulina de la producción endógena de glucosa. Hemos demostrado que la inducción de la gluconeogénesis intestinal desempeña un papel principal en estos fenómenos. Además, la restauración de la secreción del péptido 1 de tipo glucagón y, por consiguiente, de la insulina, desempeña un papel clave adicional en la mejora de la tolerancia a la glucosa postprandial. Por lo tanto, la sinergia entre los efectos de la incretina y la gluconeogénesis intestinal podría ser un elemento clave en la mejora rápida del control de la glucosa en los diabéticos obesos tras la cirugía de derivación.

(Nutr Hosp 2013; 28 (Supl. 2):109-114)

Palabras clave: *Derivación gástrica. Cerebro. Hígado. Gluconeogénesis intestinal. Sensibilidad a la insulina. Péptido 1 de tipo glucagón.*

Correspondence: Gilles Mithieux.
Inserm U855. Faculté de Médecine Laennec.
69372 Lyon Cedex 08, France.
E-mail: gilles.mithieux@inserm.fr

Introduction

The worldwide increase of obesity, now considered as an epidemic, has necessitated the development of new therapeutic approaches of this metabolic state. In the case of morbid obesity, which also increased dramatically, bariatric surgery may be relevant when the patient is in treatment failure with respect to the control of body weight. Two types of gastric surgery are generally used. The best known, gastric banding is restrictive. Its aim is to reduce the size of the stomach using a gastric band. A second type of technique, more invasive, is the so-called gastric bypass, which in addition to reducing stomach creates a diversion of food into the distal small intestine, with the aim to associate a malabsorption of nutrients. There are different variants of the bypass surgery, such as the "Roux-en-Y", duodenojejunal exclusion, or biliopancreatic diversion (see 1 for review). However, all produce similar metabolic effects.

A question still unresolved 5 years ago relates to the mechanisms underlying the metabolic differences observed between the major surgeries for morbid obesity, especially when obesity is associated with type 2 diabetes. Both types of operation induce substantial weight loss. However, "bypass" patients generally refer to their physician a significant loss of their feelings of hunger, which is not the case of "banding" patients. Patients also frequently mention changes in the appetite for fatty food. Weight loss is also greater after bypass than after banding.[1] The various hypotheses proposed, generally based on differences in the induced secretion of gastrointestinal hormones that influence the phenomena of hunger and satiety (ghrelin, cholecystokinine, glucagon like peptide-1 (GLP-1)), have proved insufficient to explain the major difference between the two techniques. For example, the secretion of ghrelin, an orexigenic hormone, is unaffected by gastric bypass.[2] In addition, the results relating to the secretion of GLP-1, a hunger-curbing hormone, were sometimes contradictory among different studies.[3,4] Another unexplained feature of gastric bypass in obese diabetics is a dramatic improvement in their diabetes.[5] This improvement takes place very rapidly (within some days), i.e. well before any weight loss induced by surgery.[5] In contrast, patients treated using the banding technique show an improvement in their diabetes much later, once they have lost weight. The mechanism involved here was still unexplained. The term "metabolic surgery" applied to the gastric bypass was born from these observations.

Central control of endogenous glucose production

Endogenous glucose production (EGP) is a crucial function, which allows the body to maintain plasma glucose concentration around 1 g/L in absence of food, i.e. between the periods of assimilation of meals and during the night. It is admitted that increased EGP is a feature of type 2 diabetes, and that the augmentation of EGP determines that insulin resistance without diabetes finally becomes frank diabetes.[6] Three organs only can perform this function, because they are the only organs known to express glucose-6-phosphatase (Glc6Pase), the key enzyme of EGP.[6] All three organs express all the enzymes needed for glucose synthesis,[7-9] and are able to release glucose, e.g. during fasting.[10-12] In line with this key role in fasting glucose homeostasis, Glc6Pase together with phosphoenolpyruvate carboxykinase (PEPCK), the other key regulatory enzyme of EGP, are regulated by nutrients and hormones (notably insulin) at the level of gene expression and enzymatic activity in the liver, kidney and small intestine.[7-10,13-17] Among the three organs capable of EGP, the liver is often regarded as the major contributor. This is essentially due to its specific capacity of glycogen storage, a store of glucose that it can mobilize via the activation of glycogenolysis. This allows it to rapidly and finely tune blood glucose concentration. The other two organs (kidney and intestine) do not exhibit this capacity, and it is generally observed that they increase their participation in EGP as fasting in lasting.[6,11,13,18,19] For this reason, a vast majority of previous studies about the regulation of EGP have focused on hepatic glucose fluxes.

In addition to the control by insulin, the hypothalamus, via the modulation of the sympatheticparasympathetic balance, takes part in the control of whole body glucose metabolism, notably at a liver level. The hypothalamus influences insulin secretion,[20] glucose utilization in the skeletal muscle[21] and liver glucose storage and production.[22,23] Particularly, the nervous efferents connecting the hypothalamus to the liver tightly control EGP via the regulation of hepatic glycogen storage.[22,23] More specifically, neurons in the ventromedial hypothalamus control the stimulation of liver glycogenolysis, through the activation of the sympathetic system. Conversely, neurons in the lateral hypothalamus stimulate liver glycogenogenesis, via the activation of the parasympathetic system. Additional circuits from the paraventricular nucleus to the liver have also been involved in the control of hepatic glycogen storage, via a modulation of the sympathetic-parasympathetic balance. In addition, the paraventricular nucleus has been suggested to also serve as a relay for signals from both the ventromedial and the lateral hypothalamus to the liver.[22]

Furthermore, the role of the hypothalamus in the control of hepatic glucose production has been recently specified, either in rats or in mice with targeted gene mutations affecting insulin receptor expression and signalling. A key role for insulin within the hypothalamus has been suggested. Hence, insulin's suppression of EGP is decreased in rats with decreased insulin signalling in the hypothalamus.[24,25] Moreover, insulin receptor-KO mice with partial restoration of insulin receptor in the brain, liver and pancreatic b-cells are rescued from neonatal death and diabetes ketoacidosis.

However, despite a full restoration of insulin signalling in the liver, they still exhibit defects in the control of HGP by insulin, due to persisting partial deficiency of insulin signalling in the arcuate and paraventricular hypothalamic nuclei.[26] At an intracellular mechanistic level, a central sensing of long chain fatty-acids, through their oxidation, and a relay via hypothalamic ATP-dependent potassium channels, has been suggested to be involved in the suppression of EGP by insulin.[27-29] Moreover, the descending nerve fibres of the hepatic branch of the vagus have been shown to convey a causal efferent signal to the liver.[28,29] In addition, the efferent signal is also able to regulate both hepatic Glc6Pase and PEPCK gene expression.[29]

Among the most recent advances in the central control of both glucose and energy homeostasis, the role of AMP-activated protein kinase (AMPK), a key fuel sensor enzyme expressed in the whole body — including the brain— occupies a central place.[30] Hypothalamic AMPK, indeed, is a key target of both insulin and leptin, which are two major hormones able to curb hunger and to control glucose homeostasis. Both hormones inhibit AMPK, which in turn modifies the activity of acetyl-CoA carboxylase and the lipid metabolism of those neurons involved in the control of food intake and glucose metabolism.[30] As a result, the neurons expressing the neuromediators acting on the melanocortin receptors of type 3 (controlling energy expenditure) and of type 4 (controlling food intake), may coordinately regulate both glucose and energy homeostasis under the control of leptin and/or insulin.[3]

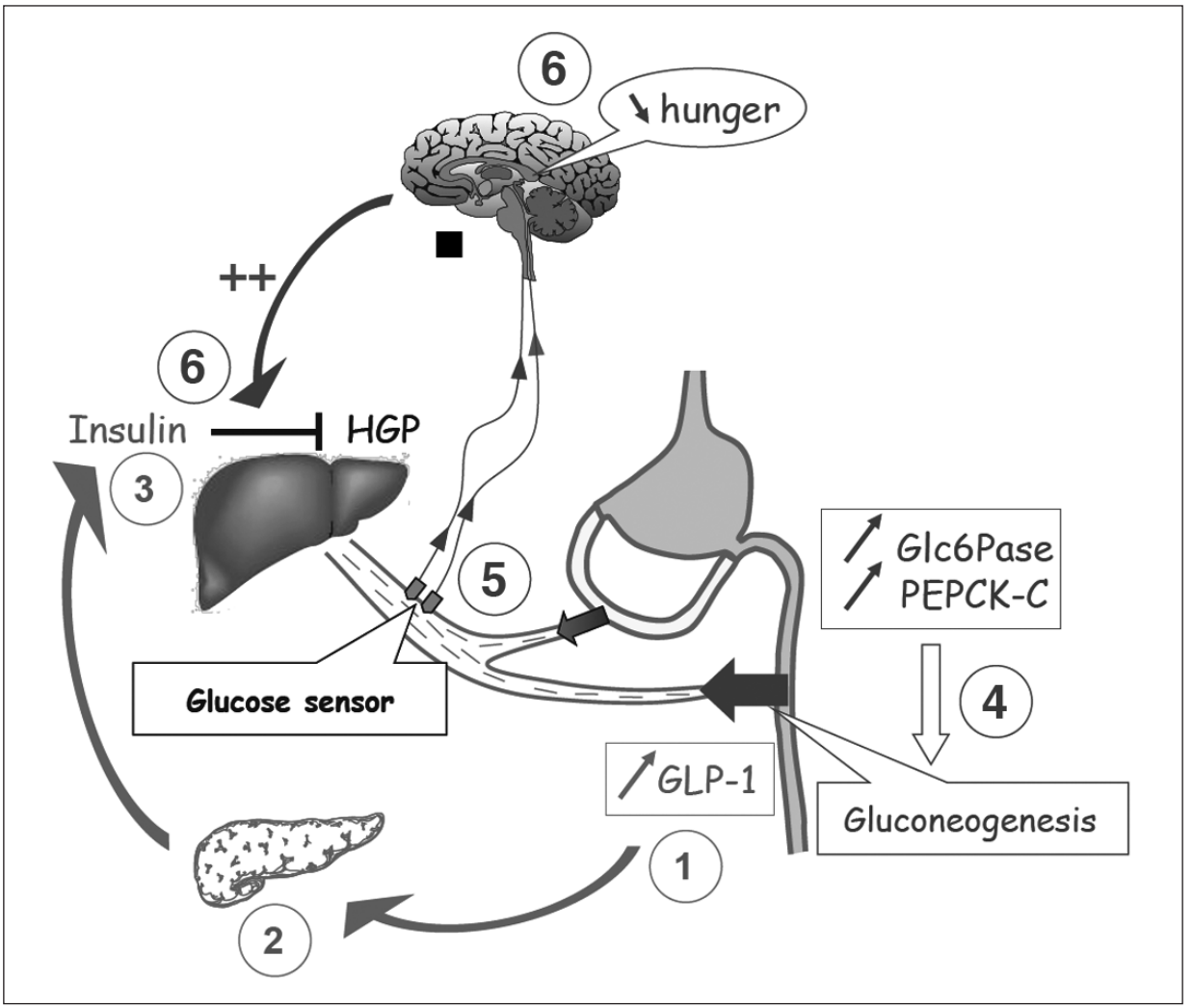

Fig. 1.—Synergy between IGNG and GLP-1 in the control of food intake and glucose homeostasis after gastric bypass: The two pathways operate in synergy. (1) the derivation of food in the distal small intestine (the grey route in the scheme) causes increased secretion of GLP-1 in response to the meal. (2) This stimulates secretion of insulin. (3) Insulin inhibits hepatic glucose production (HGP). (4) the derivation of food in the distal small intestine induces gene expression of IGNG in this portion, which expresses little or no IGNG in the "out of surgery" situation. The genes of IGNG are thus expressed strongly over the length of the small intestine. This leads to the release of glucose into the portal blood, which lasts between meals, and adds to the proximal IGNG to activate the portal glucose sensing system. (5) The portal glucose sensor transmits the information to the brain via the afferent nervous system. (6) The brain's response involves a decrease in hunger and an enhanced suppression of hepatic glucose production by insulin.

Role of a gut-brain-liver axis in gastric bypass

To understand the metabolic differences between gastric banding and gastric bypass, two mouse models representing the two types of surgery have been developed. For the bypass, a simple enterogastroanastomose (EGA) without reducing the size of the stomach was performed (fig. 1). Before surgery, mice were fed for 12 weeks with a diet enriched in fat and sugars to make them obese and insulin-resistant. The sham-operated mice recover their pre-surgical food intake in a few days. On the contrary, the EGA mice reduce their food intake by 70% immediately after the operation.[6] It should be emphasized that they have a normal size of the stomach, which strongly suggests that this decrease is due to a diminution of their feelings of hunger. On the contrary, even if the banded mice eat less, due to the size restriction of their stomach, they tend to increase their food intake again after one week. They eventually die if we do not restrict their food, exhibiting notably a strong expansion of the esophagus, suggesting that their feelings of hunger are always present.

What is the role of GLP-1?

The different hormonal hypotheses frequently proposed were studied. None has helped to explain the observed differences in food intake for the two surgeries. Regarding the possible role of GLP-1, a hypothesis that was often put forward (see above), EGA mice recover significant secretion of the hormone (and consecutively of insulin) in response to an oral glucose load[31] (fig. 1). Since both GLP-1 and insulin are anorectic, it was crucial to study the possible role of GLP-1. This was done using exendin-9, a potent antagonist of GLP-1 receptor. Continuous infusion of exendin-9 canceled insulin secretion in response to a glucose load, reflecting the effectiveness of the antagonist, but only partially reversed the effects of EGA on food intake. This strongly suggests that GLP-1 may have an important role in the recovery of insulin secretion after bypass, and thus in the observed improvement of glucose homeostasis in general, but that neither GLP-1 nor insulin, would play the key role in reducing food intake.[31]

What is the role of the portal glucose signal and intestinal gluconeogenesis?

On decreased hunger

Since the eighties, we know that glucose, when infused into the portal blood of fasting animals, results in a decrease of their food intake.[32] It is also established that this signal, often called "portal glucose signal" is detected in the walls of the portal vein, and is transmitted by nervous afferents to the nervous centers — hypothalamus and nucleus of the solitary tract—, which are the major areas of control of energy homeostasis.[33] This particular location of the glucose sensor gives the intestinal gluconeogenesis (IGNG)[34] the potential to be a player in the control of feelings of food intake.[35] IGNG, ideally located just upstream the site of detection of glucose, allows the intestine to release glucose into the portal vein and thus to activate the portal glucose signal. We have provided the proof of concept of this new paradigm by demonstrating that induction of IGNG and activation of portal glucose signal is the causal link between the ingestion of protein-enriched meals and their well-known effects of satiety, property used for a long time by nutritionists to help their obese patients to loose weight.[36]

Thus, we considered the hypothesis of a possible role of IGNG in the appetite suppressant effects of gastric bypass. Hence, we showed that a strong induction of expression of regulatory genes of gluconeogenesis, glucose-6 phosphatase and phosphoenolpyruvate carboxykinase-C, occurs in the distal small intestine of EGA mice and not in "sham" or "band" mice.[31] In the normal situation, the gluconeogenic function is expressed in the proximal intestine mainly, and virtually not in the distal small intestine.[37-39] As in rats fed high-protein diet, the induction of genes in EGA mice results in a release of glucose into the portal blood (fig. 1). This lasts during the post-absorptive period.[31] A demonstration of its causal role in the sharp decrease of food intake in EGA mice was provided by two complementary approaches. 1) The inactivation of the portal vein afferents at the time of surgery completely cancels the suppression of subsequent food intake induced by EGA. 2) No effect of EGA is observed on food intake of mice invalidated for the gene of the glucose transporter Glut2, the glucose carrier necessary for the detection of portal glucose in rodents.[31]

On improved glucose control

The portal glucose signal, in addition to its effects on food intake, is also likely to interfere with control of glucose homeostasis. Notably, it has been strongly suggested that it inhibits the production of glucose by the liver.[40] It seemed logical to think that it could also play a causal role in improving glycemic control induced by gastric bypass. To study glucose tolerance and insulin sensitivity in mouse models of "banding" and EGA equivalent in nutritional conditions, the different groups of mice were fed on a "pair-fed" basis, adjusted on the consumption of EGA mice. EGA mice showed an improvement in glucose tolerance and insulin sensitivity at 10 days after surgery. While weight loss was the same as that of "banding" or "sham" mice, the two latter do not show significant improvement in their glucose control.[31] By experiments of hyperinsulinemic euglycemic clamp, the improve-

ment was shown to relate to the inhibition by insulin of EGP, more specifically in the liver (fig. 1). EGA mice, probably because of increased insulin sensitivity, have a decreased expression of the gene of glucose-6 phosphatase in the liver.[31] Note that many hypotheses were considered to try to explain this improved insulin sensitivity (based on changes in leptin, adiponectin, resistin, TNF, AMPK activity, etc.). None accounted for the improvements observed. Similarly, "EGA" mice treated with exendin-9 show a partial reversal of their glucose tolerance, due to the cancellation of insulin secretion, but are still sensitive to insulin during the insulin tolerance test. However, the benefits of the EGA do not take place in KO-Glut2 mice, or in mice after denervation of the portal vein, which demonstrates again the crucial role of the portal nervous sensing of glucose in these effects. Taken together, these data strongly suggest that, if the restoration of secretion of GLP-1 and insulin has an important role in improving glucose tolerance, it is the gut-brain-liver axis of induction of IGNG and activation of the portal glucose signal which is the mechanical link accounting for improved insulin sensitivity after gastric bypass. It is interesting to note that in the particular nutritional situation that are the high-protein diets, insulin suppression of endogenous glucose production is potentiated as in EGA.[41] In this situation also, the effect occurs at the level of production of glucose by the liver, which is particularly evident from improved liver glycogen storage during the clamp.[41]

Both incretin effect and intestinal gluconeogenesis explain the benefits of bypass on glucose control

In conclusion, the specificity of bypass surgery in terms of benefits on glucose and energy homeostasis can be summarized as follows. Without excluding other mechanisms (many of them could play a role after the remodeling of the structure of the digestive system), the specificity of gastric bypass in obese mice relates to major changes in the sensations of hunger and to rapid improvement of glucose control. 1) The induction of IGNG plays a major role in changing the sensations of hunger, and in restoring insulin sensitivity of endogenous glucose production. 2) The restoration of the secretion of GLP-1 and insulin plays a key additional role, in this context of insulin sensitivity recovered, in the improvement of postprandial glucose tolerance. It is noteworthy that the occurrence of a net portal release of glucose during the post-absorptive period has been recently confirmed 6 days after gastric bypass in morbid obese.[42] Moreover, the improvement of insulin sensitivity (and not the changes in GLP-1 or insulin secretions) has been recently suggested underlying the improvement in glucose metabolism shortly after bypass in obese diabetics.[43] The findings in mice may therefore perfectly apply to what takes place in humans.

References

1. Thaler JP, Cummings DE. Minireview: Hormonal and metabolic mechanism of diabetes remission after gastrointestinal surgery. *Endocrinology* 2009; 150: 2518-2525.
2. Korner J, Bessler M, Cirilo LJ et al. Effects or Roux-en-Y gastric bypass surgery on fasting and postprandial concentrations of plasma ghrelin, peptide YY, and insulin. *J Clin Endocrinol Metab* 2005; 90: 359-365.
3. Le Roux CW, Welbourn R, Werling M et al. Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. *Ann Surg* 2007; 246: 780-785.
4. Reinehr T, Roth CL, Schernthaner GH et al. Peptide YY and glucagon-like peptide-1 in morbidly obese patients before and after surgically induced weight loss. *Obes Surg* 2007; 17: 1571-1577.
5. Pérez-Tilve D, D'Alessio DA, Tschöp MH. A sweet spot for the bariatric surgeon. *Cell Metab* 2008; 8: 177-179.
6. Mithieux G, Rajas F, Gautier-Stein A. A novel role for glucose-6 phosphatase in the small intestine in the control of glucose homeostasis. *J Biol Chem* 2004; 279: 44231-44234.
7. Mithieux G, Vidal H, Zitoun C, Bruni N, Daniele N, Minassian C. Glucose-6-phosphatase mRNA and activity are increased to the same extent in kidney and liver of diabetic rats. *Diabetes* 1996; 45: 891-896.
8. Rajas F, Bruni N, Montano S, Zitoun C, Mithieux G. The glucose-6 phosphatase gene is expressed in human and rat small intestines : regulation of expression in fasted and diabetic rats. *Gastroenterology* 1999; 117: 132-139.
9. Rajas F, Croset M, Zitoun C, Montano S, Mithieux G. Induction of PEPCK gene expression in insulinopenia in rat small intestine. *Diabetes* 2000; 49: 1165-1168.
10. Croset M, Rajas F, Zitoun C, Hurot JM, Montano S, Mithieux G. Rat small intestine is an insulin-sensitive gluconeogenic organ. *Diabetes* 2001; 50: 740-746.
11. Mithieux G, Bady I, Gautier A, Croset M, Rajas F, Zitoun C. Induction of-E control genes in intestinal gluconeogenesis is sequential during fasting and maximal in diabetes. *Am J Physiol Endocrinol Metab* 2004; 286: E370-375.
12. Mithieux G, Gautier-Stein A, Rajas F, Zitoun C. Contribution of intestine and kidney to glucose fluxes in different nutritional states in rat. *Comp Biochem Physiol B Biochem Mol Biol* 2006; 143: 195-200.
13. Minassian C, Mithieux G. Differential time course of liver and kidney glucose-6 phosphatase activity during fasting in rats. *Comp Biochem Physiol B Biochem Mol Biol* 2006; 109: 99-104.
14. Minassian C, Zitoun C, Mithieux G. Differential time course of liver and kidney glucose-6 phosphatase activity during long-term fasting in rat correlates with differential time course of messenger RNA level. *Mol Cell Biochem* 1996; 155: 37-41.
15. Guignot L, Mithieux G. Mechanisms by which insulin, associated or not with glucose, may inhibit hepatic glucose production in the rat. *Am J Physiol* 1999; 277: E984-989.
16. Mithieux G, Daniele N, Payrastre B, Zitoun C. Liver microsomal glucose-6 phosphatase is competitively inhibited by the lipid products of phosphatidylnositol 3-kinase. *J Biol Chem* 1998; 273: 17-19.
17. Daniele N, Rajas F, Payrastre B, Mauco G, Zitoun C, Mithieux G. Phosphatidylinositol 3-kinase translocates onto liver endoplasmic reticulum and may account for the inhibition of glucose-6-phosphatase during refeeding. *J Biol Chem* 1999; 274: 3597-3601.
18. Owen OE, Felig P, Morgan AP, Wahren J, Cahill GF. Liver and kidney metabolism during prolonged starvation. *J Clin Invest* 1969; 48: 574-583.
19. Kida K, Nakajo S, Kamiya F, Toyama Y, Nishio T, Nakagawa H. Renal net glucose release in vivo and its contribution to blood glucose in rats. *J Clin Invest* 1978; 62: 721-726.
20. Magnan C, Collins S, Berthault MF, Kassis N, Vincent M, Gilbert M, Penicaud L, Ktorza A, Assimacopoulos-Jeannet F. Lipid infusion lowers sympathetic nervous activity and leads to

increased beta-cell responsiveness to glucose. *J Clin Invest* 1999; 103: 413-419.
21. Burcelin R, Dolci W, Thorens B. Portal glucose infusion in the mouse induces hypoglycaemia: evidence that the hepatoportal glucose sensor stimulates glucose utilization. *Diabetes* 2000; 49: 1635-1642.
22. Uyama N, Geerts A, Reynaert H. Neural connections between the hypothalamus and the liver. *Anat Rec A Discov Mol Cell Evol Biol* 2004; 280: 808-820.
23. Shimazu T. Neuronal regulation of hepatic glucose metabolism in mammals. *Diabetes Metab Rev* 1987; 3: 185-206.
24. Obici S, Zhang BB, Karkanias G, Rossetti L. Hypothalamic insulin signaling is required for inhibition of glucose production. *Nat Med* 2002; 8: 1376-1382.
25. Obici S, Feng Z, Karkanias G, Baskin DG, Rossetti L. Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. *Nat Neurosci* 2002; 5: 566-572.
26. Okamoto H, Obici S, Accili D, Rossetti L. Restoration of liver insulin signaling in Insr knockout mice fails to normalize hepatic insulin action. *J Clin Invest* 2005; 115: 1314-22.
27. Obici S, Feng Z, Arduini A, Conti R, Rossetti L. Inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake and glucose production. *Nat Med* 2003; 9: 756-761.
28. Lam TK, Pocai A, Gutierrez-Juarez R, Obici S, Bryan J, Aguilar-Bryan L, Schwartz GJ, Rossetti L. Hypothalamic sensing of circulating fatty acids is required for glucose homeostasis. *Nat Med* 2005; 11: 320-327.
29. Pocai A, Obici S, Schwartz GJ, Rossetti L. A brain liver circuit regulates glucose homeostasis. *Cell Metab* 2005; 1: 53-61.
30. Kahn BB, Alquier T, Carling D, Hardie DG. AMP-activated protein kinase: ancient enery gauge provides clues to modern understanding of metabolism. *Cell Metab* 2006; 1: 15-25.
31. Troy S, M Soty, Ribeiro L et al. Intestinal gluconeogenesis is a key factor for early metabolic changes after gastric bypass but not gastric after lap-band in mice. *Cell Metab* 2008, 8: 201-211.
32. Tordoff MG, Tluczek JP, Friedman MJ. Effect of hepatic portal glucose concentration on food intake and metabolism. *Am J Physiol* 1989; 257: R1474-R1480.
33. Shimizu N, Oomura Y, Novin D et al. Functional correlations between lateral hypothalamic glucose-sensitive neurons and hepatic portal glucose-sensitive units in rat. *Brain Res* 1983; 265: 49-54.
34. Croset M, Rajas F, C Zitoun et al. Rat small intestine is an insulin-sensitive gluconeogenic organ. *Diabetes* 2001; 50: 740-746.
35. Delaere F, Magnan C, Mithieux G. Hypothalamic integration of portal glucose signals and control of food intake and insulin sensitivity. *Diabetes & Metabolism* 2010: 36: 257-262.
36. Mithieux G, Misery P, Magnan C, et al. Portal sensing of intestinal gluconeogenesis is a mechanistic link in the reduction of food intake induced by diet protein. *Cell Metab* 2005; 2: 321-329.
37. Rajas F. Bruni N, Montano S et al. The glucose-6 phosphatase gene is expressed in human and rat small intestine: regulation of expression in fasted and diabetic rats. *Gastroenterology* 1999; 117: 132-139.
38. Mithieux G, Bady I, Gautier A, et al. Induction of control genes in intestinal gluconeogenesis is sequential during fasting and maximal in diabetes. *Am J Physiol Endocrinol Metab* 2004; 286: E370-E375.
39. Mithieux G, Rajas F, Gautier-Stein A. A novel role for glucose-6 phosphatase in the small intestine in the control of glucose homeostasis. *J Biol Chem* 2004; 279: 44231-44234.
40. Cardin S, Emshwiller M, Jackson PA, Snead WL, Hastings J, Edgerton DS et al. Portal glucose infusion increases hepatic glycogen deposition in conscious unrestrained rats. *J Appl Physiol* 1999; 87: 1470-1475.
41. Pillot B, Soty M, Gautier-Stein A, C Zitoun, Mithieux G. Protein feeding promotes redistribution of endogenous glucose production to the kidney and potentiates its suppression by insulin. *Endocrinology* 2009; 150: 616-624.
42. Hayes MT, Foo J, Besic V et al. Is intestinal gluconeogenesis a key factor in the early changes in glucose homeosatasis following gastric bypass? *Obes Surg* 2011; 21: 759-762.
43. Svelikova E, Zahiragic S, Pieber TE et al. Improved glucose metabolism early after gastric bypass surgery relies primarily on enhanced insulin sensitivity. *Diabetologia* 2011; 54 (Suppl. 1): S83.