Roux-en-Y gastric bypass and calorie restriction : differences and similarities of endocrine and metabolic effects in obesity and type 2 diabetes mellitus

Lips, M.A.

Chapter 1

General introduction and outline of thesis

OBESITY AND TYPE 2 DIABETES MELLITUS

Epidemiology and definitions

Overweight and obesity are currently increasing globally, which is attributable to a number of factors including the overall availability of palatable and energy dense food and a trend towards decreased physical activity and a more sedentary life style. "Overweight" is defined by the World Health Organization (http://www.who.int/mediacentre/factsheets; factsheet obesity and overweight) as a Body Mass Index (BMI) (calculated as the bodyweight in kilograms divided by the square height in meters) equal to or more than 25 kg/$m^{2,}$ and "obesity" as a BMI equal to or more that 30kg/m^2. A BMI equal to or more than 35 kg/m^2 is defined as morbid obesity and confers a significant increase in morbidity risks due to the increased amount of adipose tissue.

Since 1980, the worldwide prevalence of obesity has doubled. In 2008, 1.5 billion adults of 20 years and older were overweight, and between them, 200 million men and 300 million women were obese. Obesity *per se* is associated with an increased mortality rate, and overweight and obesity are the fifth leading risk for global deaths. In addition, overweight and obesity are associated with insulin resistance, hyperlipidemia and hypertension, and consequently increase the risk of developing chronic diseases such as type 2 diabetes (T2DM). The risk attributable to overweight and obesity for the development of T2DM and other chronic diseases increases progressively with BMI (1;2).

The estimated worldwide prevalence of diabetes among adults was 285 million (6,4%) in 2010, and this value is predicted to rise around 439 million (7.7%) by 2030 (3;4). Diagnostic criteria for T2DM defined by the WHO are HbA1c above 6,5% or fasting plasma glucose equal to or above 7,0 mmol/L or 2-hour glucose equal to or above 11.1 mmol/L during a 75 grams oral glucose tolerance test or when symptoms of hyperglycemia are present and a random plasma glucose equal or above 11.1 mmol/L is measured.

It should be noted, however, that even though the diabetes risk is inextricably linked to an increasing BMI at the population level, there is still a large amount of relatively "healthy obese" people, even among the highest BMI classes. The question why one obese individual develops diabetes and the other remains diabetes-free challenges current scientific research. It is suggested that especially visceral fat accumulation is an important determinant of the risk to develop T2DM among all BMI (5).

PATHOGENESIS OF OBESITY AND TYPE 2 DIABETES MELLITUS

Etiology of obesity and type 2 diabetes

Even though the exact pathogenesis of obesity and T2DM is currently unknown, scientific knowledge suggests that metabolic, neuroendocrine and inflammatory adaptations to chronic fuel surfeit are involved (6;7). A generally accepted hypothesis is that, given our origin as hunters and gatherers in times when food was intermittently scarce, our body has a tendency to conserve energy and gain weight. Numerous physiological mechanisms secure the storage of excess energy in times of surplus, and decrease expenditure in times of scarcity. In predisposed subjects, these mechanisms have not adapted to the constant surplus of energy, inducing a tendency to gain weight, even when already obese. Moreover, these mechanisms will be activated with intentional weight loss, which attenuates actual weight loss in obesity (8).

Cross-sectional evidence suggests that there is a strong genetic component of T2DM. The lifetime risk of T2DM is 7% in the general population; it increases to 38% in offspring of 1 parent with T2DM and further to 70% when both parents have the disease (9). Furthermore, it is well established that around 80% of T2DM is associated with obesity, visceral fat accumulation and a sedentary lifestyle (10).

Thus, apart from a certain genetic predisposition, our current lifestyle challenges physiological mechanisms, thereby inducing both progressive insulin resistance in liver, muscle and adipose tissue in combination with pancreatic beta-cell failure to compensate the fuel surfeit. This leads to defects in insulin mediated glucose uptake in skeletal muscle, dysfunction of the adipocyte as a storage and secretory organ, enhanced endogenous glucose production by the liver, inadequate postprandial metabolic responses of the gut and a progressive decline in beta-cell function and mass in the pancreas, resulting in impaired insulin secretion.

Insulin resistance of muscle, liver and adipose tissue

Around 80% of insulin stimulated glucose uptake by the body regards the uptake in skeletal muscle (11;12). In the view of diabetes being a disease of chronic fuel surfeit, nutrient replete or overloaded skeletal muscle tissue is suggested to respond with insulin resistance as protection against steatosis or metabolic stress (13;14). Insulin resistance is thought to be functional and developed to divert excess nutrients to safe storage in adipose tissue cells (15).

Insulin mediated glucose uptake in adipose tissue accounts for only 10% of insulin stimulated glucose uptake. However, the capacity of healthy white adipose tissue to store

excess amounts of free fatty acids (FFAs) prevents nutrient spillover to other tissues and protects against metabolic diseases (14). Genetic predisposition and chronic nutrient surfeit lead to adipose tissue hyperthrophy and an increased macrophage content that is responsible for an altered adipokine secretion profile. Furthermore, impaired adipocyte differentiation and increased lipolysis in adipose tissue results in redirection of lipids to be stored in non-adipose tissues (16;17). The altered adipokine secretion profile, includes adipokines (leptin, adiponectin) and pro-inflammatory cytokines (Il-6, IL-10, TNF-a). These factors further induce low grade systemic inflammation and affect proper insulin signaling, thereby aggravating insulin resistance (18-20) .

Furthermore, the inability of insulin to inhibit the basal rate of lipolysis in obesity and T2DM elevates (postprandial) plasma FFA concentrations. Surplus fatty acids enter non-oxidative pathways leading to triglycerides accumulation in the non-adipose cell. Fatty acid derivatives like diacylgycerols and ceramides are the harmfull components of triglycerides, due to their capacity to negatively influence cellular pathways.

In healthy humans, the liver is mainly responsible for endogenous glucose production (glycogenolysis and gluconeogenesis) in the post absorptive state, reassuring sufficient glucose efflux to supply the brain's needs. Hepatic insulin resistance in obesity and diabetes is associated with enhanced endogenous glucose production, despite fasting and postprandial hyperinsulinemia. As such, endogenous glucose production by the liver is the primary determinant of enhanced fasting plasma glucose levels in T2DM (21)

Beta-cell degeneration and Incretins

Whereas adipose tissue accumulation in obesity is unequivocally associated with insulin resistance, T2DM only slowly progresses along with the degeneration of beta-cells. In the early stages of insulin resistance, a compensatory increase in insulin secretion safeguards normal glucose tolerance. When beta cells are unable to maintain the previously elevated rate of insulin secretion in response to a glucose challenge, impaired glucose tolerance progresses to T2DM (22).

The incretin effect, the added increase in insulin secretion from an oral glucose compared to a glycemia matching intravenous glucose load, is severely impaired in T2DM (23;24). The incretin effect is depends on the activity of GLP-1 and GIP; gut hormones that have the potency to induce gut-glucose stimulated insulin release, which will be discussed in the following section. Importantly, both GIP and GLP-1 have the potency to induce beta-cell proliferation and insulin synthesis, which will be challenged in the insulin resistant patient.

Endocrine axes affected by obesity

As described before, during the development of obesity, the body activates several mechanisms to minimize the harmful effects of the fuel surfeit. Apart from diverting the surplus glucose and lipids away from vulnerable tissues, the overall energy expenditure will rise in order to compensate the energy surplus. This affects several endocrine axes, for example the thyroid axis, and the function of the autonomic nervous system. The autonomic nervous system (ANS) has a role in the regulation of long and short term energy balance (25). In insulin sensitive patients, postprandial hyperinsulinemia coincides with a transient dominance of the sympathetic nervous system in order to enhance resting energy expenditure to counteract hyperglycemia (26-28). In T2DM, the transient enhancement of energy expenditure is insufficient to decrease glucose levels, and hyperglycemia impairs b-adrenergic signaling. Consequently, the responsiveness of the autonomic nervous system to variations in metabolic rate is reduced (29;30). Furthermore, in obesity, moderately elevated serum triiodothyronine (T3) and thyroid stimulating hormone (TSH) concentrations enable enhancement of energy expenditure (31-33). Leptin is an important regulator of hypothalamic TSH production and increased TSH levels in obesity are thought to be causally related to leptin levels (34).

Physiology and pathophysiology of food intake

Two major players in the regulation of body weight are the gut and the brain. In short term energy regulation, peptides released from the gut convey information to brain areas involved in homeostatic control of food intake. For long term energy regulation, the brain receives signals from the available energy stores in the body.

Brain function in the regulation of food intake

The hypothalamus, the control center of energy homeostasis (25;35), directly senses informational cues concerning presence of short and long term energy supplies to initiate an integrated behavioral and metabolic response in order to maintain energy homeostasis. Signals travel primarily via the vagus nerve to the brainstem and then to the hypothalamic arcuate nucleus where they pass the blood brain barrier (36). Hormones and nutrients from the gut, for example Ghrelin and, peptide-YY (PYY), induce respectively orexigenic and anorexigenic signaling pathways in the brain. Adiposity signals, for example Insulin and Leptin (37) convey information about the available fat storage. By adequately combining these signals, the hypothalamus adapts its activity to regulate energy intake. In fMRI studies it has been shown that during physiological hunger, ad libitum food intake is predicted by hypothalamic activity (38).

During the normal response to food intake, the hypothalamic activity signal is inhibited. This inhibition is attenuated or decreased in obese subjects (39).

Emerging evidence suggests that brain areas related to reward and cognition also control food intake. The hypothalamus is connected to various corticolimbic structures, the orbitofrontal, insular and olfactory cortex, that are important for the rewarding function of food. In healthy humans, the presence of the satiety signals changes food regulation from the homeostatic hypothalamus to the hedonic orbital frontal area (38). Leptin (the "adipose tissue hormone") is suggested to down regulate the 'hedonic' activation in reward areas and simultaneously up-regulate homeostatic control by enhancing the central response to satiety signals (40). Overstimulation by leptin in obesity may therefore decrease the response to physiological satiety or food related stimuli, which may trigger motivation for non-homeostatic eating (41-43).

Gut peptides in the regulation of food intake

As mentioned before, several peptides, released by the gut in presence or absence of food, are implicated in the regulation of food intake. Of these peptides, glucagon-like-peptide-1 (GLP-1) may be the most important. GLP-1 is secreted by L-cells, primarily located in the distal ileum, in response to stimulation by luminal carbohydrates and lipids. GLP-1 potently stimulates glucose dependent insulin release, decreased beta-cell apoptosis (44;45), inhibits gastric emptying and decreases food intake (46). Furthermore, GLP-1 inhibits glucagon production and slows the rate of endogenous glucose production (47). T2DM subjects show diminished secretion and impaired function of GLP-1, whereas administration of GLP-1 to patients restores beta-cell glucose sensitivity and insulin secretion (47).

Co-secreted from L-cell along with GLP-1, peptide-YY (PYY) is probably the most potent satiety hormone. PYY exerts is effect by stimulation of the Y2R in the arcuate nucleus (48). PYY is stimulated in proportion to the calorie content of the meal; however, stimulation seems more potent after protein rich meals (49). The postprandial increase in PYY is attenuated in obese subjects, and external administration of PYY is able to decreases food intake in obesity (50).

Glucose-dependant-insulinotrophic-peptide (GIP) is produced by K-cells, primarily located in the duodenum (51). GIP is secreted in response to luminal nutrients, with carbohydrates obtaining the most important effect. GIP mediates insulin secretion in a glucose dependent manner, by binding to the GIP receptor at pancreatic beta-cells. In addition, it promotes beta-cell proliferation and survival, enhances insulin-stimulated

incorporation of free fatty acids into triglycerides and stimulates lipoprotein lipase activity (52). In T2DM, plasma concentrations of GIP have shown to be normal (53) but the insulinotrophic effect is deficient possibly through a defect at the receptor level (54-56).

Ghrelin is an orexigenic hormone, which is released by endocrine cells in the stomach in the absence of food and suppressed by food intake (57;58). Ghrelin induces its orexigenic effects via the hypothalamic arcuate nucleus, but also in the mesolimbic reward areas in rodents (59). Ghrelin levels are typically low in obesity, and correlate to hyperinsulinemia and insulin resistance (60).

Glucagon

In physiology, glucagon's role is to induce hepatic gluconeogenesis during fasting. Postprandial, in physiological circumstances, a decrease in circulating glucagon is harvested by glucose sensing of the alpha cells, rising GLP-1 and Insulin levels. In T2DM, fasting glucagon levels are inappropriately enhanced, relative to enhanced glucose levels (61;62). This stimulates endogenous glucose production and enhances fasting glucose whereas the suppressive effect of insulin is defect (63;64). Obesity with normal glucose tolerance may be associated with enhanced fasting glucagon levels as a very early step in the pathophysiology of T2DM (65). Delayed postprandial inhibition, or even an increase in postprandial glucagon levels, further contributes to postprandial hyperglycemia in T2DM (66). Since GLP-1 secretion in type 2 diabetes is reduced, glucagon secretion is no longer inhibited.

Other gut and liver derived factors

Apart from gutpeptides, recently other important neuroendocrine gut-liver-brain pathways to regulate glucose homeostasis were discovered. It was shown that fatty acids that enter the proximal gut activate sensing mechanisms that suppress endogenous glucose production via a neural gut-brain-liver axis in healthy (non-diabetic) rats (67;68) Furthermore, rodent studies have shown a role for distal small intestine induced gluconeogenesis (69;70). Gluconeogenic genes are increasingly expressed when food enters the distal intestine as in enhanced protein feeding (71) or after bypass surgery (72). This induction leads to release of glucose in the portal blood, which continues between meals and activates glucose sensing. Via afferent neurons, this information is transmitted to the brain to induce satiety (73).

Members of the fibroblast growth factor (FGF) family, involved in a variety of biological processes including development, differentiation, cell survival and growth, have

recently been attributed an endocrine function in the regulation of carbohydrate and lipid metabolism (74). FGF19 is expressed in the distal small intestine after the postprandial uptake of bile acids, and is an important regulator of bile acid synthesis itself (75). FGF19, independently of insulin, stimulates hepatic protein and glycogen synthesis, without inducing lipogenesis (76). Bile acids activate G-protein coupled receptor TGR5 in brown adipose tissue and muscle, which induces intestinal glucagon-like-peptide-1 release (77) and induces a rise in energy expenditure (78). Circulating bile acids are correlated with measures of insulin sensitivity (79) (80) and bile acid sequestrants improve glycemic control in type 2 diabetes (81).

FGF21 is expressed abundantly in the liver, in white adipose tissue, pancreas and muscle where its expression is respectively controlled by PPARα and PPARγ (74). FGF21 stimulates glucose uptake in adipocytes, upregulates fatty acid oxidation and increases energy expenditure (82;83). FGF21 is a key mediator of the effect induced directly by PPARα in liver and PPARγ in adipose tissue in response to fasting. In the fasting state FGF21 stimulates lipolysis in white adipose tissue and ketogenesis in liver (84;85). Few human studies have shown a positive correlation of FGF21 with insulin resistance, hyperinsulinemia states and other metabolic parameters (86;87).

TREATMENT OF OBESITY AND TYPE 2 DIABETES

Weight reduction is of primary importance in the treatment of obesity and T2DM. Although pharmacological therapy is able to relieve symptomatic hyperglycemia, T2DM is a progressive disease, which will not be subdued by any therapy yet, unless insulin resistance and the toxic effect of adipose tissue are reduced. Calorie restriction per se (88) and weight loss is an effective way to decrease fasting and postprandial glucose levels, hepatic insulin resistance and peripheral skeletal muscle insulin resistance.

Life style interventions and low calorie diets

Long term follow up trials show that lifestyle interventions, frequent weight loss counseling combined with meal replacements or weight-loss medication, in obese patients result in a more favorable metabolic profile as compared to standard care which usually shows the normal progression of obesity and T2DM (89). Moreover, life-style interventions have shown to be effective in the prevention of T2DM in people at risk (90). The Diabetes Prevention Program (91) and the Look AHEAD (92) (Action for Health in Diabetes) have provided evidence regarding the beneficial impact of lifestyle intervention on development of diabetes, the sustainability of lifestyle changes and

prevention of diabetes complications and the beneficial effect on progression of diabetes. Moreover, it was shown that among changes in diet, physical activity and weight reduction, interventions aimed at reducing diabetes risk, should primarily target weight reduction (93).

Very low calorie diets are more rigorous than the life style intervention programs. As alluded to before, low calorie diets carry an important beneficial effect attributable to calorie restriction per se and to loss of adipose tissue. A three-day very low calorie diet in T2DM patients is able to reduce endogenous glucose production, fasting and postprandial glucose levels. Prolonged caloric restriction, when loss of adipose tissue becomes apparent, has effects on hepatic and peripheral insulin resistance (94;95). The effect of short term calorie restriction seems to last a substantial time, even when weight is regained (96). Furthermore, prolonged caloric restriction beneficially affects systemic inflammatory parameters and visceral fat volumes, myocardial and hepatic triglyceride stores on the long term, even when weight is regained (97-99).

Recent evidence suggests that a diets' nutrient composition may be important for its outcome and sustainability due to differences in palatability and satiety -and hunger triggers (100;101). Especially protein rich diets, maintaining normal or enhanced protein intake in the face of decreased or normal energy intake, seem to be more efficient in enhancement of satiety, thermogenesis, energy efficiency and improvement of body composition (102). Proteins seem to induce the release of anorexigenic gut hormones glucagon-like peptide-1 and peptide YY. In addition, there is some evidence that the circulating level of certain amino acids, for example leucine, could impact food intake by modulating the energy and nutrient sensor pathways in the hypothalamus (103). Moreover, as elegantly shown in rodent models, intestinal gluconeogenesis and subsequent portal glucose sensing induce satiety at the hypothalamic level and reduce hepatic gluconeogenesis (69;71).

One should not forget however, that weight loss trials always carry a certain inclusion-bias; given the fact that people concerned about their lifestyle and risks are more likely to participate. Moreover, this suggests, that even people randomized in "standard care" arms of clinical trials, might even perform better than the general population that does not participate in any trial. Even so, weight is usually regained in the long term after lifestyle interventions. Indeed, bariatric surgery may be a more effective intervention in the long run (104).

Bariatric surgery

Ever since the introduction of bariatric surgery as a treatment for obesity, it has shown to be effective in a majority of cases. Nowadays, due to improved surgical techniques, morbidity and mortality of bariatric procedures are comparable to other elective laparoscopic interventions (105). Results from the Swedisch Obesity Study, a non-randomized prospective study investigating the effects of bariatric surgery (gastric banding and gastric bypass procedures) on morbidity and mortality, shows significant reductions in the incidence and mortality of cancer and total cardiovascular events as compared to controls (106-108). Moreover, bariatric surgery is associated with a 90% reduction in diabetes related mortality, and some bariatric procedures engage seemingly weight independent mechanisms, causing remission of type 2 diabetes in 80% of cases within a couple of weeks after surgery (109). Thus, the effect of bariatric procedures depends to a large extent on the procedure, whether this is purely restrictive, gastric banding, or entails rearrangement of the gastric intestinal segments as well, as in gastric bypass. The potential mechanisms leading to the beneficial effects of bariatric surgery are likely complex and involve a number of organs and communicating pathways as will be discussed in the following section.

Gastric banding (GB)

GB consists of encircling the stomach with a silicone band, to create a small proximal gastric pouch and a large distal remnant connected through a narrow constriction. Weight loss is mainly dependent on calorie restriction (110). Some evidence suggests that changes in satiety hormones and a possible as yet undefined satiety mechanism after gastric banding may add to enhanced satiety after GB (110;111). However, long term results of gastric banding are disappointing. The long term outcomes have been attributed to appearance of orexigenic compensatory mechanisms in response to weight loss, i.e. alterations in levels of PYY and Ghrelin (110;112).

Roux-en-Y gastric bypass (RYGB)

RYGB is constructed by dividing the stomach in a 15 to 20 milliliters proximal gastric pouch and a large separate distal remnant. The upper pouch is connected to the proximal jejunum through a narrow Roux-en-Y gastrojejunostomy. In addition to gastric volume reduction, which limits calorie intake, RYGB entails rearrangement of gastrointestinal architecture, which involves profound changes in nutrient processing and postprandial gut hormone release. To the surprise of many experts, RYGB was associated with improved fasting and postprandial glucose homeostasis within days to weeks after surgery, independent of weight loss (113-115). Various mechanisms have

been proposed as mediator of the effects or RYGB on short term glucose homeostasis and long term weight loss.

Calorie restriction: Like in gastric banding, gastric volume reduction restricts the volume of food that can be taken in at once, and food intake is fairly limited the first weeks to months after this major gastrointestinal procedure (116). On the long term, caloric restriction and subsequent weight loss are important factors improving peripheral glucose uptake after RYGB (117). By exclusion of the main part of the stomach, Ghrelin secreting cells are excluded from the gastro-intestinal tract, preventing the paradoxical rise of Ghrelin levels to stimulate appetite, which is seen after calorie restriction. Ghrelin levels remain suppressed after RYGB, which possibly adds to the anorexigenic effect of the procedure (112).

Excluding the duodenum from the gastrointestinal tract is suggested to exclude potential diabetogenic mechanisms subsiding here (67;118;119). Moreover, it induces distal intestinal gluconeogenesis which triggers glucose sensing in the portal vein, the liver and brain to induce satiety and inhibit hepatic glucose production (120;121). Furthermore, expeditious delivery of nutrient-rich chyme to jejunal and ileal L-cells after RYGB is supposed to exaggerate postprandial GLP-1 and PYY secretion, thereby enhancing insulin secretion and satiety, and ameliorating compromised b-cell function on the long term (122-124). Moreover, GLP-1 and PYY may have important effects on central regulation of food intake (38;125). RYGB was also reported to increase GIP levels, adding to the incretin effect, however data on GIP levels are not consistent (114;126).

Other mechanisms: Through an as yet unknown mechanism, serum bile acids may be elevated and bile acid signalling may be changed after RYGB (127). Bile acids induce energy expenditure and further enhance GLP-1 secretion (78). Scarce data suggest that branched chain amino acids and their metabolites are decreased after RYGB independently of weight loss (128) and correlate with levels of insulin resistance. Although the mechanism is unrevealed, one could imagine that the gastro intestinal rearrangements after RYGB induce alterations in amino acid metabolism.

In view of these multiple mechanistic effects of the gastrointestinal arrangements of the roux-en-y gastric bypass procedure, it is conceivable that there is indeed a strong metabolic effect occurring directly after treatment. However, the relative contributions of calorie restriction *versus* the endocrine corollaries of bypass surgery to the metabolic benefits of RYGB remain elusive. To clarify this issue, we conducted a clinical trial

comparing the endocrine and metabolic response to GB/severe calorie restriction or RYGB in obese individuals with normal glucose tolerance and equally obese subjects with T2DM. In this trial, the results of both types of interventions were studied from a broad perspective, evaluating the effects on postprandial gut hormone release and the brain, the autonomic nervous system and the thyroid axis, the endocrine active fibroblast growth factors FGF19 and FGF21 and on circulating inflammatory factors, lipids and amino acids. The results of this trial are described in this thesis.

OUTLINE OF THESIS

The most important aim of this thesis was to describe the direct effects of either restrictive treatment or RYGB surgery on fasting and postprandial glucose metabolism and to define the additive effect of the gastrointestinal arrangements of RYGB to the effects of caloric restriction per se. In **chapter 2**, we therefore describe the effect of both interventions on postprandial glucose, insulin and gut hormone levels. As glucagon is regulated by insulin and gutpeptides, but also important in the response to starvation, we hypothesized an important role for glucagon in postprandial glucose metabolism and in the effects of calorie restriction and RYGB. The postprandial response of this diabetogenic hormone in obesity and T2DM, and the effects of calorie restriction and RYGB are described in **chapter 3**.

RYGB surgery, on the other hand, is suggested to affect bile acid metabolism, thereby increasing circulating bile acids and consequently inducing a rise in energy expenditure. We hypothesized that this effect would not be seen after pure calorie restriction. Therefore we aimed to evaluate the effect on fasting and postprandial bile acids and FGF19 (by which bile acids induce some of their favourable effects). The other hormonally active fibroblast growth factor, FGF21, regulates lipolysis and ketogenesis in the adaptive response to starvation. Since the effects of RYGB and calorie restriction on circulating FGF21 levels are unknown, we aimed to quantify them in fasting and postprandial state. These results are described in **chapter 4**.

It is known that during weight loss the body decreases its energy expenditure, by activating anabolic pathways and decreasing catabolic pathways in order to minimise the “fuel” lost. This is accomplished, among other factors, by decreased activity of the pituitary-thyroid-axis. In **chapter 5** we describe the effect of the different intervention types on thyroid hormone levels. The decrease in energy expenditure is accompanied

also by a recovery of the enhanced sympathetic nervous tone. Because calorie restriction and perioperative stress and anaesthetics may aggravate sympathetic nervous tone as well, we compared the effects of restriction and RYGB on the autonomic nervous system both three weeks and three months after surgery, which is described in **chapter 6.**

With the advent of systems biology, it is now possible to define the broad array of circulating lipids and lipid derivatives that are responsible for some of the harmful effects of the enhanced circulating fatty acid pool in chronic fuel surfeit. We aimed to quantify differences in the circulating lipid pool between obese NGT and T2DM subjects. Furthermore we aimed to analyse the direct effect of the different weight loss strategies on circulating lipids and lipid derivatives. We describe the lipidomic corollaries of the two surgical procedures and calorie restriction per se in **chapter 7.** With the same approach, circulating plasma levels of amino acid can be analysed. Given the importance of proteins and amino acids in the maintenance of lean body mass during weight loss, and the suggested alterations in amino acid metabolism after RYGB, we hypothesized that weight loss by GB, RYGB and a high protein low calorie diet, would differentially affect these amino acid levels. In **chapter 8**, we define the important differences between the three different weight loss strategies on circulating amino acids.

Given the important role of the brain in regulating short term and long term energy homeostasis, we set out to define functional connectivity of several brain areas implicated in this control of energy homeostasis. In **chapter 9** we describe the differences in brain functional connectivity between lean, obese NGT and obese T2DM subjects in the fasting state and in response to food intake. In view of the differences in brain functional connectivity in obese as compared to lean controls at baseline, ànd given the suggested effect of several gut peptides on the brain's homeostatic control centres, we evaluated the response to food intake on functional brain connectivity after RYGB and restrictive weight loss, of which the results are described in **chapter 10**.

Chapter 11 will provide an overall summary and discussion of the results described in this thesis.

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