SUMMARY

Obesity is defined as a disproportional increase in body fat mass. The frequency of its occurrence has been increasing in western style societies due to the availability of sufficient and palatable food supply, and the sedentary way of living. Problems for society arise mainly from diseases associated with obesity. The risk to develop high blood pressure and coronary diseases is increased in obesity. Furthermore, the majority of patients suffering from Non-insulin dependent diabetes mellitus (NIDDM) are obese. The causal relationship between obesity and NIDDM remain to be established.

Obesity is the manifestation of a disturbance of the equilibrium between energy intake and energy expenditure. The balance between these components is achieved by the interaction of many factors. Several recent studies, and also this thesis, indcate that the central nervous system play a crucial role in this control of metabolism. This control is mainly effectuated via the autonomic nervous system. Three factors, associated with the autonomic nervous system, were investigated in this thesis with respect to their importance in the development and maintenance of obesity. Firstly, regulation of insulin secretion as preeminent factor directing the flow of nutrients. Secondly, the amount of nutrients consumed. Thirdly, mobilisation of stored nutrients, especially free fatty acids, from adipose tissue.

Insulin increases glucose uptake in most tissues, and inhibits lipolysis in adipose tissue. By this action insulin is the most important anabolic hormone. Hyperinsulinemia is a characteristic of obesity and is also present in many patients suffering from NIDDM. Glucose tolerance, however, is often normal in obesity, but is disturbed by definition in NIDDM. In the first chapters of this thesis the role of the autonomic nervous system with respect to the development of hyperinsulinemia in obesity, and the consequences for glucose tolerance are investigated. In **chapter 2** the influences of hyperinsulinemia (induced by vagal hyperactivity) and excessive food intake were studied separately and in combination for their effects on oral, intravenous, and intragastric glucose tolerance. The results indicated that both neurally-induced hyperinsulinemia and hyperphagia can produce obesity. However, only the combination of both factors results in reduced glucose tolerance.

In order to preserve insulin sensitivity, an appropriate control of insulin secretion needs to be maintained. In recent years it has been demonstrated that besides the classical neurotransmitters of the autonomic nervous system this control involves also several (neuro-) peptides. Moreover, peptides secreted by the gastro-intestinal tract influence the ß cells. The most extensively studied incretine is gastric-inhibitory polypeptide (GIP). However, secretion patterns of GIP do not correlate with the disturbed insulin secretion in obesity and NIDDM. Another peptide secreted by the duodenum and also peripheral nerves in the islets of Langerhans is cholecystokinin (CCK). In **chapter 3** the influences of CCK on insulin secretion in normal and obese rats has been studied. It appears that CCK provokes an insulin response very similar that during an intravenous glucose challenge. However, in contrast to the latter, the infusion of CCK results in reduced blood glucose concentrations. In obese animals the insulin secretion during infusion of CCK is amplified more than would be necessary to overcome the established insulin insensitivity. This change in ß cell responsiveness to CCK might result in exaggerated insulin responses, reducing insulin sensitivity, and possibly to exhaustion of pancreatic ß cells.

The results of **chapter 2** indicate that the presence of hyperphagia has profound consequences for insulin secretion and glucose homeostasis in obesity. Although, as has been demonstrated in that chapter, hyperphagia is not a prerequisite for the development of obesity after lesioning of the ventromedial hypothalamus (VMH) it is a characteristic of nearly all forms of obesity, in animal and man. From the complex of interactions that leads to an appropriate regulation of food intake, one has been investigated in **chapter 4** that might be responsible (in part) for the hyperphagia after VMH lesions. Cholecystokinin infused into the VMH produces a decrease of food intake (satiety), whereas infusion of an antagonist has the opposite effect. It is proposed that the VMH constitutes the last part of a long pathway of CCK-containing neurons from the periphery that are probably involved in the signalling of short term satiety. Disruption of this system might beexpected to result in the ingestion of large meals instead of small ones, which is the case in VMH-lesioned rats.

In obesity, hyperphagia and high plasma insulin concentrations will produce an excessive storage of nutrients in adipose tissue. However, as has been demonstrated in **chapter 5 & 8** also the mobilisation of fats during muscular exercise is reduced in obese animals. This effect is produced by a diminished activation of the sympathetic nervous system during exercise, reflected by a smaller norepinephrine response (norepinephrine is the endogenous stimulator of lipolysis). Aditionally, the sensitivity of white adipocytes to stimulation of lipolysis by norepinephrine is decreased in obese rats (**chapter 6 & 8**). The activation of the norepinephrine release is likely to be regulated by the availability of nutrients, which does not neccessarily mean the availability of energy stores (**chapter 7 & 9**). Although the precise nature of this mechanism has not yet been

l of insulin secretion needs
les the classical neurotrans-
several (neuro-) peptides.
ce the ß cells. The most
Iowever, secretion patterns
sity and NIDDM. Another
he islets of Langerhans is
n secretion in normal and
response very similar that
atter, the infusion of CCK
ie insulin secretion during
me the established insulin
ult in exaggerated insulin
ncreatic ß cells.

yperphagia has profound
y. Although, as has been
ie development of obesity
teristic of nearly all forms
t leads to an appropriate
might be responsible (in
nto the VMH produces a
the opposite effect. It is
CCK-containing neurons
term satiety. Disruption
ls instead of small ones,

vill produce an excessive
ed in **chapter 5 & 8** also
animals. This effect is
uring exercise, reflected
stimulator of lipolysis).
is by norepinephrine is
rine release is likely to
nean the availability of
nism has not yet been

unravelled, elevated plasma insulin concentrations might well play an important role in this respect.

Several factors might have produced the reduced sensitivity of adipose tissue to adrenergic stimulation in the rat models of obesity studied here. In **chapter 9** the influences of chronic hyperinsulinemia and hypothyroidism are discussed with respect to their possible role in obesity. It is argued that hyperinsulinemia, even in presence of normoglycemia and unaltered glucose tolerance favours the utilization of carbohydrates as metabolic fuel during increased activity, and might thereby preserve stored fats. In obese subjects, increased glucose mobilization in concert with diminished FFA release not only promotes adiposity, but also increases the burden for pancreatic ß cells. When this factor and insulin insensitivity are present for a prolonged period, as descibed in **chapter 8**, deterioration of glucose homeostasis can occur. Reduction of food intake appears to be a very potent way to normalize this situation since plasma insulin levels are reduced and the sympathetic activation of lipolysis is increased (**chapter 7**).

In conclusion, various deviations within the autonomic nervous system can result in the development of obesity. In addition, alterations in the activity of the sympathetic nervous system that occur secondary to the development of obesity appear to reduce fat mobilization during exercise. Although some of the change are functional in that they increase energy expenditure, the general result seems to be a sparing of stored fats. The occurrance of factors, especially when they are present together can result in an unability of the ß cells to cope with the increased neccessity to secrete insulin. Finally, this may result in the development of non insulin-dependent diabetes mellitus.