Chapter 1
General Introduction
Recent data strongly suggest that treatment with antipsychotic (AP) drugs is associated with various metabolic anomalies, including weight gain, dyslipidemia and diabetes mellitus. The mechanism underlying these serious metabolic side effects is unclear.

All classes of antipsychotic drugs share affinity for dopamine D2 receptor as a common pharmacological feature which appears to be mandatory for antipsychotic action. Conventional and atypical AP drugs differ however in their affinity for monoamine receptors; conventional AP drugs have a strong affinity for dopamine D2 and α1 adrenergic receptors while atypical drugs have relatively low affinity for dopamine D2 receptors but an important affinity for other dopaminergic subclasses (D3 and D4) and monoamine receptor subtypes (i.e. 5-HT2A, 2C, histamine H1, and muscarinic receptors) (1).

OVERWEIGHT AND OBESITY: DEFINITIONS

Overweight and obesity are commonly assessed by using body mass index (BMI) defined as weight in kilograms divided by the square of the height in meters (kg/m²). A BMI > 25 kg/m² is defined as overweight and a BMI > 30 kg/m² as obesity (WHO website: http://www.who.int/bmi/index.jsp).

DIABETES MELLITUS

Diabetes is a major health problem in westernized societies. During the past two decades there has been an explosive increase in the number of people diagnosed with diabetes worldwide (2,3). Pronounced alteration in lifestyle, including abundance of energy rich foods in combination with sedentary life style has resulted in escalating rates of both obesity and diabetes mellitus.

Diabetes mellitus: definitions

In normal individuals the fasting glucose concentration ranges between 4.4 and 6.0 mmol/L. Fasting glucose concentration of ≥ 7.0 mmol/L and (2 h) postprandial glucose concentrations of ≥ 11.1 mmol/L is defined as diabetes mellitus (WHO website: http://www.who.int/bmi/index.jsp).

Diabetes mellitus: difference in type 1 and type 2

There are two main forms of diabetes. Type 1 diabetes is caused by autoimmune destruction of insulin producing (pancreatic) β-cells, which results in absolute insulin deficiency. People with type 1 diabetes must be treated with exogenous insulin to prevent the development of ketoacidosis, a life threatening complication of the disease. Its prevalence is relatively low as compared
to type 2 diabetes, which accounts for 90% of cases globally. Type 2 diabetes is characterised by insulin resistance and/or insulin secretion defect. Previously, type 2 diabetes was referred to as “adult-onset” diabetes as it usually became manifest later in life (> 30 years).

**Determinants of insulin sensitivity**

Insulin sensitivity is determined by variety of genetic and environmental factors, one of the most important being obesity (4-6). Evidence suggests that insulin sensitivity in itself is a heritable entity (7,8). Environmental factors that exert a negative influence on insulin sensitivity are e.g. infections, sedentary lifestyle, aging, medications (i.e. glucocorticoid), puberty and pregnancy while factors improving insulin sensitivity are: exercise, weight loss and parturition. In healthy individuals, reduction in insulin sensitivity leads to a compensatory increase in insulin secretion by the pancreatic β-cell. Increased insulin secretion then provides sufficient insulin concentration to overcome hepatic and muscular insulin resistance, and glucose levels are maintained within the normal range. When β-cells fail to increase their insulin secretion type 2 diabetes develops.

**ANTIPSYCHOTIC DRUGS AND WEIGHT GAIN**

Patients with schizophrenia are more likely to be overweight or obese than healthy individuals (9). Both schizophrenia itself and its treatment with antipsychotic drugs contribute to the weight gain (9,10), although the extent of their involvement is unclear. Low level of physical activity in combination with a preference for unhealthy diet, poor in fibre with excessive saturated fat and carbohydrates content (11-13) also contribute to the weight gain.

The prevalence of obesity was estimated to range between 30-60% in patients treated with AP drugs (9,14-17). This data is though difficult to interpret because of methodological problems. The literature on the prevalence of obesity in drug naïve schizophrenic patients is limited and mostly fails to control for confounding factors such as previous use of medication, age, lifestyle and ethnicity (18). In a recent study however, intra-abdominal fat was increased in drug naïve schizophrenic patients as compared to healthy individuals (19).

**Conventional antipsychotic medications**

The use of conventional/typical AP medications was first associated with weight gain in the late 1950s after the introduction of chlorpromazine (phenothiazine) (20-22). Conventional AP drugs that are of lower potency (i.e. chlorpromazine and thioridazine) appear to have a stronger association with weight gain than drugs with higher potency (i.e. haloperidol and fluphenazine) (10). The treatment with conventional AP drugs is unfortunately often complicated by debilitat-
ing neurological toxicity in the form of drug-induced parkinsonism, restlessness (akathisia), and irreversible choreoathetoid movements (tardive dyskinesia) (23).

Atypical antipsychotic medications
Treatment with the newer, atypical antipsychotic medications has been associated with more pronounced weight gain (14) and less neurological side effects than conventional agents (23). In the late 1980s, treatment with clozapine was reported to increase weight (24-26). Since then, virtually all available atypical AP drugs have been associated with weight gain to some extent. Atypical AP drugs differ in their propensity to induce obesity. Clozapine and olanzapine appear to be the most harmful, causing an increase of respectively 4.45 and 4.15 kg after treatment for only 10 weeks, while ziprazidone and quietiapine have the least propensity to induce weight gain (10,27). Data from long-term studies showed that olanzapine continues to increase weight for as long as 36-52 weeks (28-30) while clozapine induced weight gain continues beyond 46 months (31). Though short-term studies generally describe moderate weight gain, massive increase in body weight for up to ~ 40 kg have been observed during olanzapine (32) and clozapine (33) treatment.

ANTIPSYCHOTIC DRUGS AND DYSLIPIDEMIA

Treatment with various antipsychotic drugs is associated with development of lipid abnormalities which often go unnoticed and add to the already increased risk of cardiovascular diseases in patients with schizophrenia (34). Also, severe hypertriglyceridemia forms a considerable risk for acute pancreatitis (35). Both conventional and atypical antipsychotic drugs are associated with dyslipidemia. Among conventional AP drugs, drugs with lower potency such as phenothiazines (e.g. chlorpromazine and thioridazine) elevate both triglycerides (TG) and total cholesterol (TC) concentrations while drugs with higher potency such as butyrophenone derivates (e.g. haloperidol) do not (36,37). Atypical AP drugs also differ in their propensity to induce lipid abnormalities. Treatment with olanzapine and clozapine is associated with increased risk of lipid abnormalities whereas treatment with ziprasidone and aripiprazone is not (31,34,38-43). Olanzapine and clozapine elevate in particular triglyceride concentrations while the effect on total cholesterol is less clear (34,39). The interpretation of the literature is however difficult as the treatment with AP drugs is frequently complicated by significant weight gain. Some studies did establish significant correlation between hypertriglyceridemia and weight changes (44,45), while others did not (35,46). Furthermore, since most studies analyzing the effect of AP medication on lipids are not conducted in drug naïve schizophrenic patients their prior use of AP medication can act as a confounding factor.
ANTIPSYCHOTIC DRUGS AND ABNORMALITIES IN GLUCOSE HOMEOSTASIS

Antipsychotic drugs: effects in patients with schizophrenia

A range of evidence suggests that treatment with certain antipsychotic medication is associated with increased risk of insulin resistance, hyperglycaemia and diabetes mellitus. The interpretation of the available data is however complicated by the fact that prior to the introduction of AP medications, patients with major mental illnesses, such as schizophrenia, exhibited a higher prevalence of abnormal glucose regulation (47-49). Interestingly, the prevalence of type 2 diabetes is also highly increased in families of patients with schizophrenia (50), and approaches the prevalence of diabetes observed in families of patients with type 2 diabetes (51). This data suggests that genetic factors may play a role in the pathogenesis of diabetes in patients with schizophrenia. The fact, that drug naïve schizophrenic patients are more insulin resistant than healthy subjects of similar age, sex and adiposity (52) also supports the notion that genetic factors may be of importance.

Cross sectional observational studies evaluating the prevalence of diabetes in schizophrenic patients suggest that the prevalence may be at least two times higher than in the general population (53-55). Most studies on this subject conclude that atypical AP drugs with high weight inducing properties, including clozapine and olanzapine, are associated with increased risk of diabetes mellitus while conventional and atypical AP medication with less weight inducing properties (e.g. risperidone) are associated with lower risk (56-59).

Loads of data obtained from case reports, case series and observational studies has linked the use of antipsychotic drugs with diabetes mellitus. More cases of diabetes emerged during treatment with atypical drugs (60,61) than during treatment with conventional agents (62). New cases of diabetes usually appear within 6 months of initiation of treatment, and are typically accompanied by substantial weight gain (60-62). However, in some cases diabetes developed within few days/weeks of treatment initiation without a significant increase in weight (63,64) and was in some instances complicated by ketoacidosis (60-63,65-69), which suggests that insulin secretion may have been affected. The metabolic profile often improved right upon drug discontinuation (60,61,64,70) and hyperglycemia sometimes recurred shortly after a rechallenge with the same drug (61,64,70). This data strongly suggests that antipsychotic medication may act directly to induce insulin resistance and/or to inhibit insulin secretion, and thereby cause diabetes.

Controlled experimental studies analyzing the effect of AP drugs on glucose homeostasis are limited. In patients already treated with AP drugs, glucose levels were higher in patients on atypical agents (olanzapine and clozapine) than in patients on conventional AP agents and healthy individuals, as evaluated by (modified) oral glucose tolerance test (71). In prospective clinical trials, short-term treatment with atypical AP drug (olanzapine) significantly induced insulin resistance in patients with schizophrenia when compared to healthy (untreated) subjects (72) while treatment with both atypical (olanzapine and clozapine) and conventional
(haloperidol) AP drugs were associated with increase in plasma glucose concentrations (73). In drug naïve schizophrenic patients, treatment with clozapine and olanzapine had greater potential to induce abnormalities in the glucose metabolism than treatment with risperidone (atypical) and sulpiride (conventional) (74). The available data thus indicates that AP drugs may influence glucose homeostasis, that atypical AP drugs may be more harmful than conventional ones and that atypical AP drugs may differ in their potential to induce abnormalities in the glucose metabolism. These prospective studies were however all characterized by weight gain, which in itself can influence glucose homeostasis (72-74).

A major problem in assessing the effects of AP drugs in patients with psychiatric diseases is that schizophrenia itself can cause many of the manifestations leading to diabetes, including weight gain and sedentary lifestyle. It then becomes problematic to separate the effect of the disease from the effect of the treatment.

Antipsychotic drugs: effects in healthy subjects

Studies evaluating the effects of AP drugs on glucose metabolism in healthy subjects are of great importance as they are not confounded by the pathophysiology of schizophrenia. Studies in healthy subjects are however limited and often inconclusive.

Insulin sensitivity was recently assessed in healthy subjects after 3 weeks treatment with olanzapine, risperidone or placebo by hyperinsulinemic euglycemic clamp technique (75). Despite substantial weight gain in both treatment groups, whole body insulin sensitivity was not affected by either treatment. However, treatment with olanzapine significantly increased fasting insulin and glucose levels, while treatment with risperidone or placebo did not. This data is quite difficult to reconcile and it is questionable why the insulin sensitivity was not affected despite the substantial weight gain, as there is a known correlation between body mass index and insulin resistance in individuals with normal glucose tolerance (76). In this study, specific insulin sensitivity of muscle and liver was not evaluated. More recently, insulin sensitivity was evaluated by hyperinsulinemic euglycemic clamp after 10 days treatment with olanzapine (10 mg/day) and ziprazidone (80 mg/day). The whole body insulin sensitivity decreased and fasting insulin concentration increased in the olanzapine group, while these variables were not affected in the ziprazidone group (77). However, significant weight gain was observed in the olanzapine group which may affect the study results. Insulin secretion, evaluated by hyperglycaemic clamp, was not affected after 3 weeks treatment with olanzapine or risperidone (78). The weight increased significantly in the treatment groups, insulin response increased and insulin sensitivity decreased. However, after multivariate regression analyses, these changes were not independent of weight gain (78). The interpretation of data obtained in healthy volunteers is difficult as treatment with AP medication were in all instances complicated by significant weight gain, and the effect of the treatment per se can not be differentiated from the effect of the increased body weight.
MECHANISM OF ACTION

The propensity of atypical AP medication to stimulate appetite, induce weight and influence carbohydrate metabolism can be considered as major adverse effects. The hypothalamus is an important area in the central nervous system (CNS) which is involved in the regulation of food intake, energy expenditure and glucose homeostasis (79-81). Atypical AP medication antagonises various monoamine neurotransmitter receptors (82). Their adverse metabolic effects may therefore be mediated by antagonising actions on monoamine neurotransmitter receptors in the hypothalamus. Although the mechanism is still unclear; it appears that drugs with high affinities for receptors such as the histamine H1, 5-HT2C, α1 adrenergic and dopamine D2, have stronger correlation with increased body weight and development of diabetes (83-85).

Recently, more insight on the role of histamine H1 neurotransmission in weight regulation was gained. Olanzapine and clozapine, that exert strong affinity for histamine H1, were shown to stimulate AMP-kinase (86), a fuel-sensing enzyme, that is located in the CNS and known to increase food intake and body weight (87). This action was abolished in histamine H1 receptor knock out mice (86). Clozapine also reversed leptin induced reduction in AMP-kinase (86). Recent data also suggests that the 5HT2C receptor is closely involved in atypical AP drugs induced weight gain (88). 5HT2C receptors are located in both the rat (89,90) and human (91) hypothalamus. Leptin decreases food intake by suppressing NPY level in the hypothalamus (92). 5HT2C receptor antagonist attenuated the leptin induced reduction in food intake (93), suggesting that 5HT2C neurotransmission is involved in the mechanism of leptin induced anorexia. Chronic administration of clozapine and acute administration of olanzapine, agents that have high affinity for the 5HT2C receptor, increased NPY level in the rat hypothalamus (88,94), which further supports the importance of 5HT2C receptor in atypical AP drug induced weight gain. Atypical AP drugs affinity for α1 adrenergic receptors appear to predict the magnitude of antipsychotic induced weight gain (95) and microinjection of selective α1 adrenergic agonist in the paraventricular nucleus of rats suppresses feeding behaviour (96). Local injection of dopamine into the lateral hypothalamus (LH) decreased feeding in rats (probably via D2 receptor) (97) whereas treatment with dopamine agonist (D1/D2) normalized body weight, hyperglycemia, and reduced elevated hypothalamic NPY levels in ob/ob (leptin deficient) mice (98).

The ability of antipsychotic drugs to inhibit glucose transport may be associated with the development of type 2 diabetes. Atypical AP drugs acutely (<3 h) induce hyperglycemia in mice, while typical AP drugs do not (99). The ability of AP drugs to induce hyperglycemia in vivo is tightly correlated with their effect on glucose transport in pheochromocytoma (PC12) cells in vitro (99,100). However, PC12 cells do not express the GLUT-4 transporter, which is abundant in muscle and responsive to insulin (101), and the concentration of drugs required to block glucose uptake in these cell systems is generally very high.
AIMS OF THE THESIS

Treatment with antipsychotic medications is frequently complicated by substantial weight gain, dyslipidemia and development of diabetes mellitus. Weight gain has been postulated to be primarily responsible for the unfavourable effects of the drugs on glucose and lipid metabolism. However, numerous case reports indicate that diabetes can readily occur before weight has increased and statistical analyses of various large studies suggest that diabetes and weight gain are not mechanistically linked. Moreover, schizophrenia in itself is associated with diabetes. Thus, the first aim of this thesis was to investigate whether AP drugs induce insulin resistance independent of weight gain in non-psychotic normal weight individuals. Hyperinsulinemic euglycemic clamp technique, with stable isotopes, was used to assess insulin sensitivity after 8 days treatment with atypical AP drug (olanzapine), with high weight inducing properties, and conventional AP drug (haloperidol), with low weight inducing properties.

Recent reports indicate that a new olanzapine formulation which dissolves instantaneously in the mouth upon administration (olanzapine orally disintegrating tablet (ODT)) causes less weight gain than standard olanzapine formulation (olanzapine oral standard tablet (OST)). The second aim of our experiments was to investigate whether olanzapine ODT has less impact on lipid and carbohydrate metabolism, and adipokines concentrations so as to explain its relatively modest effect on energy balance in the long run.

In preparation for winter time, seasonally obese animals spontaneously gain weight and develop insulin resistance and hyperlipidemia. Dopamine and serotonergic neurotransmission in hypothalamic nuclei, that drive circadian rhythmicity of various hormones orchestrating fuel flux, appear to be critically involved in these metabolic adaptations. Atypical AP drugs antagonise both dopamine and serotonergic receptors. Therefore, the third aim was to evaluate the circadian neuroendocrine effects of short-term treatment with olanzapine (OST and ODT).

The GI tract is richly innervated by the enteric nervous system (ENS) which controls and coordinates enteric behaviour. Various gut peptides, released in response to food intake (and deprivation), are involved in the regulation of energy balance. Some data suggest that the ENS modulates gut peptide synthesis and secretion. The fourth aim was to study the effect of olanzapine (OST and ODT) on gut hormone concentrations as many of the monoamine neurotransmitter receptors in the central nervous system (CNS) have also been identified in the ENS.

The hypothalamus plays a critical role in the control of glucose homeostasis and energy balance. Monoamine receptors in the hypothalamus may mediate at least some of the metabolic effects AP drugs. The fifth aim of our experiments was to evaluate hypothalamic neuronal activity in response to glucose ingestion in insulin resistant people with type 2 diabetes and in healthy volunteers of similar body weight.
**OUTLINE OF THE THESIS**

**Chapter 1** is the general introduction of the thesis. In **Chapter 2**, the effect of conventional (haloperidol) and atypical (olanzapine) antipsychotic medications on insulin sensitivity and lipolysis is evaluated in healthy normal weight subjects. **Chapter 3** evaluates the effect of two distinct olanzapine formulations (OST and ODT) on pre- and postprandial glucose and lipid metabolism, and their effects on adipokines concentrations. **Chapter 4** describes the effect of olanzapine (OST and ODT) on spontaneous 24 hours cortisol and PRL secretion in healthy normal weight subjects. In **Chapter 5**, the effect of two distinct olanzapine formulations on gut hormones concentration was studied. In **Chapter 6**, hypothalamic activity in response to glucose ingestion was studied in patients with type 2 diabetes and healthy individuals of similar weight in order to evaluate whether functional MRI technique can be used to detect metabolic anomalies on hypothalamic level.
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