Chapter 7
General discussion
Treatment with antipsychotic (AP) drugs is associated with various metabolic anomalies, including weight gain, dyslipidemia and diabetes mellitus. The causative mechanism underlying these serious side effects is unclear. The metabolic profile during the use of atypical AP drugs has many characteristics in common with type 2 diabetes. Occasionally, however, patients on AP drugs present with diabetic ketoacidosis which typifies type 1 diabetes.

All classes of AP drugs share affinity for dopamine D2 receptor that appears to be mandatory for AP drug action. Conventional and atypical AP drugs differ in their affinity for monoamine receptors; conventional AP drugs have a strong affinity for dopamine D2 and a1 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). It appears that drugs with high affinities for histamine H1, 5-HT2C and a1 adrenergic receptors have stronger correlation with increased body weight and development of diabetes.

Psychiatric disease itself can lead to changes in food intake and energy expenditure. Changes in patterns of food intake, with preference for food with high fat content, altered sleep pattern and decrease in daily activities stimulate weight gain and increase fat mass (1-4), thereby affecting insulin sensitivity. Cigarette smoking, which is almost universal in patients with schizophrenia, has a negative effect on insulin sensitivity (5). Additionally, there is some evidence for genetic predisposition for type 2 diabetes in families of patients with schizophrenia (6). The prevalence of diabetes in these families is highly increased, similar to the prevalence in families of patients with type 2 diabetes (7). Drug-naïve patients with first-episode schizophrenia have higher rates of visceral obesity (8,9) and glucose intolerance (9,10) than expected. Some have suggested that these metabolic disturbances may be an inherent part of the illness (9).

Even though the literature on metabolic side effects of atypical AP drugs is abundant, data on potential mechanism(s) responsible for these metabolic perturbations is limited. Many issues remain to be solved, some of which are addressed below:

- Are metabolic anomalies observed during the treatment with AP drugs caused by the drug per se, or are they secondary to their weight inducing effects?
- Are metabolic anomalies observed during the treatment with AP drugs independent of schizophrenia?
- Are metabolic side effects of AP drugs caused by central (CNS) or peripheral effects (muscle, liver, adipose tissue)?
- If metabolic side effects are caused by centrally regulated mechanisms, which neuroendocrinologic changes are characteristic?
- Do AP drugs affect insulin sensitivity, insulin secretion, or both?
If AP drugs induce insulin resistance, which tissues are involved, muscle, liver or adipose tissue?
If AP drugs affect insulin secretion, is this centrally or peripherally regulated?
Are gut hormones involved in the pathogenesis of these metabolic/hormonal changes?

The studies described in this thesis were designed to answer some of these issues. In order to study whether metabolic anomalies observed during the treatment with AP drugs were independent of schizophrenia, all studies on the effect of AP drugs were conducted in non-obese healthy men with no history of psychiatric illnesses. A relatively short treatment period (8 days) was chosen to prevent weight gain, which would act as a confounder. In first instance, the effect of two different classes of AP drugs was studied on insulin sensitivity and lipolytic activity. Thereafter, the effect of two different olanzapine formulations, with different weight inducing properties, was studied on glucose and lipid metabolism, gut hormones concentrations and neuroendocrine effects, in a randomized controlled manner.

ANTIPSYCHOTIC DRUGS: INSULIN SENSITIVITY AND LIPOLYTIC ACTIVITY

In the first study (chapter 2), we studied the effect of two AP drugs of different classes; olanzapine (atypical AP drug) and haloperidol (conventional AP drug), on glucose and lipid metabolism by using the hyperinsulinemic euglycemic clamp technique, which is considered to be the golden standard in evaluating insulin sensitivity. By primed continuous infusion of [6,6-2H2]-glucose, hepatic glucose output (the amount of glucose produced by the liver) and the whole body glucose disposal (the amount of glucose taken up by the peripheral tissue) were measured in fasting and hyperinsulinemic condition. By primed continuous infusion of [2H5]-glycerol, lipolysis was measured in fasting and hyperinsulinemic condition. Olanzapine hampered insulin-mediated glucose disposal, whereas haloperidol did not. Muscle is considered to be the major site of insulin-stimulated glucose uptake in vivo, while the contribution of the adipose tissue to total body glucose disposal is relatively small. The hepatic glucose output, during fasting and hyperinsulinemia, was not affected by olanzapine or haloperidol. The lipolysis rate was not affected by either drug, though olanzapine decreased plasma free fatty acids (FFA) concentrations and the suppression of FFA and triglyceride (TG) concentrations during hyperinsulinemia. In conclusion, olanzapine hampered insulin action on glucose disposal, independent of changes in adiposity and schizophrenia. These findings may explain the propensity of olanzapine to induce diabetes mellitus and dyslipidemia in the long term. In experimental animals, atypical AP drugs acutely affect glucose transport in vivo (11) in contrast to conventional AP drugs. The ability of these drugs to induce hyperglycemia correlates strongly with their effect on glucose transport in pheochromocytoma-cell line in vitro (11). The causative mechanism is unclear.
ATYPICAL ANTIPSYCHOTIC DRUGS: LIPID AND GLUCOSE METABOLISM

In order to look further into the effect of olanzapine on glucose and lipid metabolism, we looked at the effect a mixed meal by two different olanzapine formulations (chapter 3), reported to have different weight inducing effects. Eight days of treatment with both olanzapine formulations significantly increased TG concentrations and decreased FFA concentrations in response to standard meal, and in fasting condition. These results are in line with changes observed on lipid profile in patients with schizophrenia after 2-3 weeks treatment with olanzapine (12). At the same time HOMA index for insulin resistant rose significantly by both drugs. Fasting and meal induced insulin secretion were not affected by either olanzapine formulation. These findings were independent of schizophrenia, adiposity and physical activity (measured by accelerometer). The mechanism causing these lipid anomalies is not known. We propose that olanzapine inhibits the lipoprotein lipase (LPL) activity in the muscles and impairs the stimulatory action of insulin on LPL activity in adipose tissue to induce hypertriglyceridemia. Olanzapine may influence LPL activity either directly or indirectly through its neuroendocrine action to elevate plasma prolactin (PRL) concentrations and reduce circulating cortisol concentration (chapter 4), both known to reduce LPL activity in adipose tissue. Treatment with Bromocriptine, a dopamine D2 receptor agonist with sympatholitic properties (13) which suppress PRL production, had the opposite effects on plasma lipid levels to what we observed in this study (14). In this study, meal induced insulin secretion was not affected. Notably, hyperglycaemic clamp technique is a method which is used to assess insulin secretion and the beta cell sensitivity to glucose, as the glucose concentration is acutely raised with glucose infusion and subsequently held at the desired hyperglycaemic plateau. Obviously, this study was not designed to assess the effect of olanzapine on maximal insulin secretion and beta cell sensitivity. Previously, the effect of olanzapine on insulin secretion was evaluated by hyperglycaemic clamp technique (15). A significant rise in body weight was observed after treatment for 3 weeks with a decrease in insulin sensitivity index. However, there were no changes in the insulin secretory response that were independent of changes in body mass index. In an experimental setting, low concentration of olanzapine (and clozapine), selectively impaired cholingergic-induced insulin secretion by blocking muscarinic M3 receptors in isolated rat islets (16). Ideally, the effect of atypical AP drug on insulin secretion should be evaluated after a short intervention that is not complicated by weight gain. This subject warrants further research.

ATYPICAL ANTIPSYCHOTIC DRUGS: NOCTURNAL ADIPOKINES

In this thesis (chapter 3), 12 h nocturnal leptin concentrations were not affected by short-term olanzapine treatment (neither formulation), which was not complicated by increase in adiposity. Olanzapine, however, did increase 12 h nocturnal adiponectin concentrations. To our
knowledge, there are no studies that have evaluated adiponectin concentrations in healthy volunteers during intervention with atypical AP drugs. In cross sectional studies in patients with schizophrenia/schizoaffective disorder, adiponectin concentrations during treatment with atypical AP drug were reduced (17,18), unaffected (19), despite significant weight gain, or higher (20) than in the control group. In prospective studies, adiponectin level was unaffected despite significant increase in weight or body fat (21,22). In drug-naïve patients with first episode schizophrenia treatment with atypical AP drugs was associated with decreased adiponectin concentrations by significant weight gain and truncal fat accumulation (23).

**ATYPICAL ANTIPSYCHOTIC DRUGS: NEUROENDOCRINE EFFECTS**

While studying the neuroendocrine effects of olanzapine (chapter 4), we saw a significant rise in nocturnal PRL concentrations and reduction in circulating cortisol concentrations by both treatment forms. Olanzapine also shifted the maximal PRL concentrations backwards, dissociating the acrophase of prolactin and cortisol. At the same time, the HOMA index for insulin significantly increased. Elevation of PRL concentrations is frequently observed in patients treated with AP drugs. As far as we know, this is the first study to demonstrate a shift in the maximal serum PRL concentrations, dissociating the acrophase of PRL versus cortisol in humans. Similar endocrine changes coordinate seasonal adaptation of the reproductive and metabolic phenotype in a variety of vertebrate species (24). These changes precede the development of insulin resistant state in animals. In experimental animals, properly timed injections of PRL and cortisol can influence insulin sensitivity. When a hormone profile of insulin resistant state is simulated, the insulin sensitive state is reverted to insulin resistant state (25,26). The suprachiasmatic nucleus (SCN) of the hypothalamus, the biological clock, is considered to be a critical component of a neural oscillator system, which drives circadian hormone rhythms (27). In particular, dopamine and serotonergic neurotransmission seems to be critical in the biological processes regulating insulin sensitivity (28,29). Olanzapine antagonizing action on dopamine and serotonin receptors is likely to be involved in the neuroendocrine effect observed in this study. It is not known if phase relationships of circadian hormone rhythms are involved in the pathogenesis of obesity and insulin resistance in humans, some evidence suggest that the biological clock becomes progressively disturbed in human aging (30) and type 2 diabetes mellitus (31). Our data suggests, however, that PRL and cortisol may be endocrine messengers linking central regulatory pathways with peripheral tissues involved in the control of energy metabolism. Taken the experience in experimental animals into account, in which properly timed PRL and cortisol injections can influence insulin sensitivity, the timing of atypical AP drug might be of importance for the development of insulin resistance. Studies that look at the effect of different timing of atypical AP drugs are sure to be of interest. Recently, nocturnal hormone profiles were measured in patients with schizophrenia, before and after
four weeks of treatment with olanzapine. The area under the curve for cortisol and growth hormone concentrations were markedly reduced during olanzapine treatment. The suppression of cortisol secretion was proposed to be caused by olanzapine’s propensity to reduce dopamine and serotonin neurotransmission, and the reduced growth hormone secretion was proposed to be caused by dopamine D2 antagonistic action (32). Obviously, these issues warrant further research.

**ATYPICAL ANTIPSYCHOTIC DRUGS: GUT HORMONE CONCENTRATIONS**

In order to study whether metabolic effects of olanzapine were caused by changes in gut hormone secretion, we studied the effect of the treatment on these measures (chapter 5), during the intake of mixed meals. Although the secretion of gut hormones is mainly stimulated by nutrient content of the gut, the secretion of various gut hormones is also modulated by monoaminergic neurotransmission of the enteric nervous system (ENS). Since many of the small monoamine neurotransmitter of the CNS have also been identified in the ENS, it is conceivable that olanzapine, that blocks many of these receptors, also affects neural circuit in the ENS. However, treatment with olanzapine for 8 days did not have major impact on the plasma concentration of gut hormones we measured here (PP, PYY, GLP-1, total ghrelin, total glucagon and CCK). Despite the pharmacological differences of the two olanzapine formulations, their effects on gut hormone levels did not differ. Interestingly, we saw a slight, but significant, increase in fasting CCK concentration in both treatment groups. During hyperinsulinemic euglycemia, CCK concentrations increase significantly, but declined rapidly during lipid infusion, suggesting that there might be a negative feedback of circulating FFA on CCK concentrations (33). Keeping in mind, that olanzapine did decrease FFA concentrations (chapter 3), one may wonder whether there is a causal relationship with the rise in CCK. We can not exclude the possibility that olanzapine impacts on other gut hormones, for example acylated ghrelin and bombesin, to impair insulin sensitivity and stimulate weight gain. In spite of the fact, that olanzapine did not influence gut hormone concentrations in this study, olanzapine might still affect gut hormones neurotransmissions in the CNS. Olanzapine might act as a competitive inhibitor of central gut hormone receptors preventing their physiological effect or it might affect available binding sites of gut hormones receptors in the brain, as were reported in olanzapine-treated rodents which had reduced PYY-binding densities in different parts of the brain (34).

In order to study the effects of atypical AP drugs on available receptor binding sites in the brain, one might consider to perform nuclear scans of the brain using radioactive isotope tracers. Unfortunately, this technique is complicated by radioactivity, which in many instances exceeds the allowed dose of radioactivity allowed in healthy volunteers, making this field of research more complex.
DIABETES AND HYPOTHALAMIC ACTIVITY

The brain plays a critical role in the regulation of food intake and energy balance. Circulating metabolic and hormonal cues, reflecting available fuel sources, are perceived and integrated in the hypothalamic nuclei and the brain stem. Via efferent neuroendocrine ensembles food intake and fuel metabolism is regulated. In healthy humans, glucose intake acutely inhibits hypothalamic neuronal activity. Energy imbalance and anomalous fuel fluxes are metabolic hallmarks of obesity and type 2 diabetes. In order to study if there were signs of hypothalamic dysfunction in type 2 diabetes (insulin resistance), we studied the hypothalamic neuronal activity in respond to glucose ingestion with functional MRI. In healthy subjects, glucose ingestion resulted in a prolonged significant decrease in blood oxygen level-dependent signal, representing hypothalamus activity, in the upper and lower hypothalamus. In diabetic patients glucose ingestion did not inhibit the hypothalamic neuronal activity. This finding suggests that the hypothalamus of the diabetic patients inappropriately perceives and/or processes signals reflecting available fuel sources. Failure of neural circuit to properly adapt to nutrients ingestion may contribute to metabolic imbalance in type 2 diabetes. The nature of the hypothalamic response to glucose ingestion is, unfortunately, not known. The fact that, the response to oral glucose is much stronger than to intravenous glucose (35), suggests the hypothalamic response might be influenced by gut hormones, for example GLP-1 or PYY. Moreover, this component of the gut-brain axis may reinforce insulin action after meals to effectively inhibit endogenous glucose production and promote storage of ingested nutrients.

CONCLUSION

In this thesis, we have managed to answer some of the questions addressed on the metabolic side effects during treatment with atypical AP drugs

- The studies in this thesis showed, that metabolic side effects of olanzapine are independent of both schizophrenia and changes in adiposity. Treatment of patients with schizophrenia with atypical AP drugs might though, result in more pronounced metabolic side effects than observed in healthy volunteers, as patients with schizophrenia might be more prone to metabolic anomalies leading to insulin resistant state and diabetes.
- Olanzapine negatively affected insulin sensitivity as it hampered insulin-mediated glucose disposal, which is mainly determined by glucose uptake in muscles.
- Olanzapine induced lipid anomalies that were independent of changes in adiposity and physical activity. The primary site of action of olanzapine-induced lipid anomalies is unclear.
- Olanzapine did not affect fasting or postprandial insulin secretion.
- Olanzapine altered the circadian rhythm of prolactin and cortisol secretion (central effect) as it shifted the maximal concentration of prolactin backwards, dissociating the acrophase
of prolactin and cortisol. In addition, a rise in nocturnal PRL and reduction in cortisol concentrations were observed.

- Olanzapine did not affect gut hormone concentrations. However, olanzapine might still affect gut hormone neurotransmission by other means, i.e. as competitive antagonist or by influencing central receptor binding sites.
REFERENCES


