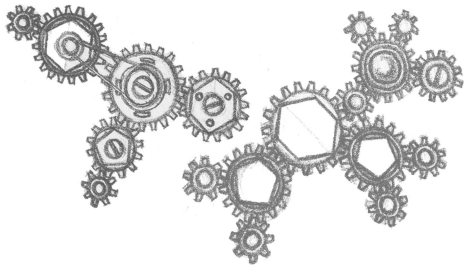

Chapter 1:

Introduction

How the antipsychotic Olanzapine causes weight gain and insulin resistance and the possibility to suppress this by using Topiramate as an adjunctive treatment.

1. Treating schizophrenia, an a-typical story.

Schizophrenia is a psychopathological disorder occurring in approximately 1% of the population characterized by a variety of clinical symptoms, including distortions of thinking and perception, cognitive impairments, motor abnormalities, avolition and apathy, difficulties in communication, and restricted affective expression. In general these abnormalities are classified as positive, negative, cognitive, disorganization, mood, and motor symptoms, which vary between patients and throughout the course of illness [1,2]. Positive symptoms reflect an excess or distortion of normal function and involve impaired reality testing and include delusions, hallucinations, and other reality distortions. Negative symptoms are functions that are normally found in healthy persons, but are diminished in schizophrenia and involve a blunting or loss of affective experience and expression, alogia (poverty of speech), anhedonia (inability to experience pleasure), avolition (lack of initiative), and apathy (lack of interest)[3].

One of the first psychiatrists to introduce the theorem that all these different phenomena belong to a single class of mental disorder was Kreapelin (1919). Kreapelin termed the syndrome *dementia praecox* based on the early onset (adolescence or young adulthood) and chronic duration of the above mentioned disease symptoms. This distinguishes schizophrenia from other mental diseases, which tend to be more periodical (e.g. depression or bipolar disorder) and later in onset [4].

Whereas the negative symptoms of schizophrenia were admittedly part of the disease, it were the positive and motor symptoms that received most attention in the disease management and also led to development of the first generation antipsychotics (FGAs) in the early 1950's. Because FGAs are predominantly antagonistic at the dopamine receptor 2 (Drd2), the dopamine theory was coined stating that the positive symptoms and motor inabilities related to schizophrenia are linked to dopaminergic hyperactivity in the central corticomesolimbic system (e.i., prefrontal cortex and nucleus accumbens) and motor regulating areas (e.i., putamen, basal ganglia, and substantia nigra)[3].

FGAs produce extrapyramidal side effects, such as akinesia (inability to induce movement) and tardive dyskinesia (involuntary movement). From the 1980s onward, the second generation antipsychotics (SGAs) were developed and are characterized not only by antagonizing the dopamine receptors, but also have a high affinity to serotonin receptors. The benefit of SGAs compared to FGAs is that they induce less extrapyramidal side effects [5,6] and show better clinical efficacy in treating the

negative symptoms [7] and protect against cognitive impairment [8].

Olanzapine (OLZ) is a SGA that was FDA approved in 1996 and still is one of the most commonly used drugs in the treatment of schizophrenia. OLZ is - like all SGAs - an a-typical antipsychotic characterized by affinity to a broad spectrum of receptors. Bymaster *et al* [9-11] from the Elli Lilly corporation examined the receptor affinity profile of OLZ by radioligand binding and found that OLZ is primarily antagonistic at the level of the serotonin receptors 5-$HT_{2A/C,3}$, dopamine receptors $D_{1,2,4}$, histamine receptor H_1, muscarin receptors $M_{1,2,3,4,5}$, and adrenergic receptor α_2. In addition to its antagonistic properties, OLZ has minor agonistic activity at the 5-HT_{1A} receptor.

The a-typical property of OLZ is probably one of the main reasons for its clinical effectiveness in treating a heterogeneous disease like schizophrenia. A negative consequence of this variety in receptor types and the fact that these receptors are expressed throughout the body, both central and peripheral, causes OLZ to exert a variety of unwanted and pathological side effects. During the past decades OLZ became particularly notorious for its severe weight gain inducing and diabetogenic side effect. Numerous studies have been performed to investigate the underlying mechanisms. However, due to its a-typical nature, no single endocrine or neuronal pathway has yet been identified that may exclusively explain OLZ's route of action on body weight regulation and the development of type 2 diabetes.

2. Olanzapine treatment and the regulation of energy homeostasis.

Weight gain is a consequence of a positive energy balance resulting from a surplus of energy intake (i.e., absorbed calories) above energy expenditure (i.e., used calories in basal metabolic rate, locomotor activity, and thermoregulation).

Several meta-analyses have reported that OLZ induces more weight gain than most other first and second generation antipsychotics [12,13]. OLZ-induced weight gain is associated with increased adiposity which in turn increases the risk of developing metabolic syndrome, including cardiovascular disease and impaired glucose tolerance leading to the risk of developing diabetes type II [14-16]. Finally, the rapid weight gain due to OLZ treatment does not only affect morbidity and mortality, but also interferes with compliance.

a. Dysregulation of the energy balance by Olanzapine.

Disordered eating behaviors in response to hunger cues, altered appetite sensations [17] and hyperphagia [18,19] have been reported in patients treated with SGAs. Furthermore, alterations in basal metabolic rate are observed in relation to OLZ

treatment [20], as well as a shift into a more sedentary life style [21,22]. OLZ increases energy intake and concomitantly decreases energy expenditure, explaining the observed rapid weight gain. Not surprisingly OLZ has been implemented in the treatment of anorexia nervosa [23-25].

As mentioned above, the antipsychotic action via dopamine receptor antagonism is characteristic for antipsychotic drugs [26]. Evidence suggests that there is a relation between feeding behavior and Drd2 sensitivity. In rodents, food intake is inhibited by Drd2 agonists, which is consistent with the observation that antipsychotic drugs that have antagonist effects on Drd2 stimulate food intake. This is further supported by the observation that obese humans have lower Drd2 binding sites in the brain [27] and that food restriction increases Drd2 receptor levels in rodents [28].

Serotonin (5-HT) also plays an important role in regulating satiety signaling and feeding behavior. Serotonergic neurons work collectively with leptin signaling to decrease food intake. Furthermore, 5-HT2C receptor agonism causes a reduction in food intake in animals [29]. It would therefore seem logical to assume that antagonists of the 5-HT2C receptor, such as OLZ, will inhibit or delay satiety and consequently increase food intake.

Histamine neurons, located in the posterior hypothalamus, project to various brain regions and affect numerous receptor subtypes. One of these subtypes is the H1 receptor, which is also involved in feeding behavior. H1-receptor KO-mice exhibit increased food intake and become obese relative to wild-type mice, whereas H1 agonists suppress food intake [26,30]. This suggests that OLZ's antagonistic effect on the H1 receptor may, at least in part, explain the OLZ-induced increase in food intake. This is indeed confirmed by treatment of rodents with specific H1-receptor antagonists or by chemical depletion of histamine.

Fountaine et al [31] found that OLZ-induced weight gain (2.62kg) in healthy men is primarily a result of increased daily caloric intake (i.e., by 547 kcal per day) over 2 weeks of treatment. Remarkably, resting energy expenditure (REE) was increased in the OLZ treated group compared to the placebo group, whereas daily activity levels did not differ between groups. In a study by Gothelf et al [20] in adolescent schizophrenic patients OLZ-induced body weight gain was also primarily a consequence of increased food intake, without a change in diet composition. Whereas daily physical activity levels were considered very low in the OLZ-treated group, these were not different compared to physical activity levels prior to OLZ treatment. Similar results have been reported by Wichniak et al [32] showing an additional link between low physical activity during OLZ treatment and negative or depressive symptoms in schizophrenic patients. Graham et al [33] demonstrated in

adults with first-episode psychosis that OLZ did not change resting energy expenditure assessed by indirect calorimetry. However, the respiratory quotient significantly increased by 0.12 points in the OLZ-treated group and was highest in those who gained >5% of their initial weight, suggesting a change in fuel metabolism from lipid towards carbohydrate metabolism. Furthermore, Nilsson et al [34] found that the RQ in drug-treated schizophrenic patients increased faster during exercise and therefore transferred more rapidly towards carbohydrate oxidation and anaerobic metabolism, which resulted in a lower physical capacity in drug treated schizophrenic patients. These studies combined show a drug-related disruption in fuel metabolism that affects energy utilization and therefore decreases energy expenditure.

b. OLZ affects locomotor activity.

Rodent studies consistently demonstrate a reduction of locomotor activity by OLZ, which is not accompanied by a decline in food intake [35-38] to balance energy expenditure. Ninan et al [39] showed that OLZ blocks hyperlocomotion and stereotypic behavior (e.i. gnawing) induced by both a Drd1 agonist (SKF 38393) and a Drd2 agonist (B-HT 920). Additionally, they observed that low doses of OLZ (0.5-1mg/kg) reduced apomorphine-induced hyperlocomotion, but only a high dose of OLZ (4mg/kg) inhibited both apomorphine-induced hyperlocomotion and stereotypic behavior, demonstrating a divergence of drug sensitivity of distinct neuronal systems by behavioral output.

Likewise, Kiang et al [40] quantitatively examined the effect of a single dose of OLZ (10mg) on spontaneous locomotor activity in healthy male volunteers and observed that OLZ decreased total motor activity by increasing the amount of time during which subjects were immobile, rather than by affecting the magnitude of movement during periods in which there was activity. These results suggest that OLZ does not impair motor abilities (by antagonism of the nigrostriatal dopaminergic pathway inducing extrapyramidal symptoms), but decreases primarily the motivation to be active (via mesolimbic Drd2 receptor antagonism at the level of the nucleus accumbens) [41].

c. OLZ influences thermogenesis

Several studies report that reduced energy expenditure caused by decreased thermogenesis plays an important role in antipsychotic-induced weight gain [37,42,43]. This is mediated through inhibition of the activity of brown adipose tissue (BAT) via lowered noradrenergic sympathetic signaling. Metabolically active BAT with

its functional thermogenic protein uncoupling protein1 (UCP1) [45] has been identified in adult humans [44] and the involvement of BAT thermogenesis in energy regulation related to OLZ-induced weight gain may have clinical relevance [46].

3. OLZ enhances adiposity

An increase in adiposity, independent of weight gain, appears to be a specific adverse effect of OLZ in both humans and rodents. Increased adiposity is associated with the risk of developing the metabolic syndrome and diabetes, and one possible mechanism underlying this scenario is that OLZ stimulates lipogenesis directly at the peripheral organ level, such as the adipose depots and liver.

Both adipose tissue and liver play major roles in energy homeostasis and lipid metabolism. Recent studies have demonstrated that SGAs induce an up-regulation of transcriptional factors of fatty acid production on cultured human cells [47,48] and primary rat hepatocytes [49]. Cellular lipogenesis is regulated by the activation of the transcription factor sterol-regulatory element-binding protein (SREBP); which consists of several isoforms, of which SREBP1c is the most abundant in the liver and mediates the expression of genes involved in hepatic fatty acid production [47]. Fernø *et al* (2005) showed that i.p. injected clozapine induced activation of SREBP target genes in the liver subsequently resulted in hepatic accumulation of phospholipids and cholesterol. These results demonstrate that SGAs have (acute) effects on hepatic lipid homeostasis [47,49,50].

A study performed by Minet-Ringuet *et al* [51] regarding the effects of SGAs on adipose tissue lipolysis and lipogenesis further supports the idea that lipid metabolism is altered after treatment of SGAs. This study indicated that, among others, OLZ increased fatty acid synthase (FAS) and decreased hormone sensitive lipase (HSL) in adipocytes. FAS and HSL are enzymes involved in lipogenesis and lipolysis respectively, suggesting that the changes seen in these enzymes may explain the adipocyte hypertrophy seen in rats treated with OLZ [51].

Two studies performed by Albaugh *et al* [35,52] additionally support the idea that OLZ alters fat metabolism. Remarkably, Albaugh *et al* found that OLZ reduced free fatty acid (FFA) plasma concentrations; this seems contradictory with the finding that elevated FFA levels are associated with adiposity, diabetes and insulin resistance [53]. However, Albaugh *et al* showed that FFA uptake in adipose tissue of OLZ treated rats is twice as high as in controls, and that this uptake is coupled with increased adipose tissue lipogenesis [35]. In a second study Albaugh *et al* [52] consistently showed that plasma FFA concentrations are lowered by OLZ which was associated with impaired *in*

vivo lipolysis. The higher uptake of FFA was predominantly found in peripheral tissue (with an exception of the heart). Furthermore, a change in respiratory energy ratio (RER) was observed especially during refeeding from oxidation of carbohydrates to fat, which is an indication of blunted metabolic flexibility [52]. Metabolic flexibility is the ability to switch fuel usage between different metabolic states and can be observed by changes in RER. Although one would expect fat oxidation to be beneficial, recent studies indicate that this might not be true. Obesity and diabetes are both associated with elevated fat metabolism and concomitant elevated levels of reactive oxygen species due to mitochondrial overload [52]. Overall these studies performed by Albaugh, Fernø, Minet-Ringuet, and Vik-Mo, suggest that the effects of adipose tissue by SGAs can lead to undesirable side effects on the regulation of energy storage and expenditure which becomes evident in body weight gain.

4. Effects of OLZ on glucose and insulin regulation.

The alterations seen in glucose and insulin levels due to OLZ treatment in patients or rodent studies can occur as a result of different mechanisms, none of which are necessarily exclusively involved. First of all, glucose and insulin regulation could be influenced by direct effects of OLZ on specific target organs (e.g. liver, pancreas, skeletal muscle). Second, the development of insulin resistance could be the indirect consequence of increased adiposity due to behavioral changes, e.g. reduced locomotor activity and hyperphagia. Thirdly, OLZ treatment reduces insulin sensitivity indirectly by increasing up- or down-stream pathways involved in glucose and insulin regulation, e.g. increased circulating cortisol/corticosterone, leptin, GLP-1, or decreased autonomic nervous system activity.

Numerous studies have been performed to study the effects of both acute and chronic treatment of OLZ on glucose regulation.

In vitro studies performed by Johnson *et al* [54] demonstrated that the ability of OLZ to inhibit carbachol-induced insulin secretion by the pancreatic β-cell was, at a relatively high concentration, due to lower receptor affinity, similar to the muscarin receptor antagonist atropine. They concluded that at the level of the pancreas OLZ *in vivo* is capable of disrupting insulin secretion after a glucose load via a muscarin 3 receptor pathway.

In vivo studies investigating the acute effects of OLZ on total body insulin sensitivity, using the hyperinsulinemic-euglycemic clamp, demonstrated reduced glucose infusion rates in OLZ-treated rats indicative of increased insulin resistance [55-58]. In addition, Girault *et al* [59] demonstrated that acute continuous intragastric OLZ (3mg/

kg/hr) administration, but not intracerebroventricular (icv) administration (30µg/kg/h), in combination with a hyperinsulinemic-euglycemic clamp induced hyperglycemia and specifically reduced hepatic insulin sensitivity. In a second study, Girault *et al* [60] demonstrated that acute OLZ administration increases hepatic glucose production, but this effect is blunted after chronic treatment suggesting a desensitization of the liver to OLZ.

Boyda *et al* [61,62] performed glucose tolerance tests in female rats exposed to both acute and chronic treatment of OLZ. In the acute treatment, the glucose tolerance test was performed either 60, 180, or 360 minutes after intraperitoneal OLZ administration. This revealed that the effects on fasting glucose levels were both dose and time dependent, which was also true for the hyperglycemia observed during the glucose tolerance test. Larger effects were seen at a higher dose and closer in time to OLZ administration [61]. An important finding in their study is that the acute effects on glucose tolerance of OLZ are both time and dose dependent and disappear after the drug is cleared (OLZ half-life time is app. 2-3hrs in rats [61]. This suggests that circulating OLZ directly influences glucose tolerance and insulin sensitivity.

Boyda *et al* [62] investigated the effects of chronic versus intermittent OLZ treatment on sensitivity towards development of the metabolic side effects. In their experimental set-up animals were treated with OLZ for five days (15 mg/kg, i.p), followed by a two day 'washout' period, and were then re-challenged with OLZ before a glucose challenge was performed; this was then repeated for ten weeks. They found that rats treated once a week (prior to the challenge only) with OLZ had significantly increased insulin resistance and glucose intolerance, whereas the animals treated with OLZ for five days for ten weeks and with OLZ prior to the challenge showed no changes at the end of the ten weeks. Their findings demonstrated that insulin resistance and glucose dysregulation occurs acutely and remains stable over a period of ten weeks. It suggests that intermittent treatment (not on a daily base) has greater metabolic adverse effects then continuous treatment [62]. In contrast, rats treated chronically had reduced body weight gain compared to intermittent OLZ-treated and vehicle-treated groups, which might have had a beneficial effect on insulin sensitivity.

In a third study, Boyda *et al* [63] investigated in rats the potential of three classes of antidiabetic drugs to block OLZ-induced glucose dysregulation and insulin resistance, and observed that oral hypoglycemic drugs that influence hepatic glucose metabolism, such as metformin and rosiglitazone, are more effective in normalizing olanzapine-induced glucose dysregulation than drugs primarily affecting insulin release, such as glyburide.

Based on meta-analyses of human clinical trials in patients and healthy subjects treated with a-typical agents, Newcomer *et al* [21] described that drug-induced side effects such as insulin resistance, dyslipidemia, and hyperglycemia were primarily related to weight gain. However, even in the absence of weight gain, OLZ treatment has been associated with insulin resistance and increased risk for development of type 2 diabetes. Kim *et al* [64] showed that regardless of the population insulin resistance worsens as weight increases; however, OLZ treatment exacerbated the effect on insulin resistance independent of adiposity. Furthermore, both insulin resistance and type 2 diabetes have been reported to occur at higher rates in drug-naïve schizophrenic populations compared to the general population [65,66], suggesting an increased risk within the patient population per se, which possibly is enhanced by OLZ treatment.

5. Heterogeneity in Olanzapine's responsiveness

The above mentioned studies illustrate a range of mechanisms via which OLZ induces weight gain, obesity, and insulin resistance. These studies have been performed in schizophrenic patients, healthy subjects, rats, and mice, and collectively created a seemingly consistent image of responsiveness to OLZ treatment. However, Kinon *et al* [67] demonstrated in a population of 1336 schizophrenic patients that after 38 weeks of treatment only 15% of subjects actually gained more than 7% of their initial BW, approximately 55% gained some weight, and app. 30% did not gain or lost weight. Remarkably, a positive correlation was observed between weight gain and clinical improvement of the brief psychiatric rating scale (BPRS). Kinon *et al* (2005) therefore postulated that rapid weight gain (4% in 2 weeks) could be used as a marker for OLZ's clinical effectiveness. This study therefore illustrates heterogeneity of responsiveness to OLZ treatment and deserves to be further examined.

a. Disease versus healthy controls

An important cause underlying the heterogeneity in the metabolic responsiveness to OLZ treatment is the divergence of schizophrenia's categorical subtypes, e.g. the orientation towards higher positive compared to negative symptoms, and vice versa. As previously mentioned, positive symptoms are correlated to hyperdopaminergic activity. Pet-scans in schizophrenia patients revealed a decrease of Drd1 receptor expression in the prefrontal cortex [68], whereas an increase of Drd2 expression has been observed in the caudate nucleus [69]. Furthermore, the difference in density of receptor expression does not have to be restricted to brain areas, but might occur throughout the body. For example, Drd2 receptors are expressed at the pancreatic β-cell influencing insulin secretion. Arinami *et al* (1997) found a functional

polymorphism in the promoter region of the Drd2 gene associated with schizophrenia [70], which is probably present in all tissue types that express the Drd2 receptor. Second, schizophrenia patients show structural neurobiological differences that may also influence drug responsiveness. For example, schizophrenia patients have structurally larger lateral ventricles [71], reduced white matter integrity [72], and decreased hippocampal pyramidal neuron size [73]. Finally, schizophrenia is related to deficits of multiple genes [69,74-84], and no single gene deficit has been recognized to explain the complete disease phenotype.

b. Male versus female responsiveness

Most controlled drug studies in healthy volunteers have been performed in males; therefore it should be acknowledged that the results generated from these studies only apply to males. Studies within the patient population, however, have been performed in both males and females and do show some differences in responsiveness between genders. Gender differences in drug responsiveness are mostly related to the level of drug distribution (due to gender differences in adiposity distribution), pharmacokinetics (due to gender differences in drug metabolism), and effects on gonadal hormone regulation (e.g. testosterone, estrogens, and prolactin) [85].

Nonetheless, most human clinical studies did not report clinically significant weight gain differences between genders due to OLZ treatment [86], with a few exceptions reporting that men are more prone to OLZ-induced weight gain than women [87]. For example, Ascher-Svanum *et al* [88] showed that a higher percentage of males increased body weight more than 7% BW than females, but additionally showed in both genders that weight gain during OLZ therapy was linked to improvements in both positive and negative symptom dimensions in the treatment of schizophrenia. This is somewhat contradictory to Goldstein *et al* [89] who reported that women show a clinically better treatment response than men. In addition, they show that premenopausal women had a better treatment response than postmenopausal women, regardless of treatment and chronicity. Waxman *et al* [90] suggested that the higher clinical efficacy of OLZ in woman is due to lower hepatic drug metabolism in women compared to men.

c. Gender differences in animal studies

Gender differences in OLZ-induced weight gain are commonly seen in animal studies. When Olanzapine is administered to female rats, rapid weight gain and hyperphagia are observed [15,91], whereas studies using male rats predominantly reported an absence of weight gain [36,92,93]. However, these studies in male rats did report an

increase in adipose tissue despite the decrease in body weight gain and the absence of hyperphagia. There are no differences between female and male rats in the Olanzapine-induced reduction in locomotor activity [94], increases in prolactin levels [15,92], impaired whole-body insulin sensitivity [55], and hypothermia [43].

In humans, OLZ is considered a prolactin sparing drug [95]. Nonetheless, Melkersson *et al* [96] reported hyperprolectinemia in 24% of OLZ treated subjects and was more common in female subjects than men. Hyperprolactineamia induced by antipsychotic drug treatment is related to symptoms of impotence, menstrual disturbances, decreased libido, and infertility [96-98], as well as to decreased bone mineral density and osteoporosis in both humans [99] and rats [100].

6. Adjunctive therapies

Although non-pharmacological approaches to attenuate OLZ-induced weight gain by means of group intervention, cognitive-behavioral therapy, or nutritional counseling were effective [101], a search for adjunctive drug therapies to inhibit OLZ's negative metabolic effects has gained interest over the last decades. The study of such pharmacological adjunctive therapy to counteract OLZ-induced metabolic effects may also give insight in the mechanisms via which OLZ may act. Nonetheless, the adjunctive therapy is only of interest if it does not influence OLZ's clinical effectiveness.

As mentioned above, 5-HT_{2C} antagonism has been linked to weight gain, therefore several researchers studied the effectiveness of adjunctive fluoxetine treatment -a specific serotonin re-uptake inhibitor- to decrease OLZ-induced weight gain. Unfortunately, adjunctive fluoxetine treatment failed to reduce OLZ-induced weight gain [102]. In addition, it reduced OLZ's effectiveness in treating positive and disorganized symptom dimensions [103]. The combination of OLZ and fluoxetine has also been studied for the effectiveness in treating major depressive disorder (MDD), and showed to increase body weight by >7% (potentially clinically significant; PCS) during 76 weeks of treatment in 56% of patients. The patients that reached PCS after 6 weeks of treatment showed a 4.6 times higher risk of increasing body weight by >15% after 76 weeks of treatment [104]. Altogether, these results showed not only that fluoxetine is not an effective adjuvant to OLZ treatment, but also suggest that OLZ-induced weight gain is not based on its antagonistic action on serotonin receptors.

Reboxetine, a selective norepinephrine reuptake inhibitor (NRI), is an antidepressant used for the treatment of unipolar depression [105,106]. Poyurovsky *et al* [107]

demonstrated, in two controlled patient studies, that reboxetine significantly attenuates, but not completely inhibits, OLZ-induced weight gain without affecting OLZ's clinical effectiveness, suggesting that noradrenergic neurotransmission is, at least in part, involved in OLZ-induced weight gain.

Sibutramine is a serotonin-noradrenalin-dopamine re-uptake inhibitor which was marketed as a weight loss drug, but retracted from the market in 2010 due to associated increased cardiovascular events and strokes. Henderson *et al* [108] reported that sibutramine reduced OLZ-induced weight gain, even though the sibutramine treated-subjects exhibited an increase of cardiovascular pressure. In addition, cholinergic side-effects and sleep disturbances were observed twice as often compared to the OLZ+placebo group [108]. Van der Zwaal *et al* demonstrated that increased motivation for palatable food may contribute to OLZ-induced weight gain in rats. Van der Zwaal *et al* further postulated that the ability of sibutramine to reduce motivation for palatable food may play an important role in the efficacy of sibutramine as an add-on treatment to counteract OLZ-induced weight gain [109]. As already mentioned, sibutramine was retracted from the market before studies could investigate the effect of sibutramine on OLZ's clinical efficacy.

Baptista *et al* [110] first reported that the antidiabetic agent metformin failed to affect OLZ related body weight gain. In a follow-up study [111] with increased group size, adjunctive metformin therapy did induce a small, but significant, attenuation of OLZ-induced body weight gain. Metformin also improved the insulin resistance index slightly. Because of the limited effects, metformin does not appear to be a major candidate as adjunctive therapy to be considered for treatment against OLZ-induced insulin resistance.

Anderson *et al* [112] hypothesized that, since melatonin levels are decreased and circadian rhythms are altered in schizophrenic patients, the adjunctive use of melatonin in schizophrenia may augment the efficacy of antipsychotics through its anti-inflammatory and antioxidative effects. Raskind *et al* [113] demonstrated in rats that OLZ reduced night-time melatonin levels, and that melatonin replacement therapy blocked OLZ-induced weight gain. Similar results of melatonin's effectiveness in attenuating OLZ-induced weight gain have recently been reported by Modabbernia *et al* [114] in first-episode schizophrenic patients. No detrimental side-effects have been reported in these studies, which makes melatonin an interesting candidate as an adjunctive treatment to inhibit OLZ-induced weight gain.

High circulating levels of cortisol/corticosterone are associated with insulin resistance, and glucocorticoid receptor antagonists are used for treating type 2

diabetes. Multiple rat studies demonstrated increased serum levels of corticosterone after OLZ administration [115] related to hepatic insulin resistance [59]. In addition, glucocorticoid receptor antagonism has shown to inhibit OLZ-induced weight gain and to improve related glucose-insulin homeostasis in multiple rodent studies [116-118]. In contrast, Cohrs *et al* [119] found a decrease of ACTH and serum cortisol after acute OLZ treatment in healthy human volunteers. Nonetheless, Gross *et al* [118] showed in healthy men that the glucocorticoid antagonist, mifepristone, attenuated OLZ-induced weight gain over a two weeks period. All together these studies demonstrate a potential for glucocorticoid antagonists as adjunctive treatment to inhibit OLZ-induced weight gain. However, more long-term controlled studies in the patient population should be performed.

Histamine 1 receptor antagonism is related to increased food intake. Poyurovsky *et al* [120] were the first to demonstrate that betahistine, an H1 agonist/H3 antagonist, was effective as an adjunctive treatment to inhibit OLZ-induced weight gain. Deng *et al* [121] demonstrated in female Sprague-Dawley rats that adjunctive betahistine treatment attenuated OLZ-induced weight gain by -45%. Nonetheless, betahistine did not have an effect on OLZ related hypoactivity, which shows that OLZ-induced weight gain is a consequence of dysregulation on both sides of the energy balance.

Topiramate, an anticonvulsant drug, has weight reducing properties. Human trials in which OLZ has been administered together with TPM have shown potential favorable results. In a 12 week study performed by Narula *et al* (2010), first episode, drug-naïve schizophrenia patients received either OLZ+placebo or OLZ+TPM. Those that received TPM showed a decrease in BW and BMI, whereas the group receiving OLZ showed a significant increase in BW and BMI compared to baseline. Furthermore, the OLZ+placebo group showed increased levels of insulin and triglycerides [143]. Vieta *et al* (2004) observed both metabolic as well as clinical beneficial effects of adjunctive TPM treatment in schizophrenia patients treated with OLZ. Moreover, as TPM administration was titrated to app. 300mg/day, concomitant OLZ dosing decreased below 10mg/day. This suggests that adjunctive TPM treatment has some additive beneficial effects to OLZ treatment, possibly related to its mood stabilizing properties [144].

7. Topiramate

Topiramate (TPM), an anti-seizure agent used in the treatment of epilepsia, exhibits weight loss effects and seems to have potential beneficial effects on the adverse effects of OLZ [5,14,122,123]. TPM contains a naturally occurring sugar D-fructose attached to a sulfamate. It possesses several pharmacodynamic properties, which

include inhibitory effects on glutamate-activated ion channels, inhibitory effects on voltage-gated Na^+ and Ca^{2+} ion channels, and a variable modulatory effect on GABA-activated ion channels [124]. TPM is also shown to have an inhibitory effect on the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamate receptor, but not on the N-methyl-D-aspartic acid (NMDA) glutamate receptor. However, it is thought that TPM indirectly affects NMDA receptor activity via its inhibitory effects on AMPA. AMPA receptor activity is known to indirectly influence the activity of NMDA receptors [124-126].

Besides TPM's capability of positively influencing the activity of GABA and negatively influencing the activity of AMPA-glutamate receptors, it also inhibits the activity of carbonic anhydrase (CA) [125,127]. In addition, several groups demonstrated that CA inhibitors are competent inhibitors of lipogenesis and in this way contribute to the observed weight loss as a result of TPM treatment [125,128]. Despite its broad spectrum of targets, TPM does not aggravate psychotic symptoms of schizophrenic patients [129-131], but rather to have mood stabilizing properties that might be beneficial as an adjunctive treatment to OLZ [132].

Topiramate-induced weight loss has been observed in a study performed by Tremblay *et al* [133] in obese subjects. The majority of the weight loss by TPM was explained by changes in body composition, in particular a reduction in adiposity [133]. It is suggested that TPM induces body weight loss by having both central and peripheral effects. One of these effects is a decrease in spontaneous energy intake by inducing a general reduction in appetite and hunger [133]. Other studies suggest that particularly the inhibitory effects of TPM on carbonic anhydrases and other enzymes involved in de novo lipogenesis might be responsible for the observed TPM-induced weight loss [125].

Various studies suggest that TPM is able to dampen energy deposition. It has been shown that TPM inhibits fat deposition while reducing the activity of lipoprotein lipase (LPL) in white adipose tissue (WAT) [127]. A study performed by York *et al* [134] observed that the reduction in body fat accounted for all the reduction in body weight seen. TPM not only reduced fat deposition, but also decreased food intake in female rats. Important to note is that TPM increased energy expenditure in the absence of alterations in food intake [127]. Alterations in energy expenditure are suggested to be due to increases in LPL activity in the skeletal muscles and in brown adipose tissue (BAT), suggesting TPM's potential to promote stored substrate utilization [127,134].

As mentioned earlier, reduced insulin sensitivity and deregulation of fuel utilization

plays an important role in patients treated with a-typical antipsychotics [34,135]. Keeping this in mind and based on the fact that the liver plays a central role in lipid and carbohydrate metabolism, it is suggested that TPM's action on hepatic lipid metabolism [136] form the basis of TPM's (potential) anti-diabetes and anti-obesity effects. Recent studies performed in Zucker diabetic fatty (ZDF) and high-fat fed (HFD) Wistar rats revealed that TPM treatment may lead to marked improvements in insulin sensitivity [137-139]. In ZDF rats, seven-day treatment with TPM resulted in alterations of hepatic gene expressions, with down-regulation of several genes involved in hepatic fatty acid synthesis and up-regulation of two genes (3-2-trans-enoyl-CoA isomerase and mitochondrial acyl-CoA-thioesterase) involved in β-oxidation [136]. This indeed suggests that part of the mechanisms underlying the effects of TPM includes alterations in hepatic lipid metabolism.

Furthermore, TPM treatment in ZDF rats improved insulin sensitivity specifically in adipocytes and not in muscle [139]. In contrast, HFD-Wistar rats showed improved insulin sensitivity in both adipose tissue and muscle. Wilkes *et al* [138] observed elevated levels of high molecular weight (HMW) adiponectin following TPM treatment. Adiponectin, specifically the HMW form, has been shown to increase insulin sensitivity through the activation of AMPK. Wilkes *et al* showed that TPM protects HFD-fed Wistar rats from developing HFD-induced insulin resistance, which is due to the activation of AMPK activation in skeletal muscles, but not in liver [138]. Overall the findings of Wilkes and Liang suggest that TPM improves energy metabolism through improving the balance of lipolysis and lipogenesis via various transcription factors and increasing HMW adiponectin which improves insulin sensitivity through AMPK activation. Interestingly, Richard *et al* found a correlation between Olanzapine treatment and reduced serum levels of HMW adiponectin in schizophrenic patients [140].

As mentioned before, TPM is capable of reducing body weight and food intake [137]. In addition, improvements in glucose metabolism and insulin sensitivity are also seen in both rodents and (obese) patients treated with TPM. Knowing that weight loss normally improves glucose and insulin profiles it is an important issue to clarify whether the anti-hyperglycemic effect of TPM is dependent of the reduction in body weight. Liang *et al* (2005) showed that TPM reduced fasting blood glucose levels independent of weight loss. Not only were the fasting blood glucose levels reduced, but TPM also increased glucose stimulated insulin release by two fold independent of weight loss [141].

The observed improvements seen in glucose homeostasis after TPM treatment might be mediated, at least in part, by an improvement of glucose uptake in skeletal

muscle. Skeletal muscle accounts for more than 70% of glucose disposal in the body. GLUT 4, an insulin regulated glucose transporter, is translocated from the cytoplasm to the cell membrane as a result of the activation of AMPK, allowing uptake of glucose into the cell. Studies with L6 skeletal muscle cells show a twofold increase in glucose uptake when treated with TPM (Ha *et al*, 2006). Ha *et al* found that such improvements in glucose uptake were mediated through the AMPK-mediated pathway and not through the PI3K mediated pathway. AMPK and PI3K are both important mediators in the regulation of two independent pathways involved in glucose transport [142].

It seems that TPM not only stimulates lipolysis, but also improves fasting blood glucose levels and insulin sensitivity independent of weight loss. These observations can be explained by the up-regulation of factors involved in lipolysis, such as increases in HMW adiponectin can improve AMPK mediation, which in turn stimulates the uptake of glucose via GLUT 4 [136,138,139,142]. Altogether, TPM has beneficial effects on energy homeostasis and insulin sensitivity and has demonstrated potential in human trials to be an effective adjuvant to OLZ treatment, thereby preventing OLZ-induced weight gain and insulin resistance. However, not much is known about a drug-drug interaction between OLZ and TPM or the underlying mechanisms via which both drugs affect body weight regulation.

8. Scope of this thesis

The studies described in this thesis focus on OLZ's effect on total body glucose and insulin regulation and the potential of TPM to counteract these effects.

First, the acute effects of OLZ and TPM on glucose tolerance, thermogenesis, and pharmacodynamics (Chapter 2) are described. The data in these studies reveal that there are marked effects of adjunctive TPM administration on circulating OLZ levels, with direct consequences on thermogenesis, circulating corticosterone, glucose and insulin levels during an intragastric (IG)-glucose tolerance test (GTT) in male Wistar rats. Based on these data, we hypothesized that OLZ may have disruptive effects on glucose absorption from the gastrointestinal tract. In Chapter 3, we demonstrate that OLZ, indeed, influences gastrointestinal functioning and glucose absorption acutely, which might have implications for adequate insulin regulation. In Chapter 4, effects of chronic OLZ treatment on energy homeostasis in female rats are described and point out that OLZ increases BW gain and reduces locomotor activity and thermogenesis. In Chapter 5, we investigate in female Wistar rats whether OLZ increases insulin levels during an intravenous (IV)-GTT. This was indeed the case and we also observed that multiple doses of OLZ disrupted the estrous cycle and increased circulating prolactin

levels. We hypothesize that the increase of circulating prolactin might be a key factor in the gender specific weight gain effects of OLZ seen in rats. Chapter 6 discusses chronic treatment of OLZ in conjunction with TPM treatment in male Wistar rats, which do not gain weight on OLZ treatment. Male rats may therefore be used as a model to study OLZ-induced insulin resistance independent of BW gain. Chapter 6 also describes the proteomic liver profile after chronic OLZ and/or TPM treatment, and reports that the OLZ-induced signals of hyperglycemia in male Wistar rats are not counteracted by TPM. Instead, single TPM treatment was found to improve insulin sensitivity and to inhibit an increase in adiposity induced by palatable food intake. Furthermore, the proteomic liver profile suggests a role for reduced growth hormone levels due to OLZ treatment in the male Wistar rat. Next, it was hypothesized in Chapter 7 that the responsiveness to OLZ treatment is dependent of the psychogenetic background as well as the environment an animal is exposed to. Hence, we used the Roman High and Low Avoidance selection strain and housed it in a sedentary or active environment (free access to a running wheel). These rat lines have previously been shown to be different in diet induced obesity and insulin sensitivity, but also demonstrated a difference in dopaminergic reactivity. In this study we demonstrate that the selected rat lines respond differently to OLZ treatment and that the environment is of major influence on drug responsiveness. In addition, we show that these selection lines differ in central corticomesolimbic receptor expression, which may explain the difference in drug responsiveness. In addition a difference in circulating prolactin levels was observed, suggesting a difference in dopaminergic regulation of the anterior pituitary between selection lines. Finally, Chapter 8, in association with PRA Research, a study in healthy male volunteers was performed to study TPM's potential to inhibit OLZ-induced weight gain and associated metabolic side effects. This study showed that low circulating TSH (Thyroid Stimulating Hormone) levels prior to the start of drug treatment may predict increased OLZ-induced weight gain. Moreover, TPM seems to be specifically effective in reducing OLZ-induced weight gain in subjects with low TSH levels. Like prolactin and GH, the thyroid hormones are also regulated via the pituitary, suggesting that pituitary regulation is a prominent factor in OLZ-induced weight gain and disruption of energy homeostasis, which is discussed in the final chapter.

In short, the combined studies in this thesis show that OLZ exerts its effects at multiple sites in the body, both centrally as well as peripherally. In addition, it underscores that the responsiveness to chronic OLZ treatment is dependent on species, psychogenetic background, gender, and environment.

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