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The a-typical effects of olanzapine on body weight regulation

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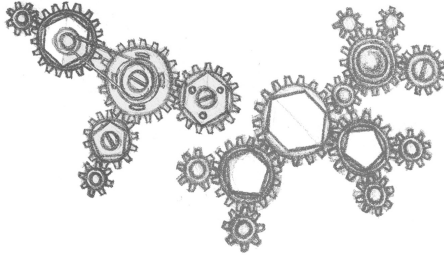
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Chapter 9

General Discussion





General discussion

The antipsychotic Olanzapine (OLZ) is a drug with an atypical receptor binding profile. This atypical nature is both its strength and its weakness. The strength is a clinical effectiveness that is considered superior to the first generation of antipsychotics; the weakness is the high variety of unwanted side-effects [1]. We found that many of the side effects of OLZ seem to be related to the same underlying pathway, a disruption of dopaminergic regulation of the anterior pituitary. In the following paragraphs the main focus will be on the neuroendocrine effects of dopaminergic (dis)functioning of the pituitary. But first the main outcomes of the studies described in this thesis will be summarized. In addition, the different animal models for studying OLZ's effect on weight gain and metabolism will be evaluated as well as the potential benefit of using the anti-epileptic drug Topiramate (TPM) as an adjunctive treatment to counteract the side effects of OLZ.

1. Main outcomes

Administration of OLZ resulted in hypothermia, locomotor inactivity, and increased circulating corticosterone levels. Topiramate (TPM) by itself had no effect on these parameters, but combined administration of TPM with OLZ enhanced the OLZ-induced effects on hypothermia, locomotor activity, and corticosterone. We found that these effects might be explained by the observed increase of circulating OLZ levels when TPM is adjunctively administered. Moreover, at the dosage used, TPM presumably inhibits OLZ metabolism (Chapter 2).

In an intragastric-glucose tolerance test (IG-GTT), circulating glucose and insulin peak levels were dampened by OLZ, independent of adjunctive TPM treatment (Chapter 2). In a follow-up study we found that glucose uptake from the gastrointestinal tract was hampered by OLZ, mainly due to decreased gastric emptying in combination with a reduction of gastrointestinal peristalsis. Furthermore, OLZ was able to inhibit acetylcholine and serotonin induced duodenal and jejunal smooth muscle contraction (Chapter 3).

Chronic OLZ treatment increased body weight and adiposity in female Wistar rats (Chapter 4,5), which was, at least in part, caused by reduced thermogenesis and locomotor activity and a deranged diurnal feeding pattern. Dependent of OLZ dosage, food intake was increased in female Wistar rats (Chapter 5). Furthermore, chronic OLZ treatment (4mg/day) in female Wistar rats resulted in an increased insulin response during an intravenous-glucose tolerance test (IV-GTT) indicative of reduced

insulin sensitivity (Chapter 5). Based on the examination of vaginal smears, chronic OLZ treatment also led to a disruption of the estrous cycle. In addition, the regular cyclic decrease of food intake on the day that circulating β -estradiol levels peaked (as seen in the controls) was absent in the OLZ treated group. The disruption of cyclicality was, however, not seen in a 5 day examination of circulating β -estradiol. All together, one may conclude that the OLZ-induced weight gain and concomitant reduction of insulin sensitivity in the female Wistar rat may be explained by the decreased thermogenesis and locomotor activity, absence of a β -estradiol anorectic effect, increased prolactin levels, and increased food intake; (Chapter 4, 5).

Our studies with the Roman High/Low Avoidance (RHA/RLA) rat strains revealed that OLZ-induced weight gain may also be dependent on the psychogenetic background. The main outcome of this study was that the effects of OLZ on body weight gain and adiposity only occurred in the RHA rat strain. We particularly focused on the possible underlying mechanisms and found that the RHA is characterized by elevated central dopaminergic activity, which corresponds with the observed lower circulating prolactin levels in the RHA. Furthermore, the increased expression of *Drd1* mRNA in the prefrontal cortex (PFC) of the RHA corresponds with the increased density of *Drd1* in the PFC of schizophrenic patients. The latter shows that the RHA may be a favorable animal model to study the underlying mechanisms of psychopathologies, such as schizophrenia, but also the behavioral and physiological responses to neuroleptic treatment (Chapter 6). This was further supported by the finding that sensitization of the dopaminergic pathways in the active environment only occurred in the RHA. The latter was primarily based on increased dopamine receptor *Drd1* expression in the PFC of the active RHA. In the RHA this hypothesis was further supported by reduced circulating prolactin levels in the active environment. This proposed sensitization of the dopaminergic system in the RHA due to running wheel activity may explain the enhanced OLZ-induced weight gain observed in the RHA housed in the active environment (Chapter 6).

In male Wistar rats, glucose and insulin responses were not different between chronically OLZ treated animals and controls. However, body weight matched control treated male Wistar rats showed a lower insulin response compared to OLZ treated and ad lib fed control groups. This points to a decrease of insulin sensitivity by OLZ (Chapter 7). Acute administration of TPM had no effect on insulin sensitivity (Chapter 2). In contrast, 14 days of chronic treatment with TPM led to a marked reduction in adiposity and a reduction in insulin response during an IG-GTT which suggests that chronic TPM may lead to improved insulin sensitivity (Chapter 7).

Chronic OLZ treatment led to an inhibition of weight gain in male Wistar rats with no

apparent changes in insulin sensitivity (Chapter 7). However, the hepatic proteomic profile of the OLZ treated animals seemed to be linked to hyperglycemia due to increased levels of aldose reductase (AR) and glucose-6-phosphate dehydrogenase (G6PD). Both enzymes are related to the polyol pathway converting glucose into sorbitol. Up-regulation of AR is related to the accumulation of intercellular sorbitol levels, which is associated with diabetic complications, e.g. nephropathy, retinopathy, and neuropathy. Furthermore, the down-regulation of hepatic CYP2C11 and the up-regulation of CYP2C12 are linked to a disruption of growth hormone secretion. This presumed effect on growth hormone release could additionally explain the observed inhibition of weight gain and reduction of skeletal muscle weight by OLZ in the male Wistar rat (Chapter 7).

Adjunctive TPM treatment enhanced the weight loss after OLZ treatment in the male Wistar rat. However, no major effects were observed of TPM on the OLZ-related changes in the hepatic proteomic profile (Chapter 7). The acute administration of OLZ and adjunctive TPM revealed that TPM increased circulating OLZ levels, indicative of reduced OLZ metabolism. Chronically administered OLZ+TPM resulted in a specific increase alanine aminotransferase, which can be a sign of liver damage [2]. Moreover, chronic TPM treatment increased UDP-glucuronosyltransferase, a protein also involved in the glucuronidation process of OLZ metabolism [3]. The latter may be a specific route of action in which TPM affects OLZ metabolism. Future studies are necessary to investigate these drug-drug interactions in a dose dependent manner to reveal the clinical importance of such an interaction. Except for the expression of sulfotransferases STA2A1 and STA2A2, TPM did not affect OLZ-induced proteomic expression levels. Therefore it seems that TPM's route of action on weight loss and insulin sensitization does not directly interfere with OLZ's route of action. Moreover, in the male Wistar rat adjunctive TPM treatment appeared to enhance OLZ's effects at a physiological level, therefore TPM does not seem to be an appropriate adjunctive therapy to OLZ treatment in the absence of weight gain (Chapter 2,7).

The variation in responsiveness to OLZ treatment observed in the Roman strains reflects the variety in responses that were seen after OLZ treatment male volunteers (Chapter 8). We found that subjects with a low basal TSH profile prior to 14 days of OLZ treatment were more susceptible to OLZ-induced weight gain compared to individuals with a high basal TSH response. Chronic OLZ treatment resulted in an increased TSH response after 6, 13, and 14 days of treatment exclusively in subjects with a low baseline TSH profile. Individuals with a low basal TSH response were also susceptible to the inhibition of OLZ-induced weight gain by adjunctive TPM

treatment. Individuals with a high basal TSH response, however, had relatively stable body weights independent of OLZ or OLZ+TPM treatment (Chapter 8). In addition, we observed that 1) body weight gain was correlated with increased HOMA-IR and insulin responses, and 2) both groups gaining or losing weight displayed an hypothermic response at the first day of OLZ or OLZ+TPM treatment.

Taken together, our data emphasize the importance of prolactin, growth hormone, and TSH in the responsiveness to OLZ treatment. All three hormones are secreted by the endocrine anterior-pituitary. Whereas prolactin and TSH secretion are down-regulated by dopamine, growth hormone secretion is up-regulated by dopamine. The antagonistic property of OLZ on the dopaminergic system may explain the observed effects of increased circulating prolactin and TSH levels as well as the suggested decrease of circulating growth hormone levels and, therefore, could be one of the main causes of OLZ-induced metabolic side effects. Interestingly, our data demonstrates a variation in the liability of OLZ-induced weight gain within the population (Chapter 6, 8).

2. Neuroendocrinology to predict OLZ treatment susceptibility.

In chapter 8 we argued that a low TSH profile may predict the susceptibility to OLZ-induced weight gain. In addition, our studies combined revealed that in particular the dopaminergic regulation of the anterior-pituitary gland may play an important role in the observed variation in responsiveness to OLZ treatment, due to increases of circulating PRL levels (Chapter 5,6) and presumably decreased GH secretion (Chapter 7).

The tuberoinfundibular system is a local network of blood vessels surrounding the infundibulum, which connects the hypothalamus with the pituitary gland (see fig. 1). Neurons from the hypothalamus secrete hormones, such as TRH, GHRH, and CRH into the tuberoinfundibular system from where they are transported to the anterior-pituitary gland and promote the secretion of resp. TSH, GH, and ACTH. Dopaminergic neurons from the arcuate nucleus and median eminence also secrete dopamine into the tuberoinfundibular system inhibiting (e.g. PRL, TSH) or stimulating (e.g. GH) hormone secretion from the anterior-pituitary gland [4,5]. Somatostatin secreted from neurons originating in the hypothalamus is stimulated by dopamine as a negative feedback inhibiting GH release [6], but also GABAA and glutamate additionally inhibit or stimulate pituitary secretion [7]. The individual variation to pharmacological challenges of the hypothalamic-pituitary axis may be insightful, and could act as a predictor for the susceptibility and individual responsiveness to neuroleptic drug treatment.

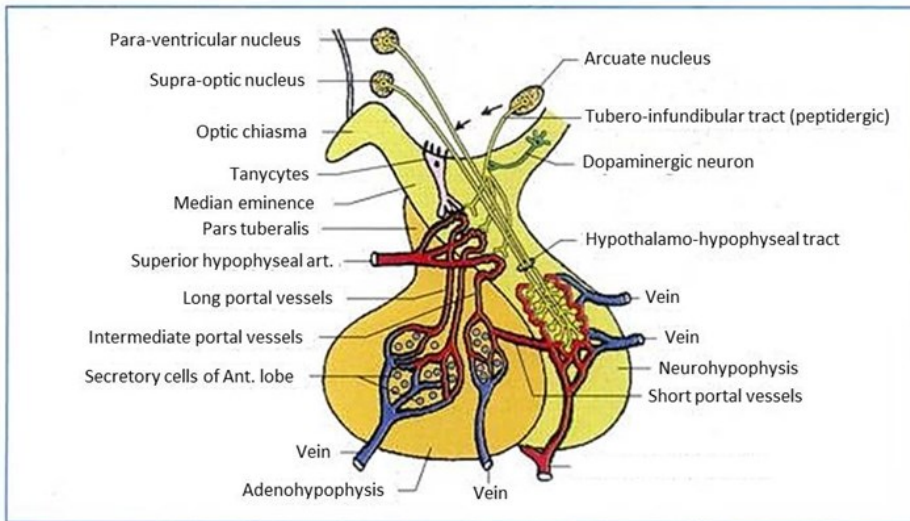


Fig 1: Blood supply and nerve supply of the hypophysis cerebri. *From: S. Pujari; Useful notes on hypophysis cerebri; Brain, General Anatomy Fig 8.7.*

Pharmacological studies investigating hypothalamic-pituitary responses in psychiatric disorders have been performed predominantly in the 1980's. Whalley et al (1984) found an increased GH response as well as a decrease of PRL levels, after administration of apomorphine -a non-selective dopamine agonist- in drug-naïve newly admitted psychotic patients compared to control subjects [8]. In addition, Zemlan and colleagues (1986) demonstrated that patients with elevated thought disorders and auditory hallucinations had elevated GH responses to apomorphine and suggested an association with central DA receptor "supersensitivity". A fixed-dose neuroleptic trial showed that thought disorder and auditory hallucinations responded rapidly to treatment with a DA receptor blocker (haloperidol), while no significant effect on other symptom cluster scores (paranoid delusions or catatonia) occurred during the initial 2 weeks of treatment. [9]. Furthermore, Meltzer et al (1984) also found that the apomorphine-induced GH response was correlated with psychosis rating and negative symptoms scale [10]. Gil-Ad and colleagues (1981) revealed an increased GH response after a luteinizing hormone releasing hormone (LRH) and thyrotropin hormone releasing hormone (TRH) challenge in schizophrenic drug-naïve male juveniles [11]. Medication with a dopamine antagonist, i.e. chlorpromazine, thiorizadine, or haloperidol, inhibited the LHR-induced GH response, but did not decrease the GH response to TRH administration. The latter implies that TRH induced GH secretion is independent of a dopaminergic pathway. However, infusion of dopamine does inhibit TRH-induced TSH release [12]. The latter may relate to Langer et al (1983), who showed that a 'blunted' TSH response prior to

neuroleptic treatment was a predictor for treatment outcome, which was based on an improvement of the brief psychiatric rating scale (BPRS) [13]. Langer and colleagues demonstrated that during neuroleptic treatment, with a dopaminergic antagonist, the TSH response to a TRH challenge was 'deblunted'. Therefore, they suggested that subjects with increased dopaminergic activity have a lower TRH-TSH response, which is reversed by dopamine antagonism [13].

Somatostatin inhibits GH release, but similarly to dopamine it attenuates TRH-induced TSH and PRL release; exemplary for the complex interactions of neurotransmitters in the hypothalamic-pituitary regulation. An increased level of somatostatin has been related to positive symptoms in schizophrenia patients, by Saiz-Ruiz and co-workers (1992). They postulated that the increase of somatostatin is in accordance with the theory of dopaminergic hyperactivity in schizophrenia, because dopamine stimulates somatostatin secretion [14]. The increase of somatostatin in schizophrenic subjects is somewhat contradictory with the findings of Morris et al (2008), who observed decreased levels of somatostatin mRNA in the PFC of schizophrenic subjects [15], and the findings of Ferrier and co-workers (1983), who found decreased levels of somatostatin in the limbic lobe [16]. The latter, however, was correlated to negative symptoms in schizophrenia, which may suggest a mechanistic difference between negative and positive symptoms based on somatostatin regulation, whereas the work of Morris et al (2008) relates to the observation of altered inhibitory circuits of the PFC in schizophrenia [15].

OLZ's clinical effectiveness, compared to first generation antipsychotics, is primarily based on the improved treatment outcome of negative symptoms of schizophrenia. However, multiple studies have demonstrated that subjects susceptible to OLZ-induced weight gain benefit primarily of improved clinical scores in positive symptoms of schizophrenia [17]. Indeed, our studies also show that subjects most susceptible to OLZ-induced weight gain display physiological parameters related to increased dopaminergic activity, e.g. low PRL and low TSH levels, and therefore to positive symptoms of schizophrenia. These physiological parameters can be accurately measured and, thus, can be used as predictors of treatment responsiveness. Unfortunately, these pharmacological neuroendocrine challenges are not exploited in common clinical practice.

3. Evaluation of the rat as a model to study OLZ-induced metabolic side effects

Schizophrenia is a heterogeneous disease expressing itself in multiple phenotypes, e.g. either predominantly positive symptoms or negative symptoms, and is distinctive

from other psychogenetic disorders through an early disease onset during adolescence or early adulthood. As mentioned before, the atypical receptor binding profile of the second generation antipsychotics, such as OLZ, is presumably the reason for its broad clinical effectiveness, but also causal to the multiple side-effects associated with OLZ treatment. One should note that OLZ's clinical effectiveness (and related side-effects) is not similar among patients. This high variation complicates the study of the underlying mechanisms of the OLZ-induced side-effects as well as the search for an appropriate animal model.

Still, one may argue that an animal model does not require all characteristics of the disease studied, but should exhibit at least one phenomenon of interest characteristic of the disease or drug-induced side-effect. But it is essential that the underlying mechanism responsible for the observed phenomenon in the animal model has the same mechanistic origin as the disease or drug-induced side-effect of interest in human.

a. Gender as a specific factor in OLZ treatment outcome.

The main observation that questions the rat as a suitable model to study OLZ-induced side-effects on energy homeostasis is the lack of OLZ-induced weight gain in male rats. This gender specific divergence in weight gain is less clear in human studies. Nonetheless, an extensive review of Abel *et al* (2010) on the sex differences within schizophrenia does conclude that 1) the occurrence of OLZ-induced body weight gain is more prominent in women, 2) the incidence of hyperprolactinemia is increased in women, and 3) women show better treatment response to OLZ. The latter has been attributed to pharmacokinetic differences of OLZ between genders, in which men have a nearly 40% faster OLZ clearance rate than women [18]. Therefore, it is important to understand the underlying mechanisms of this gender discrepancy in OLZ-induced weight gain.

Thus one may argue that the female rat can be used as a valid animal model to study the metabolic consequences of OLZ-induced weight gain. To study if OLZ-induced side-effects are weight dependent in the female rat, Skrede *et al* (2011) performed a study in which OLZ treated animals were pair-fed with control treated animals. In their study, they observed that pair-feeding of the OLZ treated animals reduced body weight gain to control levels. They did not find increased adiposity or insulin levels in the OLZ pair-fed group. However, they did observe increased levels of circulating triglycerides and several RNA markers for increased lipogenesis in the OLZ pair-fed group similar to OLZ treated *ad lib* fed animals [19].

OLZ-induced weight gain does not occur in male rats [20,21]. Nonetheless, similar to the study of Skrede and colleagues (2011), Albaugh *et al* (2011,2012) demonstrated in male rats also increased lipogenesis and repartitioning of fuel utilization towards lipid metabolism [22,23]. Therefore, the change towards lipid metabolism and impaired metabolic flexibility may be the major consequences of OLZ treatment, independent of weight gain or gender.

It is important to note that OLZ may induce insulin resistance independent of weight gain in humans [24]. The male rat may therefore still serve as a fit model to study OLZ-induced metabolic side-effects, in particular, the insulin resistance, independent of weight gain. This might be relevant for at least a part of the human situation in which some of the OLZ treated subjects also do not gain weight (see figure 2, [17]). In our study (*Chapter 7*), we observed multiple up- or down-regulations of hepatic proteins related to GH inhibition. Therefore, it is interesting that Mann *et al* (2005) could demonstrate in male schizophrenic patients that 4 weeks of OLZ treatment increased circulating levels of cortisol and prolactin, whereas circulating GH levels, especially nocturnal levels, were decreased compared to baseline measurement prior to treatment [25]. Humans, however, produce only one peak of GH per day during the night, whereas male rats display a pulsatile pattern of GH hormone secretion, which peaks approximately every 3-4 hrs [26]. This difference in diurnal GH secretion patterns may be causal to the strong weight disruptive effects found in the male rat compared to male humans. Nonetheless, the relevance of GH inhibition may be a specific male side-effect of OLZ or other neuroleptic agents antagonizing the dopaminergic system.

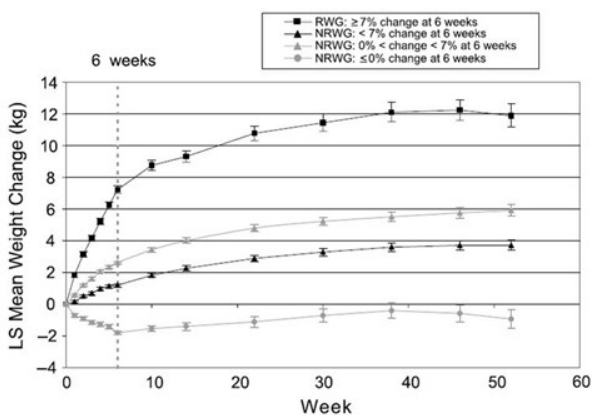


FIGURE 2. Mean weight change (kg \pm SE) for patients in the RWG and NRWG groups, MMRM analysis of variance. The number of patients per group were: NRWG group, n = 1008 at Week 1; n = 889 at Week 6 (18 in the open-label extension); n = 375 at Week 52 (130 open-label); RWG group, n = 183 at Week 1; n = 170 at Week 6 (6 open-label); n = 84 at Week 52 (27 open-label). Gray lines represent a subdivision of the NRWG group: (1) patients who gained weight up to 7% of their initial body weight (n = 679 at Week 1, n = 615 at Week 6, n = 280 at Week 52), or (2) patients who either did not gain weight or lost weight (n = 329 at Week 1, n = 274 at Week 6, n = 95 at Week 52). The number of patients at Week 6 refers to those who completed the acute olanzapine treatment phase and started either double-blind or open-label extension phases with olanzapine.

RWG: Rapid Weight Gain; NRWG: Non-Rapid Weight gain;
MMRM: mixed model repeated measures
From Kinon *et al*, *J. of Clin PsyPharm* 2005

Comparably, increased PRL levels may have more profound effects in females compared to males. Future studies are required to assess the relation between GH inhibition and presumably lowered IGF-1 levels in relation to total body insulin sensitivity.

There are no gender differences in the acute effects of OLZ on total body insulin resistance, thermogenesis, locomotor activity, or fuel utilization [22,27-31]. Still, it should be advised that both genders are used in acute as well as chronic studies on OLZ-induced metabolic effects or any other drug for that matter. First of all, such studies allow a fair comparison between genders. Second, they may elucidate some of the underlying mechanisms. By taking both genders into consideration, a better prediction of treatment outcome in humans may be expected.

b. Psychogenetic background in relation to OLZ responsiveness

Another major outcome of the studies described in this thesis is that the psychogenetic background of the individual plays an important role in the responsiveness to OLZ treatment. We found, in female rats, that chronic OLZ treatment increased body weight and adiposity exclusively in the RHA rat and not in the RLA (*Chapter 6*). Unfortunately, we have not performed a similar experiment in male rats of the Roman selection line as we did in female rats. Based on the assumption, however, that OLZ's inhibitory effect on the D2 receptors at the level of the anterior-pituitary may have played a major role in treatment outcome, it may be hypothesized that, similar to the increase of PRL in female RHA rats, the assumed OLZ-induced disruption of pulsatile secretion of GH is more effective in the male RHA rat compared to RLA. Therefore, we may dispute whether the male RHA rat gains or loses weight compared to the RLA selection line on OLZ treatment.

We found that the relation between psychogenetic background and drug responsiveness pointed towards differences in circulating GH and PRL levels. In humans, Gerra et al (2000) demonstrated a link between novelty seeking, harm avoidance, reward dependence and PRL and GH secretion. They found a positive correlation between increased GH secretion, induced by the dopamine agonist bromocriptine, and high novelty seeking; whereas a negative correlation was observed between PRL secretion and high novelty seeking [32]. These results may relate to our work, because 1) RHA score higher in novelty seeking compared to RLA [33]; and 2) RHA are more sensitive to dopamine antagonism by OLZ increasing circulating PRL levels (*Chapter 6*). These data confirm the suggested relation between personality traits, behavior, and underlying neuronal mechanisms influencing hormonal secretion; in this case increased dopaminergic sensitivity influences PRL and GH release.

The individual difference of dopaminergic regulation of the anterior-pituitary gland was further exposed in healthy male subjects treated with OLZ or OLZ+TPM (*Chapter 8*). We found that the basal TSH levels could be used as a predictor for OLZ-induced weight gain. TSH secretion is stimulated by hypothalamic TRH, but – similar to PRL secretion – is inhibited by dopamine. Low baseline TSH levels could be a result of higher dopaminergic responsiveness, most likely due to higher dopamine receptor 2 expression. Therefore, a continuous dopaminergic ‘brake’ may be active on TSH secretion in individuals with low baseline circulating TSH levels. The moment OLZ was administered, the ‘brake’ was released and, as observed, TSH levels increased during treatment in the subjects with low baseline TSH levels (*Chapter 8*).

c. Environment as a factor in manipulating treatment susceptibility.

The data from the Roman selection line further emphasized the influence of environment on central mRNA expression increasing the sensitivity of the dopaminergic system. This was best illustrated by the increase of PFC *Drd1* mRNA expression in the RHAs in the active environment, in which the rats had free access to a running wheel. It appeared that an active environment increased dopamine receptor expression in the RHAs. We hypothesize that this may have increased the sensitivity to OLZ treatment resulting in enhanced body weight gain compared to sedentary housed RHA rats. The increase of dopaminergic sensitivity was further supported by the observed decrease of circulating PRL in the control RHA housed in the active environment (*Chapter 6*).

The influence of environment has been demonstrated by Perry *et al* (2008), who found that rats reared in an enriched environment increased impulsive behavior to amphetamine, whereas animals reared in isolation showed a decreased impulsive behavior after amphetamine administration [34]. Furthermore, Fernandez-Teruel (1997) found increased relative ethanol intake and amphetamine-induced stereotypic behavior in the RHA but not in the RLA [35]. Both studies reveal an effect of an enriched environment, which may have undesired consequences, namely increased vulnerability to drugs of abuse. However, at the same time an enriched environment may improve the clinical effectiveness of antipsychotic treatment. Likewise, it is known that a strong social network may increase treatment success [35] which may not only relate to a stronger support in disease management by friends and relatives, but also improve the susceptibility to antipsychotic treatment. Unfortunately, schizophrenic subjects typically have small social networks [35].

More research is required to elucidate the influence of environmental enrichment on the responsiveness to neuroleptic agents. However, the type of enrichment may be crucial for the outcome of the studies. For example, social housing may function as an

enriched environment, but may evoke very different effects on the individual level than access to a running wheel or an enriched environment in which new attributes are placed in the animal's cage on a daily basis. Furthermore, social housing potentially has different effects on males or females grouped together [36].

All together, we would like to emphasize the importance of individual variation, due to gender or psychogenetic background, in combination with the subject's environment affecting the responsiveness to drug treatment. Studies considering such variations may elucidate the underlying mechanisms by using the variation in treatment outcome between individuals.

4. TPM as an adjunctive treatment inhibiting OLZ-induced weight gain.

The anticonvulsant TPM has been proposed as adjunctive treatment to inhibit OLZ-induced weight gain [37-39]. Nonetheless our studies led to some issues of concern on the combination of OLZ and TPM. First of all, we found that TPM increased circulating levels of OLZ enhancing the hypothermic and corticosterone effect of OLZ (*Chapter 2*). Second, the proteomics data indicated that combined TPM+OLZ therapy led to increased alanine aminotransferase, which may relate to liver damage (*Chapter 7*). Third, in male rats adjunctive TPM treatment led to an additional weight loss above that of OLZ (*Chapter 7*).

In humans, no pharmacokinetic drug-drug interactions of OLZ and TPM have been described and it was also not seen in our human trial (*Chapter 8*). Still, Vieta et al (2004) mention the importance of titration when TPM is co-administered with OLZ. They show that prescribed OLZ dosages decrease accordingly to increased administered dosage of TPM [37]. Careful titration of TPM and OLZ should have a beneficial effect on possible hepatic anomalies as well. Nonetheless, monitoring of circulating alanine aminotransferase may be advised, especially at high dosages of OLZ and TPM. The idea that adjunctive TPM allows for decreased OLZ dosage without loss of clinical effectiveness is, however, interesting and deserves further examination. For instance, it is not known if the allowed reduction of OLZ administration, due to adjunctive TPM treatment, is 1) due to decreased OLZ metabolization, or 2) due to the additive beneficial clinical effects of TPM.

In male rats we found that TPM by itself reduced adiposity levels and improved insulin sensitivity. However, we did not observe a beneficial effect on insulin sensitivity when TPM was co-administered with OLZ. Based on this, we concluded that TPM is not the desired adjunctive treatment in the absence of OLZ-induced weight gain. Moreover, we have shown that TPM is particularly effective in subjects

susceptible to OLZ-induced weight gain, characterized by low TSH levels prior to treatment. The main effect of OLZ is a change towards lipogenesis [22,23] while TPM increases lipolysis [40]. Studies in female rats (or humans) should further explore the inverse effects of OLZ and TPM on lipogenesis and lipolysis to reveal the inhibitory effects of TPM on OLZ-induced lipogenesis. Preliminary results from a study in female Wistar rats suggest that adjunctive TPM treatment inhibits OLZ-

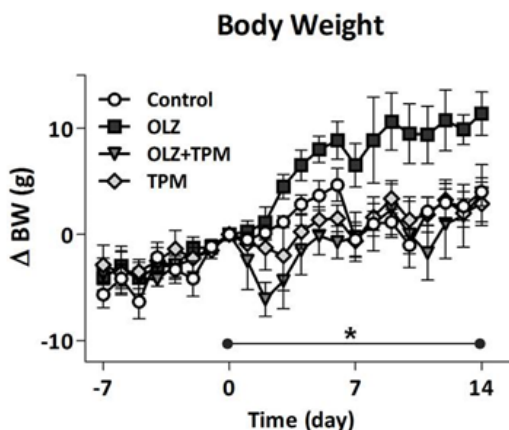


Fig 3. Body weight gain in female Wistar rats treated with Saline, OLZ (4 mg/kg/day), TPM (50mg/kg/day, or OLZ+TPM. OLZ increased BW (g) over the duration of the study compared to all other groups (* $P < 0.05$, $F_{42,350} = 1.533$, rm-ANOVA post hoc HSD. A reduction in BW was observed during the first week of adjunctive TPM treatment, which was restored to control levels at the end of the study.

induced body weight gain (see fig. 3). Unfortunately, we do not have any data on insulin sensitivity. Nonetheless, the data shows that TPM may act as an effective inhibitor of OLZ-induced weight gain, which makes it an interesting model to study the effects of both drugs on lipogenesis and lipolysis.

Finally, several other adjunctive treatments have been proposed to inhibit OLZ-induced weight gain, such as betahistine [41,42] or mifepristone [43]. However, no long-term controlled trials are available on the effectiveness or safety of these compounds. The benefit of TPM as an adjunctive to OLZ treatment is the observed improved clinical effectiveness [37,38,44]. Furthermore, TPM seems to reduce body weight in those patients most susceptible to OLZ-induced weight gain. Therefore, in a selective group of schizophrenic patients, TPM may serve as a tool to protect against OLZ-induced weight gain and concomitant metabolic consequences (*Chapter 8*).

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