The role of hypothalamic pathways in the metabolic side effects of Olanzapine
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Citation for published version (APA):
Girault, E. M. (2013). The role of hypothalamic pathways in the metabolic side effects of Olanzapine 's-Hertogenbosch: Boxpress

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Chapter 1

General introduction
1. Schizophrenia and its treatment

1.1. Definition of schizophrenia

Schizophrenia is a mental disorder characterized by a breakdown of thought processes and poor emotional responsiveness. Common symptoms include auditory hallucinations, paranoid or bizarre delusions and disorganized speech and thinking, often accompanied by significant social or occupational dysfunction. The onset of symptoms typically occurs in young adulthood with prevalence amongst adults reported to be in the range of 0.5-1.5%, although estimates tend to vary between studies (Bishara and Taylor 2008). Diagnosis of the disease is based on observed behaviour and patient’s reported experiences. Since the 1950’s, antipsychotics have been a mainstay of therapy. Antipsychotic treatment generally decreases the psychotic symptoms and usually allows the patient to experience functional recovery in terms of academics, peer relations and family life.

1.2. Schizophrenia treatment

1.2.1. Typical antipsychotics

The first generation antipsychotic drugs were developed between 1950 and 1980. They were found to be effective in treating the positive symptoms of schizophrenia such as delusions and hallucinations albeit showing a lower efficacy in the treatment of the negative symptoms such as emotional withdrawal, apathy, avolition and cognitive dysfunction (Lieberman et al. 2005). Due to their effects on the dopamine D₂ receptors (D₂R), first generation antipsychotics also caused extrapyramidal side effects (acute dystonic reactions, pseudoparkinsonism, akathisia) and tardive dyskinesia (Tandon and Jibson 2002) which made their long term use problematic (Bishara and Taylor 2008).

1.2.2. Atypical antipsychotics

In an effort to develop novel agents that would treat both positive and negative symptoms of schizophrenia while exhibiting a low propensity for movement disorders, several antipsychotic drugs were developed in the 1990s, referred to as “second generation” or “atypical antipsychotic drugs” (AAPDs). Although the new drugs showed improved efficacy in treating negative symptoms as well as a lower propensity to cause movement disorders (due to their lower affinity for D₂R), these benefits were accompanied by other side effects. AAPDs have adverse metabolic effects (Nasrallah 2008) such as weight gain (Taylor and McAskill 2000; Nasrallah 2003) and impaired glucose metabolism (Haddad 2004), resulting in an increased propensity for obesity and type 2 diabetes. Like conventional antipsychotics,
AAPDs are also antagonists of D_2R; however they show an additional range of binding activity at various other receptor sites. A complete understanding of the mechanism of action of AAPDs is important, as it may allow us to improve AAPDs already in use and, perhaps, lead to the production of a new generation of drugs without the metabolic side effects mentioned.

**Figure 1: Maintaining the energy balance.**
2. Metabolic disorders

2.1. Maintaining the energy balance

In healthy subjects, energy balance is maintained by a combination of mechanisms (Figure 1). In the physiological situation, insulin is released into the circulation to maintain glucose homeostasis, i.e. euglycemia (~5.5 mmol/L). After a meal, insulin is released into the circulation by pancreatic β-cells, facilitating glucose uptake in the liver, skeletal muscles and adipose tissues. In the liver and muscle, glucose is stored as glycogen (glycogenesis) and in adipocytes as triglycerides. At the same time, insulin inhibits hepatic glucose production. In a fasting state, circulating insulin levels are low, enabling the body to use stored sugar as an energy source. Pancreatic α-cells release glucagon which leads to breakdown of glycogen stored in the liver into glucose (glycogenolysis) which can then be used as energy source.

2.2. Obesity and Diabetes

Obesity affects more and more people in the world, and is defined as a body mass index (BMI) higher than 30 kg/m². It is now well established that obese patients are often highly susceptible to diabetes mellitus (McNaughton 2013). The total number of people with diabetes worldwide is predicted to rise from 171 million in 2000 to 366 million in 2030 (Wild et al. 2004).

There are 2 forms of diabetes. Type 1 diabetes is caused by autoimmune-mediated destruction of insulin producing (pancreatic) β-cells, which results in absolute insulin deficiency. Patients with type 1 diabetes are treated with exogenous insulin to adjust plasma glucose and to prevent ketoacidosis, a life threatening complication of the disease. Type 2 diabetes is far more common with 285 million people affected in 2010, i.e. 90% of total diabetic patients (Williams textbook of endocrinology (12th edition) Philadelphia: Elsevier/Saunders. p. 1371-1435. ISBN-978-1-4377-0324-5). It is mainly characterized by insulin resistance or insulin secretion defects. When oral anti-diabetic agents fail, patients need to be treated with insulin, which may require assessment of daily blood glucose levels in order to adjust the dosage, making management of the symptoms very challenging.

2.3. Insulin resistance

Insulin resistance is a state of hypo-responsiveness of tissues to circulatory insulin. Muscle, fat and liver cells are unable to sufficiently respond to insulin and uptake glucose, amino acids and fatty acids which results in higher blood glucose and triglycerides levels. Insulin resistance concomitant with obesity, however, may cause adverse health effects such as
cardiovascular disease and hypertension, owing to the resulting hyperglycemia and hypertriglyceridemia. As a consequence, glucose production cannot be sufficiently lowered by the liver, resulting in a further increase of plasma glucose levels. Causal links between insulin resistance, obesity and dietary factors are not completely understood. It is plausible that one factor leads to the other; or that insulin resistance and excess body weight are mutually exclusive at the onset, as a consequence of a third factor, ending up reinforcing each other. It is also plausible that due to genetic susceptibility, a proportion of patients suffering from insulin resistance may be predisposed to certain factors. The gold standard for investigating and quantifying insulin resistance is the "hyperinsulinemic-euglycemic clamp" so called because it measures the amount of glucose necessary to maintain euglycemia while compensating for targeted increased insulin levels. Combining the hyperinsulinemic-euglycemic clamp at different insulin plasma concentrations with the infusion of a labeled glucose isotope enables the separation of the effects of insulin on glucose production and glucose uptake, i.e., hepatic insulin sensitivity and systemic insulin sensitivity.

3. Olanzapine

3.1. Olanzapine profile
Olanzapine (Ola), a thienobenzodiazepine derivative, was introduced as an atypical antipsychotic in 1996 (Bymaster et al. 1996) and has been widely used since then. Ola is used to treat schizophrenia as well as depressive episodes associated with bipolar disorder and acute manic episodes. Clinical studies indicate that Ola is as effective as haloperidol, a first generation antipsychotic, in reducing positive symptoms of schizophrenia and superior in reducing negative symptoms (Beasley, Jr. et al. 1996; Tollefson et al. 1997b; Perry et al. 1997).

3.2. Olanzapine metabolic side effects
The efficacy and safety of Ola have been extensively studied over many years (Beasley 1997). Ola like other AAPDs is known to cause metabolic side effects. It has been shown that in newly diagnosed schizophrenic patients; 90-100% gained more than 7% of the pretreatment body weight in a 1-year follow-up period (Lieberman et al. 2005; McEvoy et al. 2007; Green et al. 2006; Zipursky et al. 2005). The safety profile of oral Ola revealed potential risks for causing a "metabolic syndrome", consisting of hyperglycemia, hyperlipidemia, hyperprolactinemia, elevations in plasma transaminases and weight gain (Bishara and Taylor 2008; Chiu et al. 2006). These side effects led the US Food and Drug
Administration (FDA) in March 2004 to require a warning in the labeling of the drug about hyperglycemia and diabetes risks by Eli Lilly, the only manufacturer of the drug at that time. It has been shown that body weight gain is more frequent and more severe in patients treated with Ola than in those receiving haloperidol, a typical antipsychotic drug (Tollefson et al. 1997a; Beasley, Jr. et al. 1997; Lieberman et al. 2005). The prevalence of type 2 diabetes is higher in families of patients with schizophrenia (Mukherjee et al. 1989) and approaches the prevalence of diabetes observed in families of patients with type 2 diabetes (Cheta et al. 1990). Moreover, drug naïve schizophrenic patients have been shown to display hepatic insulin resistance (van Nimwegen et al. 2008). Thus, schizophrenic patients are at risk to develop type 2 diabetes, making it even more important to find a way to circumvent the metabolic side effects of AAPDs like Ola.

3.3. Receptor binding and their consequences

AAPDs have been so called to distinguish them from “typical” antipsychotics that mainly bind to one type of receptor (DA). AAPDs have a broader range of action. The focus in this thesis will be on Olanzapine.

Ola has high affinity for a number of receptors including serotonergic (5-HT$_{2a}$ and 5-HT$_{2c}$), dopaminergic (D$_1$, D$_2$, D$_3$ and D$_4$), histaminergic (H$_1$), adrenergic (α-adrenergic 1), and muscarinergic (M$_1$, M$_2$, M$_3$, M$_4$ and M$_5$) receptors (Fuller and Snoddy 1992; Bymaster et al. 1996; Dwyer et al. 2003; Kapur and Seeman 2001). Binding to one or a combination of these receptors has been assumed to be involved in the pathogenesis of the metabolic side effects of Ola. For example, antagonists of the 5-HT$_2$ receptor attenuate insulin sensitivity (Gilles et al. 2005). Thus, Ola as a 5-HT$_{2a}$ receptor antagonist could potentially lead to decreased uptake of glucose and thus increased plasma glucose levels. Moreover, D$_2$ antagonism, an effect shared by all antipsychotic drugs, can influence eating behavior (Clifton et al. 1991), with an increased food intake resulting from blockade of hypothalamic D$_2$R (Parada et al. 1988; Reynolds and Kirk 2010). It was also shown in animal experiments that acute (1-week) and chronic (12-weeks) Ola treatment significantly down-regulated H$_1$ receptor mRNA expression in the arcuate (Arc) and ventromedial nucleus (VMH) of the hypothalamus. In contrast, haloperidol and aripiprazole, which are antipsychotics with a lower risk of weight gain, failed to show a similar effect (Han et al. 2008). Ola-induced decreased H$_1$ receptor binding density in the VMH was associated with increased food intake and weight gain in Ola-treated rats compared to those treated with aripiprazole or haloperidol (Han et al. 2008).
4. Olanzapine, brain and metabolism

The brain and more specifically the hypothalamus have a key role in regulation of energy balance (Shioda et al. 2008; Valassi et al. 2008) (Figure 2). Increased plasma levels of leptin, a hormone secreted by adipose tissue and involved in regulation of energy intake and energy expenditure, inhibit neurons in the hypothalamic Arc that co-express the orexigenic neurotransmitters neuropeptide Y (NPY) and agouti-related peptide (AgRP), while activating the anorexic pro-opiomelanocortin (POMC) neurons that co-express cocaine- and amphetamine-related transcripts (CART). Weight gain induced by Ola appears to be associated with an increase of leptin levels (Kraus et al. 1999; Melkersson et al. 2000).

![Figure 2: The hypothalamus and regulation of energy balance.](image-url)
Another hormone important for regulation of energy balance is ghrelin. It is produced by the stomach during fasting and has the opposite effect on Arc neurons than leptin; ghrelin inhibits POMC/CART and activate the NPY/AgRP neurons. The association between Ola and plasma ghrelin is still debatable. Although some studies report higher serum ghrelin levels in patients using Ola (Murashita et al. 2005; Palik et al. 2005; Esen-Danaci et al. 2008), others found decreased levels (Togo et al. 2004; Tanaka et al. 2008; Basoglu et al. 2010; van der Zwaal et al. 2012). Many POMC/CART and NPY/AgRP neurons convey their information to second-order neurons in the paraventricular nucleus of the hypothalamus (PVN) and lateral hypothalamus (LH), such as those containing corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), Ox, and melanin-concentrating hormone (MCH) (Elias et al. 1998). Ox and MCH affect food intake in an orexigenic manner (Qu et al. 1996; deLecea et al. 1998; Sakurai et al. 1998; Shimada et al. 1998). Patients treated with Ola for 6 weeks showed a decrease in plasma Ox-A levels (Basoglu et al. 2010). Animal studies showed that Ola induces activation of Ox neurons in the LH (Wallingford et al. 2008). Moreover, Ola treatment was shown to decrease energy expenditure and sympathetic discharge in association with activation of Ox-A positive neurons (Stefanidis et al. 2009; Monda et al. 2008). A possible association between MCH and Ola side effects has not been extensively studied. However, a genetic study showed that the common allele of the PMCH gene rs7673796 (precursor of MCH) may be associated with a greater BMI in Ola-treated schizophrenic patients (Chagnon et al. 2007).

5. Hypothesis: Olanzapine metabolic side effects find their origin in the hypothalamus.

Ola has affinity for serotonergic, adrenergic, dopaminergic and histaminergic receptors and the neurotransmitters for those receptors are involved in energy homeostasis without exception. All these receptors can be found both in the central and peripheral nervous system and are known to modulate energy homeostasis. Many of them are abundantly expressed in the hypothalamus, which is a brain region intensely implicated in the control of energy and glucose metabolism as described previously. We hypothesize that the metabolic side effects of Ola find their origin in the brain and more specifically in the hypothalamus. In Chapter 2, we compare the effects of acute peripheral and central administration of Ola on glucose metabolism. We also assessed the metabolic and energetic side effects of chronic Ola administration. In Chapter 3, we investigate the possible involvement of the hypothalamic neuropeptides Ox and MCH in hyperglycemia and insulin resistance inducing effects of Ola.


