The role of hypothalamic pathways in the metabolic side effects of Olanzapine
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ENGLISH SUMMARY

Schizophrenia is a mental disorder characterized by a breakdown of thought processes and poor emotional responsiveness. Since the 1950’s, antipsychotics have been a mainstay of therapy for this disease. The first generation of antipsychotics (so-called typical antipsychotics) were found to be effective in treating positive symptoms but also caused extra-pyramidal side effects including tardive dyskinesia, due to their effects on dopamine D_2 receptors. In the 1990’s, atypical antipsychotics, a second generation of antipsychotics, were put on the market and they are now commonly used. This new generation of antipsychotics is effective both on positive and negative symptoms, and has a lower propensity to induce movement disorders. These new drugs, however, also have a drawback, as these benefits are accompanied by adverse metabolic side effects including body weight gain and impaired glucose metabolism, increasing the propensity for the development of obesity and type 2 diabetes. Olanzapine is one of these atypical antipsychotics; its safety profile reveals potential risks for causing a “metabolic syndrome” consisting of hyperglycemia, hyperlipidemia, elevations in plasma transaminases and weight gain. The mechanisms of those metabolic side effects have been of interest to many research groups all over the world and they are also the main focus of this thesis. The brain and more specifically the hypothalamus have a key role in the regulation of energy balance. The main target tissue for antipsychotic drugs such as olanzapine is the central nervous system. We therefore hypothesized that the metabolic side effects of olanzapine are explained by off-target effects of olanzapine in the hypothalamus. This thesis describes our search for evidence to prove or disprove this hypothesis.

Chapter 1 gives an overview of the metabolic side effects of olanzapine and the limited knowledge on their possible mechanism, as well as on our current knowledge on the hypothalamic systems that control glucose metabolism. Together this information provides the background for the hypothesis to be tested in this thesis.

Chapter 2 describes the first series of experiments aimed at investigating the metabolic effects of centrally or peripherally administered olanzapine in our animal model. In Chapter 2.1 we compared the effects of an acute peripheral versus central administration of olanzapine on glucose metabolism in male rats. We found that in male rats the metabolic effects of peripheral acute administration of olanzapine mimicked the adverse metabolic side effects known from clinical studies, i.e., hyperglycemia and insulin resistance. However, acute administration of olanzapine centrally did not result in any of these changes, indicating
that the initiation of the metabolic side effects of olanzapine is mainly based on a peripheral mechanism. Nevertheless, in our opinion, these results did not exclude the possibility that subsequent to these primary events in the periphery an afferent signal could be transmitted to the central nervous system and central mechanisms might thus be implicated in subsequent steps of the metabolic side effects of olanzapine. In Chapter 2.2, we describe the difficulties we encountered to determine the optimal mode of administration of olanzapine in a rat model. In fact, the short half-life of olanzapine in rats (2.5 hours vs. 21-54 hours in humans) and its solubility and stability in solution turned out to be quite challenging when designing the experiments. Moreover, central administration of olanzapine (in high concentrations) seemed to cause leakage into the general circulation, making conclusions about the site of origin of the metabolic side effects of olanzapine difficult. In Chapter 2.3, we investigated the metabolic changes induced by chronic treatment with olanzapine. We combined measures of energy intake, energy expenditure, glucose metabolism and measured plasma olanzapine in male rats chronically treated with olanzapine. Acute olanzapine administration resulted in hyperglycemia which was partly explained by an increased endogenous glucose production. Interestingly, this acute effect of olanzapine disappeared in animals who had received olanzapine chronically for 5 weeks. On the other hand, rats treated chronically with olanzapine displayed an increased relative adiposity with increased leptin levels, which was associated with changes in body substrate utilization but not with increased energy consumption or decreased energy expenditure. Finally, chronic treatment with olanzapine resulted in nocturnal hypothermia.

In Chapter 3, we focused on the possible role of the brain and more specifically the hypothalamus in the olanzapine-induced changes in energy metabolism. In the first part (3.1) of this chapter, we introduced the orexin and melanin-concentrating hormone (MCH) neurotransmitter systems. It had been shown previously that peripheral injections of olanzapine resulted in a strong activation of neurons in the lateral hypothalamus, a nucleus implicated in arousal, feeding and other motivated behaviors. Orexin- and MCH-containing neurons are abundantly expressed in the lateral hypothalamus and are known to be involved in feeding behavior. In Chapter 3.2, we investigated the possible involvement of the orexin system in the metabolic side effects of olanzapine by infusing an orexin-1 receptor antagonist, SB-408124, intracerebroventricularly (ICV) together with the peripheral administration of olanzapine. We showed that ICV treatment with SB-408124 blunted the olanzapine-induced increase in endogenous glucose production, showing the involvement of the orexin system in the metabolic side effects of olanzapine. In Chapter 3.3, we investigated the possible involvement of the MCH system in the metabolic side effects of olanzapine, as
genetic studies had shown that the common allele rs7973796 of the prepro-MCH gene, encoding for the neuropeptide MCH, is associated with a greater body mass index in olanzapine-treated schizophrenic patients. To do so, we performed acute intragastric infusions of olanzapine in both prepro-MCH gene knock-out (KO) and wild-type (WT) rats. Administration of olanzapine induced hyperglycemia, increased endogenous glucose production and corticosterone levels in both KO and WT rats. However, contrary to the WT rats, the prepro-MCH KO rats did not show an increase in insulin levels after olanzapine treatment. Therefore, we hypothesize that the olanzapine-induced hyperinsulinemia in WT rats might involve a MCH-dependent mechanism, probably in the pancreas.

In Chapter 4 we conclude that the results of this thesis support the idea that part of the metabolic side effects of olanzapine are mediated by the hypothalamic orexin system. However, the exact mechanism via which olanzapine affects the orexin system is not clear yet as olanzapine might influence the orexin neurons in the lateral hypothalamus 1) directly, 2) via the POMC/CART and NPY/AgRP neurons in the arcuate nucleus, or 3) via ascending projections from the brainstem.