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Abstract

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Does Olanzapine leads to changes in the hypothalamic opioid sytem?

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Antipsychotic medication used for the treatment of schizophrenia is associated with many debilitating adverse effects. Although second generation atypical antipsychotics, such as Olanzapine, has less extrapyramidal side effects, they result in weight gain and metabolic dysfunction in up to 80% of treated patients. In addition, it appears that Olanzapine has different side effect patterns in male and female, with increased fat deposits without weight gain in men, and increased appetite with weight gain in women. Both peripheral and central nervous system effects of Olanzapine have been studied for many years, however, very little is known about the effects on the appetite regulating center hypothalamus. Studies have shown that olanzapine leads to an increase in appetite stimulating RNAs and a decrease in appetite suppressing RNAs in the arcuate nucleus of hypothalamus. We are studying Olanzapine's effect on appetite- and energy regulating neurons of the hypothalamus in female rats. Preliminary results show a significant weight gain and increased food intake after only 72 hours of treatment. To investigate the effect of Olanzapine on opioid receptor expression in the hypothalamus we used fluorescent *in situ* hybridization staining's of rat brain sections, which were subsequently tile imaged at high magnification on a Leica fluorescent microscope. The area of interest were delineated and the number of RNA 'dots' were quantitatively detected determined using a MATLAB script. The results showed that 48 hours of olanzapine treatment results in a decreased expression of μ opioid receptor RNA in the arcuate nucleus, a central regulator of appetite in the brain. Studies have shown that the opioid system participates in the regulation of food intake in the hypothalamus, and a new phase III study has found that patients treated with olanzapine and a μ opioid receptor antagonist results in less weight gain. Further experiments are in progress to determine olanzapine driven changes in opioid receptor and serotonin receptor expression in the hypothalamus, as well as estimations on neuroanatomical changes in appetite regulating neuron populations. Knowledge obtained in this study could result in advancing a more specific medical targeting against both the adverse effects caused by atypical antipsychotic treatment, as well as obesity in general.