Effects of olanzapine and aripiprazole on glucose uptake in healthy human subcutaneous adipocytes during short incubations.

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Introduction: Second-generation Antipsychotics (SGAs) are preferable pharmacological treatment for patients with Schizophrenia, mainly due to their efficacy and reduced risk of extrapyramidal effects when compared with first generation antipsychotics. However, there are metabolic side effects associated with the administration of SGAs, namely weight gain, dyslipidaemia and impaired glucose metabolism. Literature reports that even in the absence of antipsychotic treatment patients with Schizophrenia have a propensity to develop metabolic changes that can lead to cardiovascular diseases, insulin resistance, obesity and Type 2 Diabetes. Olanzapine and aripiprazole belong to SGAs and have been reported as drugs with the highest and the lowest risk of inducing metabolic changes, respectively. However, the pharmacological mechanisms underlying their metabolic side effects remain unclear and they will be the main focus of our study.

Adipose tissue is not only specialized in storing lipids but it is also an endocrine organ that produces and secretes numerous biological active compounds that regulate metabolic homeostasis.

Our aim is to evaluate the effect of olanzapine and aripiprazole in the glucose uptake on human isolated adipocytes.

Methods: Biopsies of subcutaneous adipose tissue were collected from 16 healthy volunteers (4 men, 12 women; age: 20-76 years; BMI: 20.9-34.5 kg/m²). Subjects taking antidepressants or antipsychotics were not included. The effect of short-term incubation (30 min) with different concentrations of olanzapine (0.004, 0.04, 0.1, 0.2, 2 and 20 μM) or aripiprazole (0.02, 0.2, 0.5, 1, 10 and 100 μM) on basal and insulin-stimulated (25 and 1000 μU/ml) D-[U-14C]-glucose uptake of isolated adipocytes was measured and compared with control.

Results: Short incubation of adipocytes with olanzapine or aripiprazole showed no effect on basal or insulin-stimulated glucose uptake, with the exception of supra-physiological concentrations of aripiprazole (10 and 100 μM) where we see a systematic decrease of basal and insulin-stimulated glucose uptake; 10 μM by **20-25% (p<0.05)** and 100 μM by **60-70% (p<0.01)**.

Conclusions: Short-term treatment of isolated adipocytes with therapeutic doses of olanzapine or aripiprazole did not affect glucose uptake, suggesting no acute alteration in insulin activity. These data suggest that the plasma glucose increase seen in patients taking Olanzapine cannot be justified by acute alteration in insulin-signalling in adipocytes. Incubation with aripiprazole at 10 and 100 μM decreased the adipocyte glucose uptake but this might be justified by cell death, which will be explored in future experiments.