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Atypical antipsychotic-induced metabolic toxicity: characterisation of mechanisms using an *in vitro* human adipocyte model

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Background: Atypical antipsychotics (AAPs) are commonly prescribed for the treatment of psychiatric disorders in particular schizophrenia. However, long term use of these drugs leads to metabolic adverse effects such as weight gain, insulin resistance, and dyslipidemia (1). The prevalence of antipsychotic-associated metabolic adverse effects varies from 23-50% (2). we have investigated whether AAPs cause adipocyte toxicity in *in vitro* adipocyte models.

Methods: The preadipocytes were isolated from abdominal subcutaneous adipose tissue obtained from healthy controls (n=3; Caucasian; age range: 31-43 years; BMI: 21-25kg/m^2) and incubated with clozapine (CLO; 1-20µM), olanzapine (OLA; 0.2-20µM) and aripiprazole (ARI; 0.2-10µM) every 48 hours for 12 days. Adipogenesis was measured by Oil Red O staining. Protein and mRNA expression of PPARgamma (PPARγ*)* and lipin1 (LPIN1) were investigated by Western blot and RT-PCR, respectively. Changes in secreted adiponectin, IL-6 and leptin were analysed by ELISA. Cellular accumulation of CLO in murine (3T3-F442A) and human primary adipocytes was measured using radioactive labelled CLO. Statistical analysis was conducted by t-test and data are presented as mean ± SD

Results: CLO, but not OLA, significantly increased (0.91absorbance units±0.18; p=0.008, 10% increase) lipid accumulation compared to vehicle (0.82±0.19); however lipid accumulation was reduced by ARI (p=0.03, 10% decrease). CLO and OLA (20µM) but not ARI significantly decreased adiponectin secretion (CLO: 57% decrease, p=0.03; OLA: 48% decrease, p=0.04; ARI: 21% increase, p=NS) as compared to the vehicle control. Only ARI had an effect on IL-6 secretion (21% decrease; p=0.05). CLO (20µM) but not OLA significantly increased leptin secretion (CLO: 729.18pg/ml±150.58; p=0.01, 14% increase) whereas ARI (10µM) resulted in decreased (463.24pg/ml±69.4; p=0.04, 27% decrease) secretion of leptin. No significant change in PPARγ and LPIN1 protein expression was seen with CLO, OLA and ARI. There was a 20-fold increase in CLO uptake by the differentiating primary human adipocytes (1293.4 pmol/million cells±170.56; p=0.006) in comparison to the murine adipocytes (64.25pmol/million cells±26.96).

Conclusion: CLO, OLA and ARI showed contrasting effects on human adipocytes; further work is needed to determine how this relates to the contrasting clinical phenotypes observed with these drugs. The uptake of CLO differed vastly between murine and human-derived adipocytes; this might have implications for the selection of appropriate *in vitro-in vivo* models for studying AAP-induced metabolic disease.

(1) Sarvari AK et al (2014). Biochem Biophys Res Commun, 450, 1383-9.

(2) Nasrallah HA. (2008). Mol Psychiatr 13:27-35.