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Antipsychotic – induced metabolic toxicity: Mechanisms and biomarkers

Background: Atypical antipsychotics (AAPs) are widely prescribed for the treatment of schizophrenia. However, long term use of these drugs is associated with metabolic consequences such as weight gain, insulin resistance and dyslipidemia, all independent risk factors for diabetes and cardiovascular disease (1). The prevalence of metabolic disease in the AAP-treated population is estimated to be 23-50% with almost half of these developing cardiovascular diseases (2). Adipose tissue, a key regulator of lipid and glucose homeostasis, has been suggested to play an important role in AAP-induced metabolic disease (3). We utilised an in vitro murine adipocyte model to study whether AAPs exert any direct anti-adipogenic effect and to identify biomarkers of AAP-induced metabolic disease.

Methods: Differentiating 3T3-F442A murine adipocytes were incubated with clozapine (CLO)(1µm,2µM,20µM), olanzapine (OLA)(0.2µM,2µM,20µM) and aripiprazole (ARI)(O.2µM,1µM,20µM) every 48 hours for 10 days; this represents a chronic dosing model designed to address the effect of cumulative toxicity of AAPs on adipocytes. Cytotoxicity and adipogenesis were assessed by MTT assay and Oil Red O staining, respectively. Protein and/or mRNA expression of PPAR-gamma (pparγ), lipin1 (lpin1), adiponectin (adipoq), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF- α) were investigated by ELISAs and qPCR. Changes in free fatty acid secretion were also measured. Statistical analysis was conducted by t-test and data are presented as mean ± SD for 20µM incubations but full concentration response relationships were measured.

Results: None of the AAPs caused adipocyte cytotoxicity. An increase in lipid accumulation was observed with CLO (1.56±0.097; p=0.001) and OLA (1.57±0.14; p=0.07) but not with ARI as compared to vehicle (VEH) control (1.05±0.067). CLO upregulated the expression of pparγ (Mean fold change±SD; 3.58±0.38;p=0.007), lpin1 (1.94±0.10;p=0.004), adipoq (2.62±0.35;p=0.001) and increased the secretion of adiponectin (736.77ng/ml±66.06;p=0.001; VEH:323.26 ng/ml ±53.07) and TNF- α (45.24pg/ml±0.16;p=0.0001; VEH:32.89 pg/ml ±0.34) but did not change IL-6 levels. No effect was observed with OLA on pparγ, lpin1 and adipoq gene expression and IL-6 secretion. However, OLA decreased adiponectin (990ng/ml±6.08;p=0.0002) and TNF- α protein secretion (20.95pg/ml±0.31,p=0.08) as compared to the vehicle (ADIPOQ:1243.51 ng/ml ±31.03, TNF-α:21.69pg/ml±0.45). ARI upregulated pparγ expression (1.87±0.15;p=0.01) at higher doses but not to the extent seen with CLO; it also did not change lpin1 and adipoq gene expression. Higher doses of ARI (20µM) decreased adiponectin (322.ng/ml±4.31;p=0.0003; VEH:408.59±12.07)while no change in TNF-α (21.28±0.08pg/ml;p=0.001; VEH: 21.91±0.09 pg/ml) protein secretion but increased IL-6 secretion (74.49±2.44,p=0.0001;VEH;12.28±0.41). Both CLO (0.131nmol/µl±0.004;p=0.0006) and ARI (0.137nmol/µl±0.001;p=0.0001) but not OLA at therapeutic doses increased FFA secretion as compared to the vehicle (0.105nmol/µl±0.0009).

Conclusion: CLO and OLA caused increased lipid accumulation in murine adipocytes in comparison to ARI; this could be a potential mechanism for the weight gain seen in AAP-treated patients. The differences seen between the different antipsychotics highlights that mechanisms may vary by drug, and this needs further exploration

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