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Mini Review **Open Access**

Direct Action of Obesity-Inducing Antipsychotics on Human Adipocytes

Nira Ben-Jonathan*

University of Cincinnati, USA

***Corresponding Author**: Nira Ben-Jonathan**,** University of Cincinnati, USA,Email:benjonn@ucmail.uc.edu

Atypical antipsychotics (AAP) are prescribed to millions of patients worldwide with schizophrenia, bipolar disorder, major depression, and autism. In spite of their ability to ameliorate many mental problems, AAP have serious metabolic side-effects, including substantial weight gain, dyslipidemia, diabetes, and cardiovascular disease. The primary therapeutic target of AAP are dopamine (DAR) and serotonin (5-HTR) receptors. The mechanisms underlying the metabolic side effects of AAP are unknown, but have been attributed to their central action. We discovered expression of functional DAR and 5-HTR subtypes in human adipose tissue. Incubation of adipose explants, primary adipocytes and human adipocyte cell lines with selected AAP suppressed leptin and adiponectin, and increased basal and isoproterenol-stimulated lipolysis. Treatment of female rats with olanzapine caused a 85-90% suppression of leptin and adiponectin, and a 4-fold increase in interleukin-6 (IL-6) expression in fat tissue within 24 hrs, concomitant with increased food intake and weight gain in 2-3 days. We conclude that direct activation of DAR and 5-HTR subtypes in adipose tissue underscores peripheral actions of AAP which complement, or override, their central actions, leading to weight gain and the metabolic syndrome. Given the millions of patients who are chronically treated with AAP, most pharmaceutical companies are developing new drugs in this class. Human adipocytes could be integrated into the screening paradigms of candidate drugs for the identification of undesirable metabolic activities prior to costly animal studies and clinical trials. This investigation also identified a potential novel target for the treatment of obesity.

Adipose tissue (AT) is no longer considered merely as insulation or padding for human organs. It is an endocrine organ in its own right, which includes composite cells with the ability to differentiate into multiple cell lines.In fact, there is increasing evidence to support the theory that the causation of obesity and its associated metabolic disorders originate at the cellular or tissue level. Adipocyte dysfunction and chronic inflammatory states are able to modulate triglyceride storage and mobilization directly through cytokine and adipokine release.

Significant variability exists between adipocyte isolation and culture techniques which subsequently can impact experimental results. We aim to explain the importance of controlling these variables, to assist tailoring methodological choice towards the investigational outcomes, and modifications of the techniques used accordingly.

The techniques described in this chapter yield cell and adipose tissue which can be utilised in many different ways, including adipose tissue stem cells for differentiation, DNA analysis, RT-PCR, immunohistochemistry, lipolysis, glucose uptake, and LPL activity.

The functions of adipose tissue (AT) have not been fully elucidated. Adipocytes store energy as triglycerides, the main energy source for the body, and release it in the form of non-esterified fatty acids, when required. AT also releases multiple cytokines, some with local paracrine effects, e.g. TNF-α and IL-6 which have pro-inflammatory effects. In addition, adipocytes can respond to and secrete hormones, e.g. leptin and adiponectin as well as acylation-stimulating protein and others, which are of paramount importance in the regulation of energy intake and expenditure as well as systemic inflammation and metabolism. This suggests that adipose tissue is the largest, and potentially one of the most important, endocrine organ in the body.

Adipose-resident stem cells acquired from collagenase digestion of adipose tissue are multipotent with the ability to differentiate into many different cell lines, including adipocytes, bone, cartilage, endothelium, neural, and liver cells.This, combined with their ease of harvesting, suggests their potential as the most important adult stem cell reservoir

Mechanisms underlying antipsychotic cardiometabolic adverse effects are incompletely understood. This hampers the identification of high-risk patients, low-risk antipsychotics and preventive/ameliorative treatments. Recent clinical, molecular, and genetic data suggest that i) antipsychotic-naïve samples provide the greatest power for mechanistic studies; ii) weight and metabolic effects can be discordant, pointing to overlapping and distinct mechanisms; iii) antipsychotics affect satiety and energy homeostasis signaling; iv) the specific peptides mediating these effects are unknown but likely overlap with those involved in idiopathic obesity; and v) single nucleotide polymorphisms in genes encoding known neurotransmitter receptors and metabolic proteins are promising pharmacogenomic targets for countering adverse affects. However, sophisticated molecular studies and genome-wide association studies, ideally in antipsychotic-naïve/first episode samples, are needed to further advance the field

Overweight and obesity have become a pandemic. Patients with severe mental disorders are at even higher risk than the general population for obesity, cardiometabolic risk factors, and related morbidity and mortality .In addition to medical consequences, obesity in the mentally ill can cause treatment nonadherence and decreased quality of life.

Although antipsychotic drugs are the cornerstone of treatment for many psychiatric disorders, these medications are significantly associated with weight gain, the development of obesity, and the accrual of cardiovascular risk factors. These adverse effects of these medications are important factors in the reduced quality of life and premature death from cardiovascular disorders in patients with severe mental illnesses compared to the general population. Moreover, treatments to prevent or ameliorate cardiometabolic side effects are scarce, only modestly more effective than placebo, and do not restore pretreatment body weight