

Direct action of obesity-inducing antipsychotics on human adipocytes

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Abstract

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.

Biography

Nira Ben-Jonathan has published 165 manuscripts, edited one book, and contributed 12 chapters to textbooks and encyclopedias. Early in her career she studied the neuroendocrine regulation of pituitary functions while the current focus of her research is on breast cancer, adipose tissue and human obesity. She was awarded the NIH Research Career Development Award, was elected Fellow of the AAAS, elected Chairman of the Gordon Research Conference, and received the Rieveschl Award for Outstanding Scientific Research. She has been a member on numerous committees, serving as chairman on five NIH study sections.