European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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REVIEW

Antipsychotics-induced metabolic alterations: Focus on adipose tissue and molecular mechanisms

Pedro Gonçalves[1,a], João Ricardo Araújo[b,1], Fátima Martel[c,*]

[a]*INSERM (French Institute of Health and Medical Research), Unit 1151, INEM (Research Center in Molecular Medicine), Faculty of Medicine of Paris Descartes University, Paris, France*
[b]*INSERM (French Institute of Health and Medical Research), Unit 786, Molecular Microbial Pathogenesis Unit, Institut Pasteur, Paris, France*
[c]*Department of Biochemistry (U38-FCT), Faculty of Medicine, University of Porto, Porto, Portugal*

Received 22 July 2014; received in revised form 14 October 2014; accepted 13 November 2014

KEYWORDS
Antipsychotics;
Adipose tissue;
Weight gain;
Dyslipidemia;
Glucose intolerance

Abstract
The use of antipsychotic drugs for the treatment of mood disorders and psychosis has increased dramatically over the last decade. Despite its consumption being associated with beneficial neuropsychiatric effects in patients, atypical antipsychotics (which are the most frequently prescribed antipsychotics) use is accompanied by some secondary adverse metabolic effects such as weight gain, dyslipidemia and glucose intolerance. The molecular mechanisms underlying these adverse effects are not fully understood but have been suggested to involve a dysregulation of adipose tissue homeostasis. As such, the aim of this paper is to review and discuss the role of adipose tissue in the development of secondary adverse metabolic effects induced by atypical antipsychotics. Data analyzed in this article suggest that atypical antipsychotics may increase adipose tissue (particularly visceral adipose tissue) lipogenesis, differentiation/hyperplasia, pro-inflammatory mediator secretion and insulin resistance and decrease adipose tissue lipolysis. Consequently, patients receiving antipsychotic medication could be at risk of developing obesity, type 2 diabetes and cardiovascular disease. A better knowledge of the impact of these drugs on adipose tissue homeostasis may unveil strategies to develop novel antipsychotic drugs with less adverse metabolic effects and to develop adjuvant therapies (e.g. behavioral and nutritional therapies) to neuropsychiatric patients receiving antipsychotic medication.

*Correspondence to: Department of Biochemistry, Faculty of Medicine of Porto, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal. Tel.: +351 22 0426654; fax: +351 22 5513624.
E-mail address: fmartel@med.up.pt (F. Martel).

[1]Pedro Gonçalves and João R. Araújo equally contributed to the work.

http://dx.doi.org/10.1016/j.euroneuro.2014.11.008
0924-977X/

Please cite this article as: Gonçalves, P., et al., Antipsychotics-induced metabolic alterations: Focus on adipose tissue and molecular mechanisms. European Neuropsychopharmacology (2014), http://dx.doi.org/10.1016/j.euroneuro.2014.11.008

1. Introduction

Diabetes mellitus is a severe global public health problem in both developed and developing countries due to a growing prevalence, morbidity and mortality. The number of estimated diabetics constitutes a universe of nearly 366 million people all over the world (Wild et al., 2004). The most prevalent form of diabetes is type 2 diabetes mellitus (T2DM) (Wild et al., 2004). The increased prevalence of T2DM is a global crisis with a negative impact in lifestyle and healthcare systems, currently rendering this disease a heavy socioeconomic burden. Obesity has also become a worldwide health problem because it is strongly associated with the development of T2DM (Hotamisligil, 2006). Although the etiology of type 1 diabetes mellitus is well known and involves an absolute deficiency of insulin, T2DM is a highly complex, multifactorial metabolic disease, characterized by a decreased insulin action and, consequently, insulin resistance and by a progressive β-cell failure (relative insulin deficiency) (Cusi, 2010).

Many common therapeutic agents used for the treatment or prevention of certain diseases influence glucose metabolism. Acting through multiple mechanisms of action including pancreatic, hepatic and peripheral effects (e.g. adipose tissue), several therapeutic drugs originate glucose intolerance, induce diabetes in previously nondiabetic subjects or worsen hyperglycemia in known diabetic patients (Izzedine et al., 2005). These drugs include glucocorticoids and other immunosuppressive agents (IAs), diuretics, β-blockers and antipsychotic agents (Table 1) (Izzedine et al., 2005). Briefly, thiazide diuretics reduce insulin secretion (Harper et al., 1994; Pollare et al., 1989a, 1989b) and induce insulin resistance (Lithell, 1991; Sarafidis and Bakris, 2006). The traditional β-blockers (e.g. propranolol and atenolol) decrease insulin sensitivity (Bakris et al., 2004; Giugliano et al., 1997; Haenni and Lithell, 1994; Jacob et al., 1996). Glucocorticoids induce insulin resistance (Olefsky, 1975; Olefsky et al., 1975; Qi and Rodrigues, 2007) and suppress insulin secretion (Khan et al., 1992; Lambillotte et al., 1997; Ranta et al., 2006; Ullrich et al., 2005). Calcineurin inhibitors (e.g. tacrolimus and cyclosporine) impair insulin secretion (Duijnhoven et al., 2001; Menegazzo et al., 1998; van Hooff et al., 2004) and induce insulin resistance in adipose tissue (Pereira et al., 2012, 2014). Finally, the mTOR inhibitors (e.g. sirolimus) impair insulin secretion (Bussiere et al., 2006; Kwon et al., 2006) and promote insulin resistance (Syed and Khandelwal, 2000) also in adipose tissue (Pereira et al., 2012, 2014).

Table 1 Drugs that induce diabetes or glucose intolerance and mechanisms of action.

Drug	Impaired insulin secretion	Impaired insulin action
Diuretics		
Thiazides	+	±
Loop diuretics	+	0
Diazoxide	+	+
β-adrenergic antagonists	+	+
Atypical antipsychotics	+	+
Glucocorticoids	0	+
Calcineurin inhibitors	+	+
mTOR inhibitors	+	+
Oral contraceptives	0	+
Pyriminil (Vacor)	+	±
Pentamidine	+	0
Diphenylhydantoin	+	0
Nicotinic acid	0	+
Opiates	+	±

+=Effect; 0=no effect; ±=discrepant results (taken from MI, 1995).

As to antipsychotic drugs, their consumption has been demonstrated to induce adverse metabolic effects such was weight gain/obesity, glucose intolerance, T2DM, dyslipidemia and cardiovascular disease (MI, 1995). The cellular and molecular mechanisms underlying the adverse metabolic effects associated with the consumption of antipsychotic drugs and are not fully understood, but a dysregulation in adipose tissue homeostasis has been suggested as a plausible explanation. As such, the aim of this paper is to review the impact of antipsychotic drugs consumption on the development of adverse metabolic outcomes and to explain the role of adipose tissue in that process.

2. Insulin resistance and adipose tissue

Insulin regulates blood glucose levels primarily by promoting glucose uptake from the blood into tissues such as adipose tissue and by suppressing hepatic glucose production (Figure 1) (Saltiel and Kahn, 2001). At the adipose tissue level, insulin stimulates translocation of glucose transporter type 4 (GLUT4) from an intracellular compartment to the cell membrane (Sano et al., 2003), thus accelerating the uptake and utilization of glucose (Figure 1) (Saltiel and Kahn, 2001). Interestingly, GLUT4 mRNA and protein levels are downregulated in adipose tissue in the setting of T2DM in both rodents and humans (Shepherd and Kahn, 1999). At the cellular level, development of insulin resistance is associated with an impairment in the insulin signaling pathway. More specifically, impaired GLUT4 translocation into the cell membrane has been attributed to defects in signaling involving the insulin receptor substrate 1 (IRS-1) (Hotamisligil et al., 1996; Morino et al., 2008), Akt (also known as protein kinase B (PKB)) (Teruel et al., 2001; Tonks et al., 2013) and effectors downstream of Akt (Ng et al., 2010). Adipose tissue also influences glucose homeostasis indirectly by regulating

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