

Effects of immunosuppressive drugs on human adipose tissue metabolism



UNIVERSITY OF GOTHENBURG

Akademisk avhandling
som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademik vid Göteborgs universitet kommer att offentligheten försvaras i Hörsal Ivan Östholm, LNC,
Medicinaregatan 13, Göteborg

Fredagen den 16 November 2012, kl 9.00

av

MARIA JOÃO PEREIRA

Fakultetsopponent: Professor Eva Degerman,
Institutionen för experimentell vetenskap, Lunds universitet

Avhandlingen baseras på följande del arbeten:

- I. Maria J Pereira, Jenny Palming, Magnus Rizell, Manuel Aureliano, Eugénia Carvalho, Maria K Svensson, Jan W Eriksson
mTOR inhibition with rapamycin causes impaired insulin signalling and glucose uptake in human subcutaneous and omental adipocytes.
Mol Cell Endocrinol 355:96-105, 2012
- II. Maria J Pereira, Jenny Palming, Magnus Rizell, Manuel Aureliano, Eugénia Carvalho, Maria K Svensson, Jan W Eriksson
Cyclosporin A and tacrolimus reduce cell-surface amount of GLUT4 via increased endocytosis: a potential mechanism for the diabetogenic effects of immunosuppressive agents
Submitted (2012)
- III. Maria J Pereira, Jenny Palming, Magnus Rizell, Manuel Aureliano, Eugénia Carvalho, Maria K Svensson, Jan W Eriksson
The immunosuppressive agents rapamycin, cyclosporin A and tacrolimus increase lipolysis, inhibit lipid storage and alter expression of genes involved in lipid metabolism in human adipocytes
Submitted (2012)
- IV. Maria J Pereira*, Jenny Palming*, Maria K Svensson, Magnus Rizell, Jan Dalenbäck, Mårten Hammar, Per-Arne Svensson, Jan W Eriksson
Effects of dexamethasone on gene expression in human subcutaneous and omental adipose tissue - is FKBP5 a novel link between insulin resistance and immune modulation?
*these authors contributed equally
Submitted (2012)

Effects of immunosuppressive drugs on human adipose tissue metabolism

Maria João Pereira

Department of Molecular and Clinical Medicine
The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, 2012

The immunosuppressive agents (IAs) rapamycin, cyclosporin A and tacrolimus, as well as glucocorticoids are used to prevent rejection of transplanted organs and to treat autoimmune disorders. Despite their desired action on the immune system, these agents have serious long-term metabolic side-effects, including dyslipidemia and new onset diabetes mellitus after transplantation. The overall aim is to study the effects of IAs on human adipose tissue glucose and lipid metabolism, and to increase our understanding of the molecular mechanisms underlying the development of insulin resistance during immunosuppressive therapy.

In *Paper I* and *II*, it was shown that rapamycin and the calcineurin inhibitors, cyclosporin A and tacrolimus, at therapeutic concentrations, had a concentration-dependent inhibitory effect on basal and insulin-stimulated glucose uptake in human subcutaneous and omental adipocytes. Rapamycin inhibited mammalian target of rapamycin complex (mTORC) 1 and 2 assembly and phosphorylation of protein kinase B (PKB) at Ser473 and of the PKB substrate AS160, and this leads to impaired insulin signalling (*Paper I*). On the other hand, cyclosporin A and tacrolimus had no effects on expression or phosphorylation of insulin signalling proteins (insulin receptor substrate 1 and 2, PKB, AS160), as well as the glucose transport proteins, GLUT4 and GLUT1 (*Paper II*). Instead, removal of GLUT4 from the cell surface was observed, probably mediated through increased endocytosis, as shown in L6 muscle-derived cells. These studies suggest a different mechanism for cyclosporin A and tacrolimus, in comparison to rapamycin, with respect to impairment of glucose uptake in adipocytes.

In *Paper III*, all three IAs increased isoproterenol-stimulated lipolysis and enhanced phosphorylation of one of the main lipases involved in lipolysis, hormone-sensitive lipase. The agents also inhibited lipid storage, and tacrolimus and rapamycin down-regulated gene expression of lipogenic genes in adipose tissue. All three IAs increased interleukin-6 (IL-6), but not tumor necrosis factor α (TNF- α) or adiponectin, gene expression and secretion.

In *Paper IV*, we proposed that FKBP5 is a novel gene regulated by dexamethasone, a synthetic glucocorticoid, in both subcutaneous and omental adipose tissue. FKBP5 expression in subcutaneous adipose tissue is correlated with clinical and biochemical markers of insulin resistance and adiposity. In addition, the FKBP5 gene product was more abundant in omental than in subcutaneous adipose tissue.

In conclusion, adverse effects of immunosuppressive drugs on human adipose tissue glucose and lipid metabolism can contribute to the development of insulin resistance, type 2 diabetes and dyslipidemia in patients on immunosuppressive therapy. The cellular mechanisms that are described in this thesis should be further explored in order to mitigate the metabolic perturbations caused by current immunosuppressive therapies. The findings in this thesis could potentially also provide novel pharmacological mechanisms for type 2 diabetes as well as other forms of diabetes.

Keywords: Cyclosporin A, tacrolimus, rapamycin, glucocorticoids, new onset diabetes after transplantation, adipocytes, insulin signalling, glucose uptake, lipolysis, lipogenesis

ISBN 978-91-628-8561-8

<http://hdl.handle.net/2077/30256>

Gothenburg 2012