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Biomarkers for novel diabetes therapies in early clinical development. Examples on markers of target activity, gene expression, efficacy and safety from an 11-beta HSD1 inhibitor program

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Cortisol is produced by the adrenal cortex and by local regeneration via the enzyme 11-beta HSD1, eg in adipose tissue. This glucocorticoid hormone has strong insulin-antagonistic effects and it is suggested to play a role in the development of the metabolic syndrome, visceral obesity and type 2 diabetes. We studied the effect of the synthetic glucocorticoid, dexamethasone (Dex), on gene expression and glucose uptake capacity in human subcutaneous and omental adipose tissue aiming to identify new mechanisms and biomarkers for glucocorticoid-induced insulin resistance as well as for 11-beta HSD1 inhibitor treatment aiming for a reduction in local cortisol action. Moreover, phase I studies were done to characterize a novel selective 11-beta HSD1 inhibitor in healthy lean or obese male subjects, and subcutaneous adipose biopsies were performed . We assessed 11-beta HSD1 activity, genome-wide mRNA expression (microarray analysis) as well as circulating markers (novel markers based on gene expression data as well as established markers related to the cortisol axis).

Dex changed the expression of more than 500 genes in both subcutaneous and omental adipose tissue and pathway analysis of Dex-regulated genes showed a clear over-representation of functions and pathways related to inflammation. Single genes affecting lipolysis, glucose uptake and oxidation or adipocyte differentiation were changed after Dex incubation. The expression of the secreted peptides leptin and TIMP4 (metallopeptidase inhibitor 4) were increased by Dex in both depots. Dex dose-dependently impaired basal and insulin-stimulated glucose uptake in omental, and to a lesser degree in subcutaneous, adipocytes.

Repeated dosing of the novel 11-beta HSD1 inhibitor (AZD4017) in healthy subjects markedly reduced 11-beta HSD1 activity in the liver assessed by a prednisone challenge test and by the ratio of urinary cortisol:cortisone metabolites. 11-beta HSD1 inhibition was demonstrated also in adipose tissue after a single dose, but this effect seemed not to be sustained following repeated dosing for 9 days. Effects on circulating markers are being analysed and will be discussed.

A proposed strategy for use of translational and early clinical biomarkers in the development of novel diabetes treatments, as exemplified above, will be described.

Biography

MD, PhD, Full Professor in Internal Medicine. Board-certified specialist in Internal Medicine and Endocrinology. Currently part-time position as Professor, Dept of Molecular and Clinical Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden.Medical Science Director, Diabetes Disease Area, Cardiovascular/ Gastrointestinal Clinical Development, AstraZeneca R&D. Mölndal, Sweden.

During more than 20 years several positions as senior consultant physician, mainly in diabetology and endocrinology at University Hospitals in Göteborg, Lund, Umeå in Sweden. These include senior leadership roles such as Head of Department and Head of Research Units. In the same time period leader of research projects in experimental and clinical diabetology and metabolism. Focus on mechanisms of insulin resistance, in particular translational aspects. Author of approx. 150 scientific papers.

Since 2007 Medical Science Director in Clinical Development, Diabetes (and Obesity) at AstraZeneca R&D. Leader of a large group of MDs, PhDs and other scientists that is responsible for translational and early clinical research in numerous drug projects. PI or co-PI for several internal and external scientific networks and collaborations, for example focusing on mechanisms and markers of insulin resistance and on markers of beta cell function and mass in diabetes.