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Sulfonylureas inhibit PPARγ phosphorylation in primary human adipocytes resulting in a positive anti-diabetic expression profile

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The anti-diabetic effects of glitazones, which are ligands at the transcription factor PPARγ, appear in part to be mediated by inhibition of cyclin-dependent kinase 5 (CDK5)-mediated phosphorylation of PPARγ at Ser273 in adipocytes resulting in a positive anti-diabetic expression profile. Cytokines (adipokines) such as tumor necrosis factor γ (TNFγ) have been shown to induce PPARγ Ser273 phosphorylation, thereby increasing the expression of pro-diabetic adipokines like monocyte chemotactic protein-1 (MCP-1). Here, we investigated whether the widely used sulfonylureas (SUs) glibenclamide and glimepiride alter phosphorylation of PPARγ at Ser273 in an *in vitro* phosphorylation assay, in human primary adipocytes *in vitro* and in adipose tissue in mice. In addition, the effects of SUs on adipocyte differentiation and changes in the anti-diabetic expression profile were examined by real-time PCR. TNFγ induced PPARγ Ser273 phosphorylation in a time- and concentration-dependent manner in primary human adipocytes and in adipose tissue of TNFγ injected mice. Treatment of cells and mice with SUs, Rosiglitazone or the PPARγpartial agonist SR1664 prior to TNFγ challenge resulted in a reduction of PPARγ Ser273 phosphorylation *in vitro* and *in vivo*. Furthermore, SU were able to block CDK5-mediated PPARγ phosphorylation in an *in vitro* phosphorylation assay. The alteration of the PPARγ phosphorylation state upon SU treatment was correlated with the reduced expression of pro-diabetic adipokines (e.g. MCP-1). Taken together, our data indicate that SU have anti-diabetic glitazone-like actions on human adipocytes *in vitro* and *in vivo* in mice by reducing PPARγ Ser273 phosphorylation resulting in a positive anti-diabetic expression profile.

Biography

Bodo Haas has completed his PhD from Department of Pharmacology at Ludwig-Maximilians-University Munich, Germany and Post-doctoral studies from the Institute of Pharmacology and Toxicology at Rheinische Friedrich-Wilhelms-University Bonn, Germany. He is European Certified Toxicologist (ERT), non-Clincial Assessor and research group Leader of Diabetes at the Federal Institute for Drugs and Medical Devices in Bonn, Germany. He has published more than 25 papers in reputed German and international journals, contributed to text books and has been serving as reviewer for scientific journals.

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