OATP1B3 is expressed in pancreatic β-islet cells and enhances the insulinotropic effect of the sulfonylurea derivative glibenclamide

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OATP1B3 is a membrane bound drug transporter that facilitates cellular entry of a variety of substrates. Most of the previous studies focused on its hepatic expression and function in hepatic drug elimination. In this study we report expression of OATP1B3 in human pancreatic tissue, with the abundance of the transporter localized in the islets of Langerhans. Transport studies using OATP1B3 overexpressing MDCKII cells revealed significant inhibition of the cellular uptake of the known substrate CCK-8 in presence of the insulinotropic anti-diabetic compounds tolbutamide, glibenclamide, glimepiride, and nateglinide, and identified glibenclamide as a novel substrate of OATP1B3. Sulfonylurea derivatives exert their insulinotropic effect by binding to the SUR1 subunit of the K_{ATP}-channels inducing insulin secretion in β-cells. Here we show that transient overexpression of human OATP1B3 in a murine β-cell line (MIN6) - which exhibit glucose and glibenclamide-sensitive insulin secretion - significantly enhances the insulinotropic effect of glibenclamide, without affecting glucose stimulated insulin secretion. Taken together, our data provide evidence that the drug transporter OATP1B3 functions as a determinant of the insulinotropic effect of glibenclamide on the tissue level. Changes in transport activity based on drug-drug interactions and/or genetic variability may therefore influence glibenclamide efficacy.

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