Effects of stevioside on pancreatic beta cell function during glucotoxicity, lipotoxicity and glibenclamide secondary failure: studies in vitro

Jianguo Chen, MD.

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Official opponents: Jan M.C. Genus Professor, Belgium, Jens Høiriis Nielsen, Professor, Lise Wogensen Bach, ass. Professor

Supervisors: Kjeld Hermansen, Professor, Per Bendix Jeppesen, ass. Professor

Correspondance: Jianguo Chen, MD, Aarhus University Hospital, Aarhus Sygehus Tage Hansens Gade, Dept. of Endocrinology and Metabolism C, 8000 Aarhus C, Danmark.

E-mail: jianguo.chen@ki.au.dk

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is caused by abnormal beta cell function and insulin resistance and is associated with hyperinsulinaemia, dyslipidaemia, hypertension, abdominal obesity, and impaired metabolic homeostasis. After long-term treatment with the sulfonylurea, glibenclamide (GB), T2DM patients may develop secondary failure to the drug in part due to GB desensitization.

Due to limited economic resources in developing countries, a new and effective low cost treatment for T2DM is needed. A potential candidate, stevioside, has previously been shown by us to possess direct insulinotropic effects in isolated islets and clonal beta cells (INS-1E cells).

The aims were to investigate if SVS is able to counteract the GB-induced beta cell desensitization and improve insulin secretion. Furthermore, we have explored if SVS is able also to counteract the detrimental effects of gluco- and lipotoxicity in insulin producing beta cells.

To explore the GB-induced desensitization, we incubated mouse islets 24 h in 11.1 mM glucose with or without GB and/or SVS. After 24 h pre-incubation GB (10^{-11}-10^{-3} M) caused a dose-dependent suppression of glucose-stimulated (16.7 mM glucose) insulin secretion (GSIS) ($P<0.001$). Interestingly, the GB-induced desensitization of GSIS was counteracted by both 10^{-7} M SVS ($p<0.05$) and 10^{-7} M GLP-1 ($p<0.05$). GB pretreatment did not change gene expressions of pancreas PDX-1 or GLUT2, while SVS upregulated the expression of both genes by more than two fold ($p<0.05$).

To investigate the impact of glucotoxicity, we exposed isolated mouse islets as well as clonal INS-1E beta cells for 48 h to 27 mM or 16.7 mM glucose, respectively. We found that 48 h exposure to high glucose impaired GSIS from mouse islets and INS-1E cells, an effect that was counteracted by SVS (10^{-6} M). Studies indicate that SVS may act via regulation of ACC activity.

To study lipotoxicity, we exposed rat islets as well as INS-1E cells to 1.0 mM or 0.6 mM palmitate between 24 h and 120 h. Our results showed that lipotoxicity occurred after 72 h exposure to 1.0 mM palmitate in rat islets i.e. BSIS was elevated (n=8, p=0.000) and GSIS decreased (n=8, p=0.000). These effect were antagonised by supplementation with 10-6 M SVS (n=8, p=0.000). However, palmitate significantly increased the triglyceride content in INS-1E cells (1.000.06 vs 1.550.14, n=10, p=0.003), but this effect was unchanged by addition of SVS (1.550.14 vs 1.780.08 vs, n=10, p=0.17). In conclusion, we have demonstrated that SVS pretreatment dose-dependently increases GSIS. SVS counteracts the GB-induced desensitization of beta cell function and alleviates the negative effect of glucotoxicity and lipotoxicity. In conclusion SVS may be a putative new drug for the prevention and/or treatment of T2DM.