

## Effects of Long-Term Treatment with Stevioside on the Type 2 Diabetic Goto-Kakizaki (GK) Rats – Potential as a New Antidiabetic drug.

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Extracts from leaves of *Stevia rebaudiana* Bertoni (SrB), have been used in traditional medicine in Paraguay and Brasil as treatment of diabetes. Recently, we demonstrated a direct insulinotropic effect of stevioside in vivo in isolated mouse islets and in vivo in diabetic rats.

**Aims:** To explore if stevioside exerts anti-hyperglycemic, glucagonostatic or anti-hypertensive effects during long-term feeding with stevioside in diabetic rats.

**Methods:** For 6 weeks period Goto-Kakizaki (GK) rats were given 0.025 g/kg BW/day of the glycoside stevioside (purity > 99 %) via the drinking water. The same amount of glucose as contained in the stevioside was given to the control group. The tail-blood pressure was measured every week. At week 5 an intraarterial catheter was inserted in rats of both groups. After 6 days recovery the animals were exposed to an i.v. glucose tolerance test (2.0 g/kg BW) and blood samples were drawn throughout a 180 min period.

**Results:** Stevioside caused a suppression of plasma glucose (incremental area under the curve (IAUC)):  $985 \pm 20$  (stevioside) vs  $1575 \pm 21$  (control) mM x 180 min,  $p < 0.05$ . Corresponding to this the stevioside fed animals had an enhanced first phase insulin response compared to the control group (IAUC:  $343 \pm 33$  (stevioside) vs  $136 \pm 24$  (control) mU insulin x 30 min,  $p < 0.05$ ). The second phase insulin response, in both groups occurred to be increasing during the entire observation period. The control group tended to have higher insulin output, however, not attaining statistical significance (IAUC:  $4798 \pm 34$  (control) vs  $3776 \pm$  (stevioside) mU x 150 min,  $p = 0.38$ ). Interestingly, stevioside concomitantly caused a suppression of the glucagon level corresponding to the first phase of the insulin response (IAUC:  $2026 \pm 234$  (stevioside) vs  $3535 \pm 282$  (control) pg/ml x 180 min,  $p < 0.05$ ). From week one and onwards a 7-9 % decrease in both the systolic ( $p < 0.01$ ) and diastolic ( $p < 0.05$ ) blood pressure was elicited by stevioside.

**Conclusion:** Stevioside normalizes first phase insulin response in diabetic rats during i.v glucose tolerance test, and possess anti-hyperglycemic, insulinotropic and glucagonostatic effects. In addition, stevioside exerted blood pressure suppression. Stevioside appears to be usefull in the treatment of type 2 diabetes and the metabolic syndrome.