Rebaudioside A and pancreatic β-cell function

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ABSTRACT

Natural products, mainly plant-derived constituents, have long been sources of drugs. Extracts from leaves of the plant *Stevia rebaudiana Bertoni*, a shrub native to certain regions of South America, have been used for many years in the treatment of diabetes among native indians. Stevia leaves contain diterpene glycosides that are responsible for the typical sweet taste, stevioside and rebaudioside A being the most abundant. Previously, we have demonstrated that stevioside exerts a direct insulinotropic action in isolated mouse islets and in clonal β-cell lines (INS-1 and INS-1E) and possesses antihyperglycemic effect. The question arises if rebaudioside A, which shares the main structure with stevioside, also possesses insulinotropic effects.

To investigate the effects of rebaudioside A on the β-cell function, we performed static incubations and perifusion experiments with isolated mouse islets. We found that rebaudioside A causes a concentration-, glucose- and Ca^{2+}-dependent increase in the insulin secretion. The threshold of the insulinotropic action is seen at a rebaudioside A concentration of 10^{-14} M and the maximal insulin response occurs at 10^{-10} M. Interestingly, rebaudioside A only potentiated the insulin secretion at a glucose concentrations above 6.6 mM. In perifusion experiments, 10^{-10} M of rebaudioside A elicits a pronounced and sustained monophasic increase in insulin release in the presence of high glucose (16.7 mM). Moreover, the concentration- and glucose- dependent effects on insulin secretion of rebaudioside A are supported in studies with clonal β-cells from the insulinoma β-cell line MIN6 cells.

The addition of the maximally effective concentration of rebaudioside A (10^{-9} M) increases the ATP/ADP ratio significantly in the presence of high glucose (16.7 mM) while it does not change the intracellular cAMP level. Rebaudioside A (10^{-9} M) and stevioside (10^{-6} M) reduce KATP conductance in β-cells in a critically glucose-dependent manner. Thus the concentration- and glucose-dependent stimulation of insulin secretion to rebaudioside A appear at least in part to be mediated via an increase in the ATP/ADP ratio and subsequent inhibition of K_{ATP}-channels of β-cells.

The effects on β-cell function of long-term (48-hours) exposure to rebaudioside A revealed that rebaudioside A only stimulates the glucose-stimulated insulin secretion at high (16.7 mM) but not at normal glucose concentrations. The enhancement of GSIS is accompanied by an increase in both the insulin content and insulin gene expression, indicating that the changes are due to increased insulin biosynthesis.

In conclusion, we have demonstrated that rebaudioside A possesses an insulinotropic effect that is critically glucose dependent, i.e. rebaudioside A does not stimulate insulin release at normal glucose levels, pointing to a lesser risk of hypoglycemia than e.g. with sulphonylureas. Rebaudioside A may offer distinct therapeutic advantages over sulphonylureas in the treatment of type 2 diabetes.