Insulin Secretion and Islet Lysosomal Enzyme Activities in the Mouse

Effects of Suramin

G. Skoglund,*1 B. Ahrén,1,2 and I. Lundquist3

Departments of 1Pharmacology and 2Surgery, Lund University, Sölvegatan 10, S-223 62 Lund; and Department of 3Cell Biology, University of Linköping, Linköping, Sweden

Received August 3, 1987; Revised December 24, 1987; Accepted December 26, 1987

Summary

To study the functional role of the lysosomes in islet physiology, we have in the present study investigated influences on insulin secretion induced by a primary inhibition of islet lysosomal enzyme activities by the use of the lysosomotropic drug suramin.

First, we demonstrated that the activities of the three lysosomal enzymes, acid amylglucosidase, acid α-glucosidase, and N-acetyl-β-D-glucosaminidase, were inhibited in mouse islet homogenates upon direct addition of suramin (p<0.001). Thereafter, we studied the influences of suramin on islet lysosomal enzyme activities at 24 h after an administration of suramin to mice. We thereby found that the islet lysosomal enzyme activities were not significantly altered compared to controls. However, after incubation of the islets at 3.3 mM glucose, the activities of acid amylglucosidase and acid α-glucosidase were increased (p<0.05). The activity of N-acetyl-β-D-glucosaminidase was, however, not affected.

Hence, the direct inhibitory action on islet lysosomal enzyme activities by suramin seems to be counteracted in vivo. Concurrently with the increased enzyme activities in incubated islets, glucose-induced insulin secretion was significantly potentiated by suramin pretreatment (p<0.01). In contrast, suramin pretreatment did impair the glucose-induced insulin secretion in vivo (p<0.01).

The direct effects on plasma insulin and glucose levels of acutely administered suramin were also studied. It was found that at a high dose level, suramin slightly reduced the basal plasma insulin levels (p<0.05). Suramin did not, however, affect the glucose-induced increase in plasma insulin levels. Conversely, at a low dose level, suramin potentiated glucose-induced increase in plasma insulin levels (p<0.01). A similar potentiated glucose-induced insulin secretion by suramin was also observed by a direct addition of the drug to islets in vitro.

*Author to whom all correspondence and reprint requests should be addressed.
In conclusion, this study demonstrates that suramin inhibits lysosomal enzyme activities in islet homogenates, increases the activity of acid amylglucosidase and acid α-glucosidase in incubated mouse islets after administration of the drug in vivo and potentiates glucose-stimulated insulin secretion from islets in vitro after administration of the drug in vivo. Thus, we suggest first, that in vivo, compensatory mechanisms may counteract the direct inhibitory influence of suramin on islet lysosomal enzyme activities, and second, that in vitro, islet lysosomal acid amylglucosidase and acid α-glucosidase activities and glucose-induced insulin secretion are regulated in parallel.

**Key Words:** Suramin; islet lysosomes; lysosomal enzymes; insulin secretion; mice.

**INTRODUCTION**

The functional role of the lysosomes in islet physiology is not yet fully established. Results of previous studies have indicated that lysosomes might be involved in the processes of insulin secretion (1-4) and intra-islet proinsulin, insulin, and C-peptide degradation (5-7). By direct measurements of the activities of islet lysosomal enzymes, we are currently studying the correlation between lysosomal enzyme activities and islet function. In a previous study, we thereby showed that glucose- but not isobutylmethylxanthine (IBXM)-stimulated insulin secretion was related to increased activities of the two islet lysosomal enzymes, acid amylglucosidase and acid α-glucosidase (1). This could suggest involvement of lysosomal enzyme activities in the mechanisms behind glucose-induced insulin secretion. If so, it is of interest to induce a primary alteration in islet lysosomal enzyme activities and study the consequences for insulin secretion. This was the subject of the present study. Thus, we used the lysosomotropic drug suramin, which has been shown to be taken up into lysosomes and to disturb lysosomal function (8-10). We performed our studies both in vivo and in the mouse and in vitro on isolated mouse islets.

**MATERIALS AND METHODS**

**Animals**

Female mice of the NMRI strain (Anticimex, Stockholm, Sweden), weighing 20-30 g, were used throughout the study. All animals were fed a standard pellet diet (Astra-Ewos, Södertälje, Sweden) and tap water ad libitum, before and during the experiments.

**Experimental Procedure**

**In Vivo**

Suramin (179 μmol/kg body wt) was given intravenously into a tail vein 24 h and intraperitoneally 2 h before an intravenous injection of either of the two insulin secretagogues glucose or L-isoprenaline at various dose levels. In another experimental series, suramin was given intravenously at various dose levels either alone or together with glucose at 2 min prior to blood sampling.