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Pdf2word V3.1 Download ATP-sensitive potassium channels (KATP) play a critical role in the regulation of insulin secretion, and their activity is inhibited by sulfonylureas (SU), the most important drugs in the treatment of type 2 diabetes. We have recently found that KATP channels are present in pancreatic beta-cells and that isoproterenol (ISO), a beta-adrenergic agonist, activates them in a way that is similar to the effect of sulfonylureas. ISO is also an effective stimulus of insulin release in beta-cells, and preliminary data indicate that its action is sensitive to D-myo-inositol-1,4,5-trisphosphate (InsP3), a second messenger that has been implicated in the regulation of KATP channels. The first specific aim of this proposal is to characterize the KATP currents activated by InsP3, ISO, and their combination, to determine the molecular properties of the channels, and to establish whether there is functional cooperation between KATP and voltage-dependent calcium channels in beta-cells. The second specific aim is to evaluate the possible roles of KATP in the insulin secretory response to glucose and other secretagogues, and to determine whether InsP3-elicited activation of KATP is important in the mechanism of beta-cell adaptation to glucose, under basal and stimulated conditions. These studies will use an expression system in which the KATP-related currents can be reconstituted in oocytes, and will employ the patch-clamp technique and cytosolic free calcium measurements with the fluorescent probe quin 2 to assess KATP channel function. It is expected that this work will reveal information that is relevant to the action of both sulfonylureas and the beta-cell secretagogue secretin, and that would lead to a better understanding of the regulation of insulin secretion by this class of drugs.

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