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BPDZ-154 is a potent activator of ATP-sensitive potassium channels in pancreatic beta-cells

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Diazoxide is an agonist of ATP sensitive K^+ (KATP) channels in beta-cells and is used in the treatment of hyperinsulinism caused by insulinomas or Hyperinsulinism in Infancy (HI). The responsiveness of patients to diazoxide is highly variable and complicated by side-effects which include hypertension and hypertrichosis. The aim of this study was to examine the actions of a novel benzothiadiazine-derivative, BPDZ-154, on beta-cell KATP channels and insulin release. We isolated human insulin-secreting cells from patients with HI (n=4) or adenoma (n=1) following surgery (with permission), and undertook additional studies using rat islets and the insulin-secreting cell-line BRIN-BD11.

Results: BPDZ-154 was found to inhibit 16.7mM glucose-induced insulin release with an EC50 value of 0.28microM (compared to approximately 20microM for diazoxide). The mechanism of action of BPDZ-154 involved the selective activation of KATP channels since BPDZ-154 increased the activity of KATP channels in both intact cells (10-50microM, n=5) and in inside-out patches exposed to 500microM ATP, (10nM-50microM, n=23/23). BPDZ-154 was consistently found to be more potent than diazoxide (n=7/7) and was less readily reversible upon removal of the compound. Tolbutamide, and the imidazoline efaroxan reversed the effects of BPDZ-154 induced activation of KATP channels (n=13/13). In beta-cells isolated from HI patients, BPDZ-154 was effective in those patient tissues where KATP channel function remained (10-50microM, n=24/24), but was ineffective in patients where KATP channels were absent (n=10/10). In adenoma beta-cells, BDPZ-154 consistently activated KATP channels (500microM ATP/ 10microM BPDZ-154, n=6/6).

Summary: We document the inhibition of insulin release and activation of beta-cell KATP channels by BPDZ-154. BPDZ-154 was more potent than diazoxide. With improved selectivity for SUR1/Kir6.2 channels over non-beta-cell KATP channels these types of compounds may offer a therapeutic potential in the future treatment of HI.