profiles when compared to the RLD recombinant product. As part of the ANDA review, impurities in the synthetic drugs are analyzed and controlled, in addition, the potential immunogenicity of new impurities, which are not in the RLD products, are assessed and compared using non-clinical assays. In this work, we will discuss non-clinical assays for assessing the immunogenicity risk of these impurities, for both adaptive and innate immune responses. In conclusion, the sameness of an approved generic synthetic glucagon to an RLD can be adequately established through various analytical methods and biological assays.

Diabetes Mellitus and Glucose Metabolism

BENCH TO BEDSIDE: NOVEL MECHANISMS IN DIABETES AND METABOLISM

Selective Somatostatin 5 (SST5) and Somatostatin 2 (SST2) Nonpeptide Agonists Potently Suppress Glucose- and Tolbutamide-Stimulated Dynamic Insulin Secretion From Isolated Human Islets

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Congenital hyperinsulinism (HI) is the most common cause of persistent hypoglycemia in newborns and infants and arises from dysregulated insulin secretion. Rapid recognition and treatment are vital to prevent seizures, permanent developmental delays, coma, or even death. Very few medical options exist to treat congenital HI patients: the K_{ATP} channel activator diazoxide, the injectable somatostatin receptor peptide agonists octreotide and lanreotide, or chronic glucose infusions. However, side effects and/or limited efficacy render these therapies inadequate for many patients.

Somatostatin is a 14-amino acid peptide hormone with a broad spectrum of biological actions, which are regulated through five somatostatin receptor subtypes (SST1-SST5). Somatostatin's common physiological role is to down-regulate secretion of other hormones in various tissues. Its role in the maintenance of euglycemia is to regulate insulin and glucagon secretion from pancreatic β- and α-cells, respectively. Somatostatin regulates insulin secretion by decreasing the intracellular levels of cAMP, inhibition of voltage-gated calcium channels (VGCC), activation of the G protein-activated inward rectifier K^+ channel (GIRK), and direct inhibition of insulin exocytosis.

Several studies have evaluated the effect of somatostatin, somatostatin peptide analogs, and a limited number of nonpeptide somatostatin receptor agonists on insulin secretion in static assays using isolated human islets. However, the lack of highly selective agonists has made the interpretation of the contribution of SST receptor subtypes difficult to discern. Our programs for the treatment of hyperinsulinism, acromegaly, and other indications have led to the development of selective nonpeptide SST2, SST3, SST4, and SST5 agonists, possessing EC_{50}s < 1 nM in cell-based assays of receptor activation and selectivity > 130 times over the other members of the family. The ability of these selective nonpeptide agonists to regulate glucose- and tolbutamide-stimulated dynamic insulin secretion from human islets was evaluated using a perifusion system (Biorep, FL).

We found that selective SST2 and SST5 agonists potently suppressed dynamic insulin secretion in contrast to SST3 or SST4 selective agonists. Importantly, SST5 agonists were shown to have a greater effect than selective SST2 agonists or diazoxide, demonstrating their potential utility in human conditions such as congenital HI. In addition, SST5 activation is also known to have a smaller effect on glucagon secretion and is also less prone to agonist-driven desensitization than SST2 activation. Taken together, these studies support our program to identify, characterize, and develop potent, nonpeptide, orally-bioavailable, selective SST5 agonists with appropriate pharmaceutical and safety characteristics for the treatment of congenital HI.

Diabetes Mellitus and Glucose Metabolism

BENCH TO BEDSIDE: NOVEL MECHANISMS IN DIABETES AND METABOLISM

Serum Sclerostin Is Associated With Central Fat Distribution in Patients With Type 2 Diabetes and Peripheral Neuropathy

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Background: Peripheral neuropathy (PN) is the most common chronic diabetic complication occurring in both type 1 and type 2 (T2DM) patients as well as in prediabetes states. Metabolic syndrome seems to be as important as glycemic control in determining the onset and course of DPN, but the mechanisms underlying this association is far from conclusive. Sclerostin (SCL) is a glycoprotein secreted by osteocytes that has an antagonistic effect on the Wnt/beta-catenin pathway which is related to bone formation as well as to increased ectopic fat including marrow fat. Besides to its well-documented role in bone metabolism, the relationship between SCL and adiposity and metabolic syndrome is poorly understood. **Objective:** To determine SCL levels in patients with T2DM and DPN and evaluate their relationship with metabolic and body composition parameters. **Design:** Cross-sectional study including 56 patients with T2DM and DPN. Serum SCL levels, glycemic and lipid profile, anthropometric measurements, and percent body fat (PBF) were determined. **Results:** Mean age was 61.80 ± 10.67 years, duration of T2DM 13.30 ± 8.13 years, 57.1% men, 78.6% hypertensive, body mass index 28.74 ± 5.04 kg/m^2, abdominal circumference 99.86 ± 13.37 cm, waist-to-hip ratio (WHR) 0.97 ± 0.08, fasting plasma glucose 169.73 ± 83.13 mg/dL, HbA1c 8.88 ± 2.09%, Triglycerides (TG) 163.54 ± 75.93 mg/dL, SCL 207.41 ± 215.13 pg/mL, and PBF 34.45 ± 8.42%. There were significant correlations between SCL and TG (r=0.407, p=0.003) and significant differences in TG according to quartiles (< p25 vs >p75) of SCL: 125.15 ± 47.45 mg/dL vs 223.50 ± 88.77 mg/dL,