ABSTRACT
Glucagon Receptor Antagonist LGD-6972 Is Efficacious in Streptozocin-Induced Diabetic Mice
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INTRODUCTION
Recent studies indicate that glucagon action plays an essential role in insulin-dependent diabetes. Glucagon receptor (GCG) knockout mice are resistant to diabetes even after high-dose streptozocin (STZ) treatment eliminated virtually all insulin production. We examined whether pharmacological antagonism of the GCG could result in similar effects in insulin-deficient mice. LGD-6972 is a potent and selective antagonist of the GCG that has previously demonstrated activity in preclinical models of T2DM. Male BALB/c mice were injected with multiple low doses of STZ and left untreated until hyperglycemia was confirmed. Hyperglycemic mice were orally dosed with LGD-6972 or vehicle for 28 days. Non-fasting blood glucose was significantly reduced in LGD-6972-treated mice compared with vehicle (p < 0.05 throughout the experiment). Larger effects were observed on fasting blood glucose (Vehicle: 382 mg/dL, LGD-6972: 234 mg/dL, non-diabetic controls: 118 mg/dL). An oral glucose tolerance test revealed a large increase in glucose levels and a slow recovery to baseline levels in STZ mice relative to non-diabetic controls, consistent with an insulin-deficient state. LGD-6972-treated mice had lower glucose levels than STZ mice throughout the glucose tolerance test (average decrease of 100 mg/dL) but displayed a similar delayed return to baseline. Terminal measurements of HbA1c, 3-hydroxybutyrate, and free fatty acids (FFA) were significantly elevated in STZ mice indicating prolonged hyperglycemia and ketoadiposis. LGD-6972 partially restored HbA1c and 3-hydroxybutyrate to non-diabetic levels but did not alter FFA levels. These data indicate that pharmacological inhibition of GCG may be an efficacious treatment for T1DM and could potentially be used in an insulin-sparing regimen. Pharmacological inhibition was not able, however, to completely normalize the hyperglycemic state, unlike the effects observed with an insulin-sparing regimen. Pharmacological inhibition was not able, however, to completely normalize the hyperglycemic state, unlike the effects observed with an insulin-sparing regimen. Pharmacological inhibition was not able, however, to completely normalize the hyperglycemic state, unlike the effects observed with an insulin-sparing regimen.

RESULTS
Glucagon Receptor Binding and cAMP Inhibition
LGD-6972 potently displaced human glucagon in a radiolabeled binding assay (IC50 = 0.5 nM). cAMP production was measured in glucagon-stimulated hepatocytes from human and mouse donors. LGD-6972 potently inhibited cAMP production in human (IC50 = 0.5 nM), with reduced potency vs. mouse (IC50 = 150 nM).

Glucose reduction in streptozotocin-injected mice
Male BALB/c mice were injected with multiple low doses of STZ (40 mg/kg IP for 5 days). After hyperglycemia developed, mice were administered 30 mg/kg orally in LGD-6972 or vehicle (PO, OD). Non-fasting blood glucose was monitored weekly. LGD-6972 significantly improved hyperglycemia but was unable to completely normalize glucose levels.

LGD-6972 significantly reduced fasting and non-fasting glucose and significantly reduced ketone bodies and free fatty acids in diabetic controls, consistent with an insulin-deficient state. LGD-6972 reduced ketone bodies and free fatty acids in diabetic controls, consistent with an insulin-deficient state. LGD-6972 reduced ketone bodies and free fatty acids in diabetic controls, consistent with an insulin-deficient state.

At the conclusion of the study, fasting glucose, hemoglobin A1c, ketone bodies, and free fatty acids were measured. STZ treatment increased all 4 parameters above non-diabetic levels. LGD-6972 partially normalized all 4 parameters.

Glucagon and insulin play counter-regulatory roles in glucose homeostasis. Recent studies suggest that unopposed glucagon action is largely responsible for the hyperglycemia observed in type 1 diabetes(1). Recent evidence suggests that disruption of glucagon signalling completely normalizes glucose levels in streptozocin injected mice, a model of type 1 diabetes(1,2). We have discovered a novel, selective, orally bioavailable glucagon receptor antagonist and investigated its effects on an animal model of type 1 diabetes.

SUMMARY
• LGD-6972 is a highly potent and selective glucagon receptor antagonist.
• LGD-6972 significantly reduced fasting and non-fasting glucose in a model of type 1 diabetes.
• LGD-6972 reduces basal glucose levels in diabetic mice but does not fully normalize glucose tolerance.
• LGD-6972 reduces ketone bodies and free fatty acids in diabetic mice.
• Combination therapy with insulin and LGD-6972 was more effective than insulin alone in diabetic mice.

REFERENCES

AMERICAN DIABETES ASSOCIATION (ADA) 73RD SCIENTIFIC SESSIONS; CHICAGO, IL, USA; JUNE 21-25, 2013