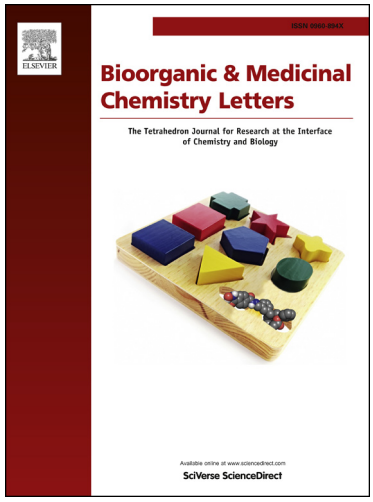

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Matthew F. Sammons, Esther C.Y. Lee

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Recent progress in the development of small-molecule glucagon receptor antagonists

Matthew F. Sammons* and Esther C.Y. Lee

Cardiovascular, Metabolic and Endocrine Diseases Chemistry, Pfizer Worldwide Research and Development, 610 Main St, Cambridge, MA 02139

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ABSTRACT

The endocrine hormone glucagon stimulates hepatic glucose output via its action at the glucagon receptor (GCGr) in the liver. In the diabetic state, dysregulation of glucagon secretion contributes to abnormally elevated hepatic glucose output. The inhibition of glucagon-induced hepatic glucose output via antagonism of the GCGr using small-molecule ligands is a promising mechanism for improving glycemic control in the diabetic state. Clinical data evaluating the therapeutic potential of small-molecule GCGr antagonists is currently emerging. Recently disclosed clinical data demonstrates the potential efficacy and possible therapeutic limitations of small-molecule GCGr antagonists. Recent pre-clinical work on the development of GCGr antagonists is also summarized.

The glucagon receptor (GCGr) is a class B G-protein coupled receptor. In the liver, stimulation of GCGr signaling by binding of glucagon, a 29-amino acid peptide hormone produced by the α-cells of the endocrine pancreas, stimulates hepatic glucose production via both glycogenolysis and gluconeogenesis. Through its action via the GCGr, glucagon plays a counter-regulatory role to insulin in the maintenance of euglycemia. In type-2 diabetes mellitus, the suppression of pancreatic glucagon secretion in response to hyperglycemia and hyperinsulinemia is inadequate, contributing to abnormally elevated hepatic glucose production in both the fasting and postprandial states.[1-5] Dysregulation of glucagon secretion has also been suggested to play a central role in the pathology of type-1 diabetes.[6, 7]

Blockade of glucagon signaling by GCGr antagonists has long been proposed as a method to improve glycemic control in the diabetic state via reduction of hepatic glucose production.[8,9] Clinical evaluation of a small-molecule GCGr antagonist was first reported in 2001, with the demonstration that oral administration of the GCGr antagonist Bay 27-9955 (**1**), **Figure 1**, to healthy male volunteers blunted the elevation in hepatic glucose production and plasma glucose concentration induced by administering exogenous glucagon.[10] Over the last few years, a number of other small-molecule GCGr antagonists have entered the clinic (**Table 1, Figure 1**). The disclosed data from these clinical experiments, most notably data reviewed below from experiments using either MK-0893 (**2**), MK-3577 (**3**), or LY2409021, demonstrate the ability of GCGr antagonists to improve glucose homeostasis in diabetic subjects. However, the therapeutic utility of this mechanism remains unclear as dose-responsive increases in circulating lipids, particularly low-density lipoprotein cholesterol (LDL-C), elevated liver enzymes, and increases in body weight have been reported in some of these studies (vide infra). The preclinical and early clinical development of small-molecule GCGr antagonists through late 2011 has been reviewed previously.[11, 12] The patent literature covering small-molecule GCGr antagonists through 2014 has also been recently reviewed.[13]

Table 1. Clinical Candidate Small-Molecule GCGr Antagonists

Antagonist	Stage of Development	Structure
Bay 27-9955	discontinued	**1**
MK-0893	discontinued	**2**
MK-3577	discontinued	**3**
LY2409021	Phase 2	not disclosed
PF-06291874	Phase 2	not disclosed
LGD-6972	Phase 1	not disclosed

Starting in 2011, a series of clinical experiments with MK-0893 (**2**), **Figure 1**, were disclosed.[11, 14] Results of a glucagon challenge study were used to select doses of MK-0893 for use in a 4-week monotherapy study in subjects with type-2 diabetes.