Novel Glucagon-Like Peptide-1 Analog Delivered Orally Reduces Postprandial Glucose Excursions in Porcine and Canine Models

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Abstract

Background:

Glucagon-like peptide-1 (GLP-1) and its analogs are associated with a gamut of physiological processes, including induction of insulin release, support of normoglycemia, β-cell function preservation, improved lipid profiles, and increased insulin sensitivity. Thus, GLP-1 harbors significant therapeutic potential for regulating type 2 diabetes mellitus, where its physiological impact is markedly impaired. To date, GLP-1 analogs are only available as injectable dosage forms, and its oral delivery is expected to provide physiological portal/peripheral concentration ratios while fostering patient compliance and adherence.

Methods:

Healthy, fasting, enterically cannulated pigs and beagle canines were administered a single dose of the exenatide-based ORMD-0901 formulation 30 min before oral glucose challenges. Blood samples were collected every 15 min for evaluation of ORMD-0901 safety and efficacy in regulating postchallenge glucose excursions.

Results:

Enterically delivered ORMD-0901 was well tolerated by all animals. ORMD-0901 formulations RG3 and AG2 led to reduced glucose excursions in pigs when delivered prior to a 5 g/kg glucose challenge, where area under the curve $(AUC)_{0-120}$ values were up to 43% lower than in control sessions. All canines challenged with a glucose load with no prior exposure to exenatide, demonstrated higher AUC_{0-150} values than in their exenatide-treated sessions. Subcutaneous exenatide delivery amounted to a 51% reduction in mean glucose AUC_{0-150}, while formulations AG4 and AG3 prompted 43% and 29% reductions, respectively.

Conclusions:

When delivered enterically, GLP-1 (ORMD-0901) is absorbed from the canine and porcine gastrointestinal tracts and retains its biological activity. Further development of this drug class in an oral dosage form is expected to enhance diabetes control and patient compliance.

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Abbreviations: (AUC) area under the curve, (DPP-4) dipeptidyl peptidase-4, (GLP-1) glucagon-like peptide-1, (GLP-1R) glucagon-like peptide-1 receptor, (T2DM) type 2 diabetes mellitus

Keywords: exenatide, glucagon-like peptide-1, oral, ORMD-0901, type 2 diabetes mellitus

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Eldor

Introduction

Glucagon-like peptide-1 (GLP-1) is a 30-amino-acid gut-derived peptide secreted by the intestinal L cells within minutes of food ingestion. Its release is controlled by a combination of neural and endocrine stimuli and by direct nutrient contact with L cells.[1] Glucagon-like peptide-1 and its analogs induce pleiotropic physiological effects manifested via stimulation of insulin secretion, glucagon secretion inhibition, reduced appetite and delayed gastric emptying.[2,3] In addition, these peptides have been shown to support prolonged normoglycemia, preserve β-cell function, reduce oxidative stress, improve cardiac function, lower blood pressure, improve lipid profiles, reverse fatty liver, and increase insulin sensitivity.[3] In this manner, GLP-1 harbors significant therapeutic potential in the management of type 2 diabetes mellitus (T2DM). The effect of GLP-1 on β-cell responsiveness measured upon glucose-induced insulin secretion in T2DM patients and in healthy volunteers has been shown to occur in a dose-dependent manner.[4] Furthermore, accruing clinical evidence correlates its plasma concentrations to sustained reductions in hemoglobin A1c and weight loss. Thus, as a novel class of drugs for T2DM, GLP-1-based therapies are attracting increasing attention because of their unique and beneficial mechanisms of action.

However, clinical use of the native form of GLP-1 is limited due to its rapid enzymatic inactivation by the ubiquitous dipeptidyl peptidase-4 (DPP-4) enzymes, resulting in a 2–3 min circulating half-life. To overcome this obstacle, both natural and synthetic, long-acting degradation-resistant peptides, GLP-1 mimetic agents, as well as DPP-4 enzyme inhibitors have been designed and introduced to the clinic. The first GLP-1 mimetic to be approved for clinical use in the United States was the naturally occurring lizard salivary gland exendin-4 peptide (exenatide/Byetta, Amylin Pharmaceuticals), a potent GLP-1 receptor (GLP-1R) agonist with a half-life of 2.4 h. A once-weekly, long-acting exenatide release formulation is currently in advanced clinical trials for T2DM management. Subcutaneous delivery of Liraglutide, a synthetic fatty acylated GLP-1 analog bearing 97% homology to human GLP-1 and a more sustained duration of action ($t_{1/2}$ ~13 h), has been recently approved in Europe and the United States for the treatment of T2DM in adults. Oral Sitagliptin (Januvia, Merck and Co., Inc.) and Saxagliptin (Onglyza™, AstraZeneca and Bristol-Myers Squibb) represent selective DPP-4-inhibiting agents and have received Food and Drug Administration clearance for the treatment of T2DM.

As T2DM and obesity commonly coexist along with a correlative reduction in insulin sensitivity, drug influence on body weight is an especially important consideration when treating such patients. While DPP-4 inhibitors have been proven potent and are available as oral agents, GLP-1R agonists have been observed to be more effective in their glucose-lowering and anorectic effects. However, to date, GLP-1 analogs are only available in injectable dosage forms. Oral dosage forms of GLP-1 mimetics, in the form of a tablet or capsule, are likely to foster compliance and adherence among patients when compared to parenteral delivery. Such dosage forms would also provide a simpler means of introducing treatment regimens at earlier stages of diabetes and, in turn, improve treatment outcome. Moreover, oral delivery of GLP-1 analogs would preserve portal/peripheral ratios naturally experienced upon its secretion, thereby more closely mimicking its physiological situation. In this study, we sought to examine the efficacy of ORMD-0901, a novel oral exenatide-based formulation designed along the principles of Oramed's drug delivery system. The study assessed the pharmacodynamic effect of the active ingredient in reducing glucose excursions after a glucose challenge in two animal models. The efficacy of the administered exenatide demonstrated in this study establishes the protective nature of the orally delivered formulation and sets the stage for its further development for the treatment of T2DM.

Methods

The study protocol was approved by the Institutional Animal Care and Use Committee of the Hebrew University and Hadassah Hospital.

Drug

A number of ORMD-0901 formulations were prepared with varying ratios of exenatide [porcine model: Assia Chemical Industries, Ltd., Beer Sheva, Israel; canine model: GL Biochem (Shanghai), Ltd., Shanghai, China] and adjuvants (**Table 1**). Each formulation was tested on independent test days, with a minimum two-day "washout" period between each.

Study Design

Porcine Model

A single ORMD-0901 dose, containing 50–150 µg exenatide, was administered to healthy, fasting female commercial pigs (29.9 ± 6.3 kg) via an indwelling jejunal cannula.

Novel Glucagon-Like Peptide-1 Analog Delivered Orally Reduces
Postprandial Glucose Excursions in Porcine and Canine Models

Eldor

Animals were then challenged with a 3 g/kg ($n = 6$) or 5 g/kg ($n = 3$) oral glucose load delivered *per os* 30 min after ORMD-0901 dosing. Control treatment sessions were performed on the same pigs challenged with an oral glucose load without any prior delivery of ORMD-0901.

Canine Model

A single ORMD-0901 dose, containing 75–100 μg exenatide, was administered to healthy, fasting beagle canines (11.5 ± 1.5 kg) via an indwelling jejunal cannula. Animals ($n = 4$) were then challenged with an oral glucose load of an 80 ml 50% dextrose solution + 100 g Mugatu dog food (7% protein, 6% fat, 1.2% fiber, 80% moisture) delivered 30 min after ORMD-0901 dosing. Control sessions included glucose challenge in the absence of exenatide or, alternatively, subcutaneous injection of 2.5 μg exenatide (GL Biochem (Shanghai) Ltd.), prepared as per the manufacturer's instructions and administered to the dogs' shoulder 30 min before glucose challenge.

All Models

For both models, blood samples were collected every 15 min for up to 2.5 h after dosing to allow for pharmacodynamics analyses. Glucose concentration measurements were assessed by glucometer (FreeStyle Lite, Abbott Laboratories, Abbott Park, IL). Tolerance and adverse effects were also monitored.

In this proof of concept study in animal models, we did not measure hormonal changes or GLP-1 levels. It has been, however, demonstrated by Beglinger and colleagues[5] that GLP-1 can be absorbed when given orally, induces a potent effect on insulin release, and suppresses ghrelin levels.

Data Analysis

Parameters measured included safety and monitoring of glucose behavior, including C_{max} and T_{max} and area under the curve (AUC) of the 0–120 min or 0–150 min postdosing period for the porcine and canine models,

respectively. Mean plasma glucose response curves were plotted as a function of time. Comparisons were made between formulations and control sessions, where animals were challenged with a glucose load without any prior treatment with ORMD-0901. Glucose AUCs were calculated using the trapezoidal rule. Paired *t* tests were used to compare the significance of changes in glucose levels seen in control versus ORMD-0901 treatment session. Due to small sample sizes, *p*-value directionality was employed to determine rejectability of the null hypothesis and to indicate any treatment-related trends.

Results

Enterically delivered ORMD-0901 was well tolerated by all animals, and no adverse reactions were noted throughout the study.

Porcine Response to ORMD-0901

Exenatide delivered in conjunction with Oramed's proprietary oral delivery formulations significantly reduced glucose excursions in pigs receiving formulations RG3 (75 μg exenatide) or AG2 (50 μg exenatide) prior to a 5 g/kg glucose challenge (**Figure 1**; *p* = 0.004 and .041, respectively). Mean AUC values of pigs pretreated with ORMD-0901 were up to 43% lower than control sessions, where animals were treated with glucose alone (**Table 2**, **Figure 1**). Individual animal responses demonstrated up to 100% lower glucose C_{max} values, relative to baseline, after 5 g/kg glucose loads, when pretreated with the various GLP-1 analog formulations (**Table 2**). Animals pretreated with ORMD-0901 formulations AG4 and AG6 prior to a 3 g/kg glucose challenge exhibited a 20–82% drop in C_{max} values, relative to baseline, when compared to nontreated animals (data not shown). However, overall AUC calculations of AG4 and AG6 sessions did not show any significant decrease in ORMD-0901-dosed pigs when compared to their respective control sessions.

Table 1.
Composition of Oral GLP-1 Analog Formulations

Formulation	Carrier (mg)	Adjuvant (mg)	Exenatide (μg)	Dosage volume (ml)	Animal model
AG2	150	125	50	0.8	porcine
AG3	150	125	75	0.8	canine
AG4	150	125	100	0.8	canine and porcine
AG6	150	125	150	0.8	porcine
EG3	150	75	75	0.8	porcine
RG3	100	75	75	0.8	porcine

Novel Glucagon-Like Peptide-1 Analog Delivered Orally Reduces
Postprandial Glucose Excursions in Porcine and Canine Models

Eldor

Canine Response to ORMD-0901

In efforts to assess ORMD-0901 efficacy in an additional animal model, beagle canines were treated with varying formulations of the exenatide-based drug. Of the 20 ORMD-0901 treatment sessions, 18 exhibited lower glucose C_{max} values in comparison to their counterpart
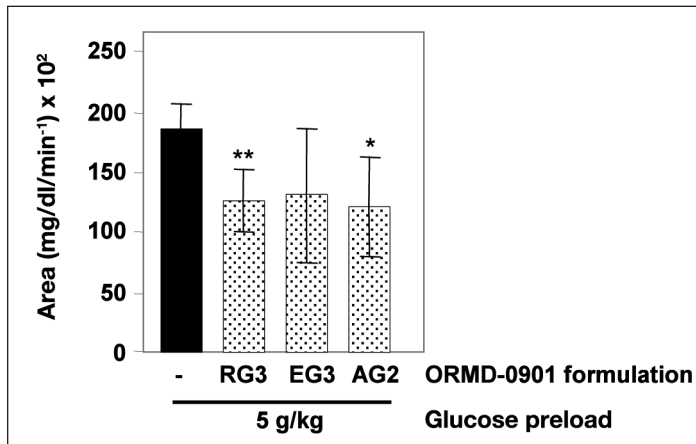
Figure 1. Pharmacodynamic evaluation of ORMD-0901 formulations in glucose-challenged pigs: mean AUC_{0-120} of glucose responses of healthy, cannulated pigs to ORMD-0901. Pigs were treated with various formulations of ORMD-0901 containing 50 µg (formulation AG2, $n = 4$) or 75 µg (formulations RG3 and EG3, $n = 6$ and $n = 3$, respectively) exenatide 30 min prior to a glucose challenge of 5 g/kg. Blood was drawn every 15 min from start of experiment, and blood glucose levels were determined using a glucometer. The single asterisk represents $p = .041$, and the double asterisk represents $p = .004$.

nontreated glucose test days (**Figure 2**). Although AG3-dosed dog R demonstrated C_{max} values above those recorded for its glucose-only sessions (**Figure 2**), mean AUC_{0-150} calculations were still 18% lower under ORMD-0901 influence. ORMD-0901 formulation AG4 (100 µg exenatide) led to a mean 19 ± 8.2% reduction in glucose C_{max} values, relative to baseline, which peaked within 30 min of glucose intake. As reference, subcutaneous injection of 2.5 µg exenatide led to a mean attenuation of C_{max} values by 32 ± 5.3 % when compared to exenatide-free glucose challenges. All four canines challenged with a glucose load with no prior exposure to ORMD-0901 formulations, or to subcutaneously injected exenatide, demonstrated higher AUC_{0-150} values than their exenatide-treated sessions (**Figure 3**). Subcutaneous exenatide delivery amounted to a 51% reduction in mean glucose AUC_{0-150}, while formulations AG4 (100 µg exenatide) and AG3 (75 µg exenatide) prompted 43% and 29% reductions, respectively ($p = 0.068$, the lowest p value possible for a four-sample group size).

Discussion

While the oral route of drug administration is considered safest, most practical, and associated with higher degrees of patient compliance, polypeptide drugs such as GLP-1 and its analogs are degraded to their constituent amino acids by enzymes located throughout the gastrointestinal

Table 2.
Pharmacodynamic Effect of ORMD-0901 Formulations in Porcines Challenged with 5 g/kg Glucose

Treatment	ORMD-0901 formulation	Exenatide dose (µg)	Pig ID	C_{max} (mg/dl)	% drop from control C_{max}	T_{max} (min)	AUC_{0-120} (mg/dl*min^{-1})	% drop from control AUC
5 g/kg glucose			2011[a]	182		75	17550	
			2099[a]	207		45	19752	
			1952	117		30	16778	
ORMD-0901 + 5 g/kg glucose	RG3	75	2011[b]	122	33	50	12238	30
			2099[a]	137	34	68	14654	26
			1952	94	20	75	9630	43
	EG3	75	2011[a]	164	10	45	15588	11
			1952	—	100	—	8078	52
	AG2	50	2099	136	34	120	11183	43
			2011[a]	160	12	53	15494	12
			1952	—	100	—	6893	59

[a] Value represents average of two sessions with identical treatment.
[b] Value represents average of three sessions with identical treatment.

Novel Glucagon-Like Peptide-1 Analog Delivered Orally Reduces
Postprandial Glucose Excursions in Porcine and Canine Models

Eldor

tract. These microcomponents are eventually absorbed by the gastrointestinal tract but lack the biological activity of the original molecule. Despite the challenges involved in formulation of oral polypeptide and protein drug preparations, the past few decades have witnessed a great deal of research focusing on attempts to develop noninvasive methods of delivering such drugs, with the oral route clearly being the most convenient and desirable.[6]

Oramed Pharmaceuticals has developed a drug delivery platform enabling the conversion of parenteral polypeptide drugs into oral dosage forms. The technology employs protectants in combination with an absorption enhancer, all of which are approved pharmacopoeial adjuvants with extensive safety track records. In this manner, passage of active ingredients through the gastrointestinal tract proceeds with minimal degradation. Oramed has demonstrated the efficacy of its technology with insulin-based formulations applied in preclinical as well as in clinical trials in healthy volunteers and in patients with type 1 diabetes mellitus and T2DM.[7–9]

The current study focused on the performance of the exenatide-based ORMD-0901 and its pharmacodynamic effect on postprandial glucose excursions in two animal species. Formulations RG3 or AG2 effectively blunted
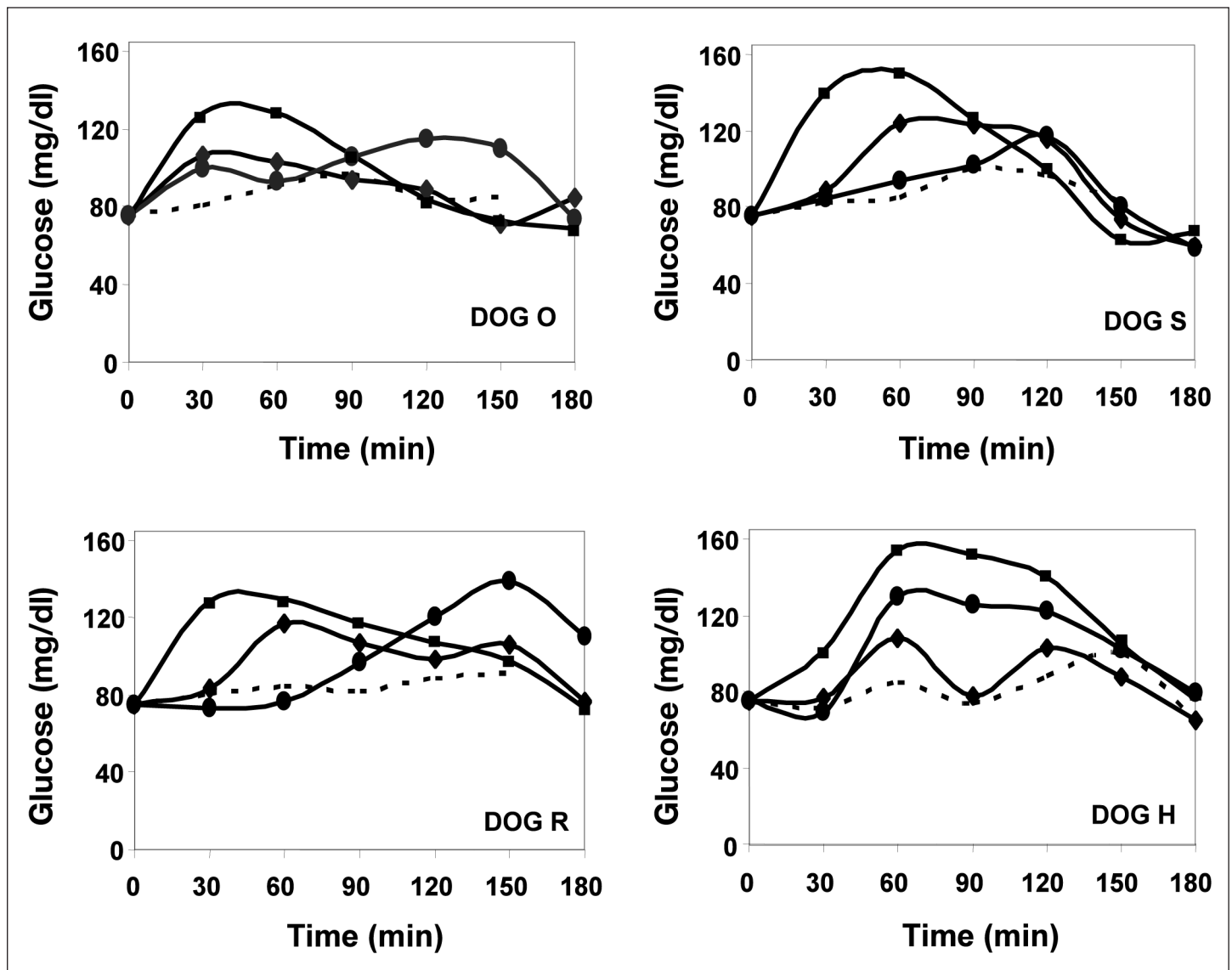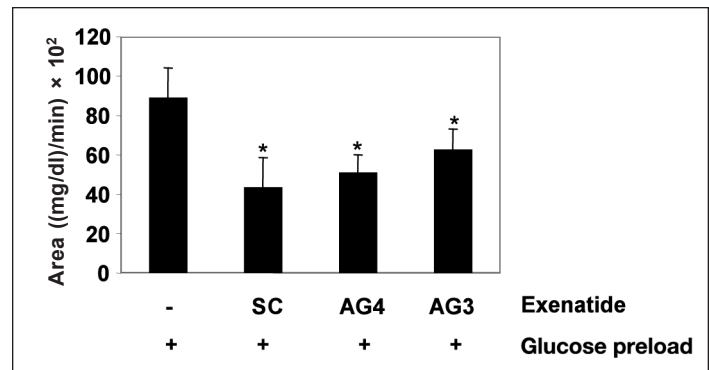

Figure 2. Glucose responses in glucose-challenged dogs pretreated with ORMD-0901. Mean glucose responses of healthy, cannulated dogs were determined after treatment with glucose alone (squares, $n = 4$ for each dog) and were graphed as a function of time. Glucose values of dogs treated with subcutaneously delivered exenatide (dashed line, $n = 3$ for all dogs aside from dog H, where $n = 1$) or enterically administered ORMD-0901 formulations AG3 (circles, 75 µg exenatide, $n = 2$ for each dog) or AG4 (diamonds, 100 µg exenatide, $n = 3$ for each dog) 30 min before glucose challenge were also measured. Blood was drawn every 15 min from start of experiment, and blood glucose levels were determined using a glucometer.

Novel Glucagon-Like Peptide-1 Analog Delivered Orally Reduces
Postprandial Glucose Excursions in Porcine and Canine Models

Eldor

glucose surges in a porcine model when compared to controls. Similarly, formulations AG4 and AG3 significantly controlled canine responses to glucose challenges. These data demonstrate that the unique protective mixture allowed for retention of the active ingredient's biological activity.

Aside from convenience and practicality, oral drug administration may provide for tangible physiological advantages. Such a delivery route recreates hormonal gradients natural to GLP-1 secretion and absorption as determined by the hepatic-portal system, triggering glucose disposal independent of both pancreatic activity and portal vein GLP-1Rs.[10,11] Upon release by L cells in response to food ingestion, GLP-1 is rapidly degraded by DPP-4 in the intestinal capillaries and liver. Less than 25% of the secreted GLP-1 leaves the gut in an intact, active form and traverses the intestinal capillaries draining into the portal vein. Of the GLP-1 that reaches the liver, approximately 40–50% is degraded, leaving only approximately 10–15% of the original secreted GLP-1 to reach the systemic circulation.[12] Thus a portal/peripheral gradient of 3–4/1 is established for GLP-1, a gradient that is slightly higher than that of insulin (2–3/1). Several lines of evidence alluded to in the following paragaphs suggest that the postprandial portal concentration of the hormone may have physiological and consequently salutary clinical implications.

A number of studies have described a vagus nerve-mediated GLP-1-sensing pathway within the portal vein, partly responsible for regulating GLP-1 action.[13–17] Another work has confirmed expression of a GLP-1R in vagal afferent neurons of the hepatoportal region, where its selective inhibition in the portal circulatory network led to significant impairment of glucose tolerance.[18,19] Moreover, emerging evidence supports the hypothesis claiming that the effect of GLP-1 on food intake is at least partially mediated via peripheral GLP-1Rs.[20] A study in this context has questioned whether gradients of GLP-1 across the different vascular compartments are differentially affected by DPP-4 inhibitors. By direct sampling of the portal vein following a GLP-1 secretory stimulus combined with intravenous administration of a DPP-4 inhibitor (vildagliptin), a 2–3 times higher GLP-1 level was measured in the portal vein when compared to that of the peripheral circulation.[21] The study suggests that the divergent effects of the DPP-4 inhibitors may be due to high portal GLP-1 concentration when compared to that in the periphery.

In further support of possible advantages derived from oral GLP-1 delivery, a pharmacokinetic study of oral

Figure 3. Pharmacodynamic evaluation of ORMD-0901 formulations in glucose-challenged dogs: mean AUC$_{0-150}$ of glucose responses of healthy, cannulated dogs to ORMD-0901. Dogs were treated with ORMD-0901 formulation AG3 ($n = 8$) or AG4 ($n = 12$), containing 75 or 100 µg exenatide, respectively, 30 min prior to an oral glucose challenge of 80 ml of a 50% dextrose solution + 100 g commercial dog food (7% protein, 6% fat, 1.2% fiber, 80% moisture). For controls, glucose challenge in the absence of exenatide ($n = 16$) or glucose challenge after subcutaneous injection of 2.5 µg exenatide ($n = 10$) was performed. Blood was drawn every 15 min from start of experiment, and blood glucose levels were determined using a glucometer. A single asterisk represents $p = .068$. SC, subcutaneous.

GLP-1 formulations administered to fasting healthy subjects at escalating doses demonstrated an extended (hours), robust insulinogenic response despite short (minutes) plasma GLP-1 spikes.[5] Prolonged reductions in both plasma glucose and ghrelin levels were observed, indicating a multifaceted means of controlling food intake. These long-lasting effects stimulated by transient GLP-1 presence are suggestive of stimulation of portal neuronal signaling pathways. Thus replication of physiological GLP-1 portal/systemic gradients can be achieved by direct portal administration via its oral administration. In contrast, systemic administration of the concentrations required to reach physiological portal vein concentration is considered impractical and has been associated with nausea and vomiting.[22]

It is well established that the incretin effect is markedly reduced or lost in T2DM patients and likely contributes to glucose intolerance.[23] Supraphysiological levels of GLP-1 have been shown to normalize glucose responsiveness, stimulate an insulinotropic effect in advanced T2DM patients, and exhibit dramatic influence on glycemic control, weight loss, and β-cell function.[23,24] An oral GLP-1-based drug that replicates the natural physiologic portal–hepatic route of absorption may be beneficial to achieve glycemic control without the risk of hypoglycemia. Furthermore, an oral dosage form is also likely to foster compliance and adherence among patients and allow for intervention early in the course of T2DM with a GLP-1 analog at a stage where resistance to parenteral treatment is prevalent.

Novel Glucagon-Like Peptide-1 Analog Delivered Orally Reduces
Postprandial Glucose Excursions in Porcine and Canine Models

Eldor

Conclusions

In both the porcine and canine animal models, enteric formulations of exenatide based on Oramed's drug delivery platform have been shown to be absorbed while retaining their biological activity. These formulations pave the way for the development of oral formulations as the main impediments for polypeptide and protein absorption are the degradation in the gastrointestinal tract and transport across the epithelial lining of this tract. Both impediments have been overcome with Oramed's technology. An oral form of a GLP-1 analog is likely to be an important added tool to the antidiabetes armamentarium. The oral route of administration is the most practical and the one that fosters most compliance and adherence and thus is predicted to have a significant therapeutic impact both on short-term glycemic control and sustainability of this effect.

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Novel Glucagon-Like Peptide-1 Analog Delivered Orally Reduces
Postprandial Glucose Excursions in Porcine and Canine Models

Eldor

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