GLP-1-Based Therapy as a New Treatment

Carolyn F. Deacon, PhD, DMSc
Department of Biomedical Sciences,
Panum Institute
University of Copenhagen

Copenhagen, 12th September 2007
Overview

1. Why do we need new treatments for diabesity?
2. What makes GLP-1 a good therapeutic target?
3. Harnessing the potential of GLP-1:
   Incretin mimetics
   Incretin enhancers
4. Conclusions
Why do we need new treatments for diabesity?
UKPDS Clearly Showed the Need for New Diabetes Treatments

The prevalence of overweight and obesity is increasing. This is contributing to the diabetes epidemic.
Why do We Need New Therapeutic Agents?

1. Metformin fails with time and has tolerability issues (GI side effects)
2. SUs have side effects (hypoglycaemia, weight gain) and may cause accelerated beta cell failure
3. TZDs may have severe side effects (heart failure, myocardial infarction, osteoporosis, fluid accumulation, weight gain, cancer)
4. Current combination therapies do not halt progression of disease
5. Insulin therapy will always be instituted too late because of side effects (hypoglycaemia, weight gain) and inconvenience

Many patients cannot maintain satisfactory glycaemic control with existing agents
Most are associated with weight gain
What makes GLP-1 a good therapeutic target?
What is GLP-1?

- A 30 amino acid peptide
- Secreted from endocrine cells in the small intestinal mucosa
- Released in response to meal ingestion
- Responsible for the incretin effect (together with GIP)

GLP-1 positive endocrine L-cells (green) in human small intestine
GLP-1 has Multiple Effects

1. Efficacious glucose lowering
   • ↑ insulin secretion (glucose-dependent)
   • Upregulates insulin gene expression & all steps in insulin biosynthesis
   • Upregulates expression of genes essential for β-cell function (Glut 2, glucokinase etc)
   • ↑ β-cell mass (animal models) - ↑ neogenesis & proliferation, ↓ apoptosis
   • ↓ glucagon secretion (glucose-dependent) → ↓ hepatic glucose output
   • Delayed gastric emptying

2. Body weight lowering
   • Delayed gastric emptying
   • ↑ fullness and satiety, ↓ appetite → ↓ food intake

3. Disease modifying potential
   • ↑ β-cell glucose sensitivity
   • Improved β-cell function
   • ↑ β-cell mass (animal models) - ↑ neogenesis & proliferation, ↓ apoptosis
   • Beneficial cardiovascular effects
GLP-1: Therapeutic Potential in Diabesity

<table>
<thead>
<tr>
<th>Type 2 diabetic phenotype</th>
<th>Actions of GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Impaired β-cell function</td>
<td>• ↑ insulin secretion and biosynthesis</td>
</tr>
<tr>
<td>• Reduced β-cell mass</td>
<td>• Improves β-cell function</td>
</tr>
<tr>
<td></td>
<td>(glucose sensitivity, proinsulin/insulin ratio)</td>
</tr>
<tr>
<td>• Glucagon hypersecretion</td>
<td>• Upregulates other genes essential for β-cell function</td>
</tr>
<tr>
<td></td>
<td>(eg. GLUT 2, glucokinase)</td>
</tr>
<tr>
<td>• Overeating, obesity</td>
<td>• ↑ β-cell proliferation/differentiation</td>
</tr>
<tr>
<td>• Macrovascular complications</td>
<td></td>
</tr>
<tr>
<td>• Insulin resistance</td>
<td></td>
</tr>
</tbody>
</table>

- ↓ β-cell apoptosis
- ↓ glucagon secretion
- ↓ gastric emptying, ↑ satiety, ↓ appetite
  → ↓ food intake & weight loss

- Beneficial cardiovascular effects

*Actions which may be secondary to improved metabolic control*

- Improvements in insulin sensitivity
Peripheral GLP-1 Accesses Areas of the Brain Associated with Food Intake, and these contain GLP-1 Receptors

Access of peripherally injected $^{125}$I-GLP-1 to area postrema

GLP-1 receptor in situ hybridisation in the area postrema

Ørskov et al, Diabetes, 1996

Philip Larsen, Rheoscience, Copenhagen
GLP-1 may Influence Food Intake by Neural and Endocrine Mechanisms

Holst & Deacon, Diabetologia 2005
Peripheral GLP-1 Reduces Appetite and Food Intake in Man

GLP-1 and energy intake (5 studies)

Decrease in energy intake (%) vs. Rate of infusion (pmol/kg x h)

n=16
n=12
n=10
n=19
n=16
n=18
n=18
n=16
n=12
n=10

Verdich et al JCEM 2001
Continuous s.c. Infusion of GLP-1 Reduces Blood Glucose and Lowers Body Weight in Patients with T2DM

Zander M et al, Lancet 2002;359:824-830

Plasma glucose (mmol/l)

8-hour BG profiles

Change in weight (%)

Body weight

Weeks
Harnessing the Potential of GLP-1
Native GLP-1 has Limited Clinical Potential Because of its Short Half-Life

Plasma $T_{1/2} = 1$-$2$ minutes (i.v.)
MCR = 5-$10$ l/min

Hansen et al, *Endocrinology* 1999

Vilsbøll et al, *JCEM* 2003

DPP-4 and GLP-1 in human small intestine
How has the Therapeutic Potential of GLP-1 been Realised?

- **DPP-4 resistant analogues of GLP-1**
  (GLP-1 receptor activators; incretin mimetics)
  
  *Purpose:*
  Raise agonist plasma concentrations into the pharmacological range

- **Inhibit DPP-4 activity**
  (DPP-4 inhibitors; incretin enhancers)
  
  *Purpose:*
  Prevent degradation of endogenously released incretin hormones to enhance plasma levels of the active peptides

Deacon et al, *Diabetes* 1995; 44:1126-1131
# Incretin-Based Therapies for Treatment of T2DM

<table>
<thead>
<tr>
<th>Company</th>
<th>Trade name</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLP-1 analogues (incretin mimetics)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Exenatide        | Lilly/Amylin | Byetta  
|                  |             | Approved in combination with metformin and/or SU in USA June 2005     |
|                  |             | Approved by EMEA Nov 2006                                              |
| Liraglutide      | Novo Nordisk | Phase III                                                              |
| **DPP-4 inhibitors (incretin enhancers)**      |            |                                                                        |
| Sitagliptin      | Merck & Co  | Januvia  
|                  |             | Approved as monotherapy and in combination with metformin or a TZD in USA October 2006 |
|                  |             | Approved in combination with metformin or TZD by EMEA in April 2007   |
|                  |             | Single tablet combination with metformin approved by FDA in March 2007|
| Vildagliptin     | Novartis   | Galvus  
|                  |             | Under FDA review                                                      |
|                  |             | Under review by EMEA                                                 |
GLP-1 Receptor Activators (Incretin Mimetics)
Exendin-4

- From saliva of the Gila Monster
- 53% homologous with GLP-1
- Insensitive to DPP-4
- Full agonist at the GLP-1 receptor
- Metabolically stable
  - $t_{1/2}$ 4-5 hr after sc injection

Liraglutide

- Based on human GLP-1 (7-37)
- 97% homologous with GLP-1
- Resistant to DPP-4
- Full agonist at the GLP-1 receptor
- Non-covalent binding to albumin, self-association, slow release from injection site gives prolonged survival time
  - $t_{1/2}$ 12 hr after sc injection

- C-16 fatty acid (palmitoyl)
Incretin Mimetics Reduce 24-h Glucose Profiles in T2DM

Degn et al, Diabetes 2004

Plasma glucose (mM)

Placebo
Liraglutide (6 μg/kg)

Hour of day

Degn et al, Diabetes 2004
Incretin Mimetics Lower Fasting Plasma Glucose and Body Weight in T2DM

**Mean change in body weight from baseline (%)**

- Metformin + liraglutide
- Metformin + glimepiride (2 mg titrated to 4 mgd)
- Liraglutide (0.5 mg titrated to 2 mg qd)
- Metformin (1000 mg bid)

**FSG (mM)**

- Metformin + glimepiride (2 mg titrated to 4 mgd)

Nauck et al, Exp Clin Endocrinol Diabetes 2006
Incretin Mimetics have Sustained Effects on HbA1c

Exenatide add-on to existing OHA; 2 year completer cohort (n=283)

Duration of Treatment (weeks)

Week 0-30  placebo-controlled trials, 5 or 10 μg bid
Week 30-34  5 μg bid
Week 34 →  open label, uncontrolled, 10 μg bid

Buse et al, Clin Ther 2007
The Majority of Subjects Experience some Weight Loss with Incretin Mimetics

Exenatide add-on to existing OHA; 2 year completer cohort (n=283)

For the entire cohort, mean weight loss was $-4.7\pm0.3$ kg (baseline 100 kg)

81% of subjects lost weight

Buse et al, Clin Ther 2007
Incretin Mimetics have Sustained Effects on HbA1c and Body Weight

HbA1c

Exenatide add-on to existing OHA

3 year completers (n=217)

Baseline A1c =8.2%

Body weight

3.5 year completers (n=151)

Baseline weight =100 kg

Week 0-30 placebo-controlled trials, 5 or 10 μg bid
Week 30-34 5 μg bid
Week 34 → open label, uncontrolled, 10 μg bid

Nielsen et al, ADA 2007, Poster 0561-P

Kendall et al, ADA 2007, Poster 0557-P
Incretin Mimetics Lower HbA1c as Effectively as Insulin in Poorly-Controlled SU+Metformin-Treated Patients, but without Body Weight Gain

- Biphasic insulin aspart (titrated for optimal control; n=248)
- Exenatide (10μg bid; n=253)

Baseline weight: ~84.5 kg

Baseline HbA1c: ~9.0%

Change in weight: -5.5 kg (p<0.001)
Patients Treated with Insulin + OHA who Substitute Insulin with Exenatide Maintain Glycaemic Control and Lose Weight

Baseline: HbA1c = 8.1%, Body weight = 93-102 kg
Exenatide Long Acting Release Formulation (Exenatide LAR; phase II)

- biodegradable polymeric microspheres for extended release
- detectable plasma concentrations of exenatide for weeks to months after a single dose

Initial release

Sustained release

Kim et al. Diabetes Care 2007
Exenatide LAR Reduces HbA1c and Body Weight after 15 Weeks

Mean Baseline A1C
- Placebo; 8.6%; n=14
- 0.8 mg; 8.6%; n=16
- 2.0 mg; 8.3%; n=15

Mean Baseline Weight
- Placebo 101.2 kg
- 0.8 mg 106.6 kg
- 2.0 mg 109.7 kg

Change in A1C (%)
- Placebo: +0.4±0.3%
- 0.8 mg: -1.4±0.3%
- 2.0 mg: -1.7±0.3%

Change in weight (kg)
- Placebo: -0.04±0.7 kg
- 0.8 mg: -0.03±0.7 kg
- 2.0 mg: -3.8±1.4 kg

Kim et al. Diabetes Care 2007
Summary: GLP-1 receptor activators

Efficacious

- Glucose-dependent action (enhance insulin, inhibit glucagon secretion)
- Reduce (but do not normalise) blood glucose
- Reduce HbA1c
- Lower body weight
- Differing durations of action (2x daily → 1x weekly)
- May cause antibody formation (some)

But, so far, are associated with GI side effects
Incretin Mimetics Reduce Food Intake and Body Weight Gain in Hyperphagic, Obese, Non-Diabetic Pigs

Raun et al, Obesity 2007
DPP-4 Inhibitors
(Incretin Enhancers)
Mechanism of Action of DPP-4 Inhibitors

- Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels ↑ in response to a meal.

Concentrations of the active intact hormones are increased by DPP-4 inhibition, thereby increasing and prolonging the actions of these hormones.
DPP-4 Inhibitors Reduce Plasma DPP-4 Activity

Valine-pyrrolidide (a prototype DPP-4 inhibitor)

Knowledge of the binding site allow for design of highly selective and potent DPP-4 inhibitors


DPP-4 inhibitors in clinical development have different durations of action
- PSN 9301: Short duration of action – meal-related dosing
- Others: Longer duration of action – once daily dosing

Ahrén et al, JCEM 2004
Herman et al, Clin Pharmacol Ther 2005
DPP-4 Inhibition Prevents N-Terminal Degradation of GLP-1 in Anaesthetised Pigs

Val-pyr = valine pyrrolidide (DPP-4 inhibitor)

Deacon et al., Diabetes, 1998
DPP-4 Inhibition Reduces Both Fasting and Postprandial Glucose Concentrations

Brazg RL et al. Diab Obes Metab 2007
DPP-4 Inhibitors have Sustained Effects on HbA1c as Monotherapy or as Add-on to Existing OHA in T2DM

Monotherapy

Add-on to metformin (≥1500 mg/day)

Vildagliptin (50 mg bid; n=368)
Metformin (1000 mg bid; n=188)

Vildagliptin (50 mg qd; n=42)
Placebo (n=29)

Sitagliptin (100 mg qd; n=382)
Glipizide (5–10 mg bid; n=411)

Schweizer et al. Diabetic Med 2004
Ahrén et al. Diabetes Care 2004
Nauck et al, Diab Obes Metab 2007
DPP-4 Inhibition is Body Weight Neutral

Monotherapy vs metformin

Add-on to metformin vs placebo

Add-on to pioglitazone vs placebo

Charbonnel et al., Diabetes Care 2006
Rosenstock et al., Clin Ther 2006
DPP-4 Inhibition Lowers HbA1c as Effectively as TZD, but without Body Weight Gain

Monotherapy

Vildagliptin (50 mg bid)  Rosiglitazone (8 mg qd)

Whole cohort  BMI ≥ 35 kg/m²

Baseline wt (kg)  91  93  ~111  n  397  209  208

Change in body weight (kg)

-2  -1  0  1  2  3

-1.1  1.6  1.7

P < 0.001  P < 0.001

P < 0.001

Rosenstock et al Diabetes Care 2007
DPP-4 Inhibition Lowers HbA1c as Effectively as SU, but without Body Weight Gain

Add-on to metformin (≥1500 mg/day)

Nauck et al, Diab Obes Metab 2007
Summary: DPP-4 inhibitors

Efficacious

- Glucose-dependent action (enhance insulin, inhibit glucagon secretion)
- Reduce (but do not normalise) blood glucose
- Reduce HbA1c
- Body weight neutral
- Little to distinguish between them clinically

Well tolerated (side effect profile similar to placebo)
Conclusions

• An incretin-based therapy of type 2 diabetes may be expected to
  - Reduce hyperglycaemia and HbA1c levels without weight gain
  - Reduce appetite and lower body weight (mimetics only)
  - Improve α-cell and β-cell function
  - Improve insulin sensitivity (secondary to improved metabolic control)
  - Combine well with existing antihyperglycaemic agents
  - Be efficacious without side effects

• Incretin mimetics may additionally have a role in obesity treatment