Pathophysiology of T2DM: is there a fundamental incretin defect?

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The incretin effect

- 70% of post-glucose insulin secretion is due to the effects of incretin
- The incretin effect is due to gut hormones – the incretin hormones
Plasma Levels of GLP-1, GIP and Insulin in Normal Subjects

- GLP-1 and GIP are secreted in response to meals (arrows) in normal subjects and correlate to insulin secretion.

- Can the insulinotropic effects of GLP-1 and GIP

Effect of GLP-1 and GIP During a Stepwise Glucose Clamp

N=8 healthy males.
Adapted from Vilsbøll T et al. Regul Pep. 2003;114:115–121.
During Glucose Clamps in Healthy Subjects

Why Is the Incretin Effect Reduced in Type 2 Diabetes?

- Is something wrong with the secretion of the incretin hormones?
- Is something wrong with the action of the incretin hormones?
Glucagon, PP and GIP

Toft-Nielsen et al. 2001

Meal

n = 55

AUC

P-glucagon (pmol/l)

P-PP (pmol/l)

P-GIP (pmol/l)

Time (min)

Meal

AUC

Toft-Nielsen et al. 2001
Decreased GLP-1 concentrations in type 2 diabetes during a 240-minute meal test

* $p < 0.05$ between the type 2 diabetes and NGT group

The meal was started at time zero and finished in the 10- to 15-minute period

Summary of the Study Toft-Nielsen et al 2001

The meal-induced secretion of GLP-1:

1. Is significantly decreased in type 2 diabetes
2. Is unaltered by diabetic neuropathy
3. Is not influenced by candidate L-cell regulators such as FFA or GIP
4. By multiple regression, the diabetic state (DM < NGT) gender (M < F), insulin sensitivity (+), and BMI (−) emerge as significant factors

FFA=free fatty acids.
Meal-Stimulated Incretin Hormone Concentrations are Positively Correlated with Insulin Sensitivity in Non-Diabetic Men

Rask et al. Diabetes Care (2001)
GLP-1 Secretion in Morbid Obesity

Effect of Jejunoileal Bypass (JIB)

* p<0.05 for before and after JIB.
** p<0.05 for obese after JIB vs control subjects.
*** p<0.05 for obese before JIB vs control subjects.

GLP-1 Response Following a 2.5 MJ* Test Meal

*Unit of energy, megajoules.
GIP: Obese, Healthy vs Lean, Healthy Subjects

Native GLP-1 is Rapidly Degraded by DPP IV

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

MCR = metabolic clearance rate.


DPP IV (red) and GLP-1 (green) in human small intestine

DPP IV = dipeptidyl peptidase IV
Hansen et al. *Endocrinology* 1999; 140:5356-5363
Survival of sc GLP-1 in Type 2 Diabetes

Intact GLP-1 + metabolite

Only ~10% GLP-1 survives intact after sc injection

Deacon et al, Diabetes 1995; 44:1126-1131
Plasma Concentrations of Active GLP-1 Are Decreased in Type 2 Diabetes

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The Impaired Secretion of GLP-1 in Type 2 Diabetes Does Not Precede Diabetes

• Vaag et al, 1996: In identical twins discordant for type 2 diabetes, GLP-1 was decreased in the diabetic twin only.

• Nyholm et al, 1999: 24-hour plasma profiles of GLP-1 were normal in healthy offspring of parents with type 2 diabetes.

• Meier et al, 2005: Incretin hormone.
Why Is the Incretin Effect Reduced in Type 2 Diabetes?

• Is it the secretion of the incretin hormones?

• Is it the action of the incretin hormones?
Effect of GLP-1 on Beta-Cell Glucose Responsiveness in Type 2 Diabetes

Effect of GLP-1 on Beta-Cell Responsiveness to Glucose

Beta-Cell Responsiveness to Glucose

GLP-1 (pmol \cdot kg^{-1} \cdot min^{-1})

ISR vs glucose (pmol \cdot kg^{-1} \cdot min^{-1}/mmol/L)

- Patients with type 2 diabetes
- Control subjects

ISR=insulin secretion rate.
Beta-cell responsiveness to glucose expressed as the slope of the linear relation between ISR and glucose concentration.
Effects of GLP-1 on insulin secretion in patients with 2DM:

- Glucose-induced insulin secretion may be restored to normal values.
- The potency of GLP-1 with respect to enhancing the beta cell responsiveness to glucose is decreased.
- This decreased potency can be improved by improved metabolic control.
Hyperglycemic Clamp + GLP-1/GIP in Patients With Type 2 Diabetes and Control Subjects

Obese Diabetic Patients

Healthy Subjects

- **Glucose**
- **Low GIP (4 pmol/kg/min)**
- **High GIP (16 pmol/kg/min)**
- **GLP-1 (1 pmol/kg/min)**

Second-Phase Insulin Responses to Hyperglycaemic Clamp During IV GIP and GLP-1

All subjects were obese (BMI 29 kg/m²); patients with type 2 diabetes (n=8); control subjects (n=6).

All patients were obese with type 2 diabetes (n=8).
This graph shows the insulin responses to the glucose clamp alone and with a low and high dose of GIP.
Inhibition of Glucagon Secretion by Glucose + GIP or GLP-1 in Patients With Type 2 Diabetes and Matched Control Subjects

Patients were obese with type 2 diabetes (n=8); healthy subjects (n=6).

Loss of incretin function in type 2 diabetes mellitus

- Secretion of GLP-1 impaired
- Beta-cell sensitivity to GLP-1 decreased
- Secretion of GIP normal (or slightly impaired)
- Effect of GIP abolished or grossly impaired
- Inhibition of glucagon impaired
- The defect is secondary to diabetes
If the impaired incretin response contributes significantly to the defective insulin secretion in type 2 diabetes, will restoration of incretin action improve metabolism?
Proof of hypothesis: Glucose tolerance can be restored by iv GLP-1 in T2DM

Rachman et al., *Diabetologia* 1997;40:205-211
Summary

• Incretin hormone secretion and actions are impaired in type 2 diabetes. The defect is secondary to diabetes.

• Although β-cell responsiveness to GLP-1 is reduced, exogenous GLP-1 can still restore β-cell sensitivity to glucose and improve glucose-induced insulin secretion.

• A GLP-1 based therapy of type 2 diabetes may therefore be expected to