Pathophysiology of T2DM: is there a fundamental incretin defect?

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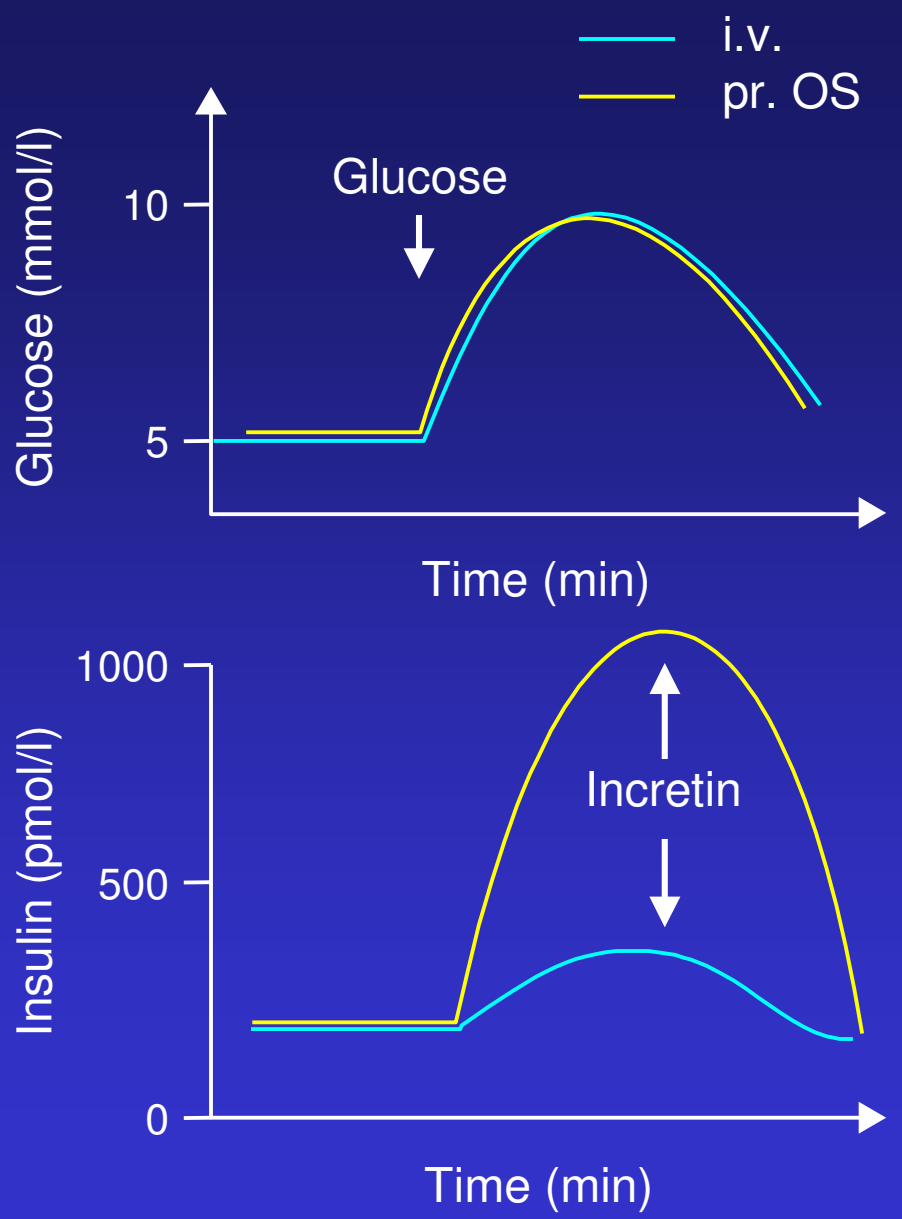
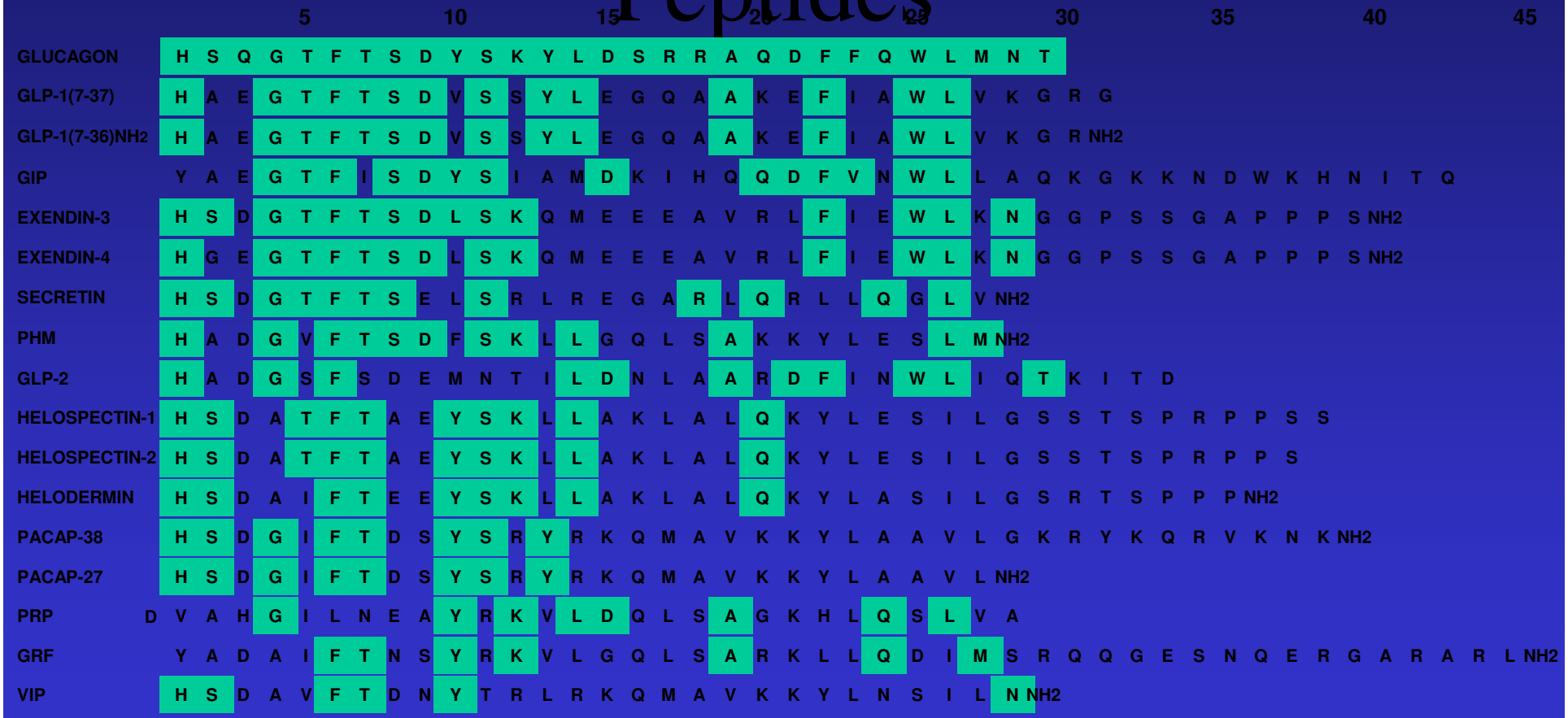
Codhy Congress,
Berlin, October 2006

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



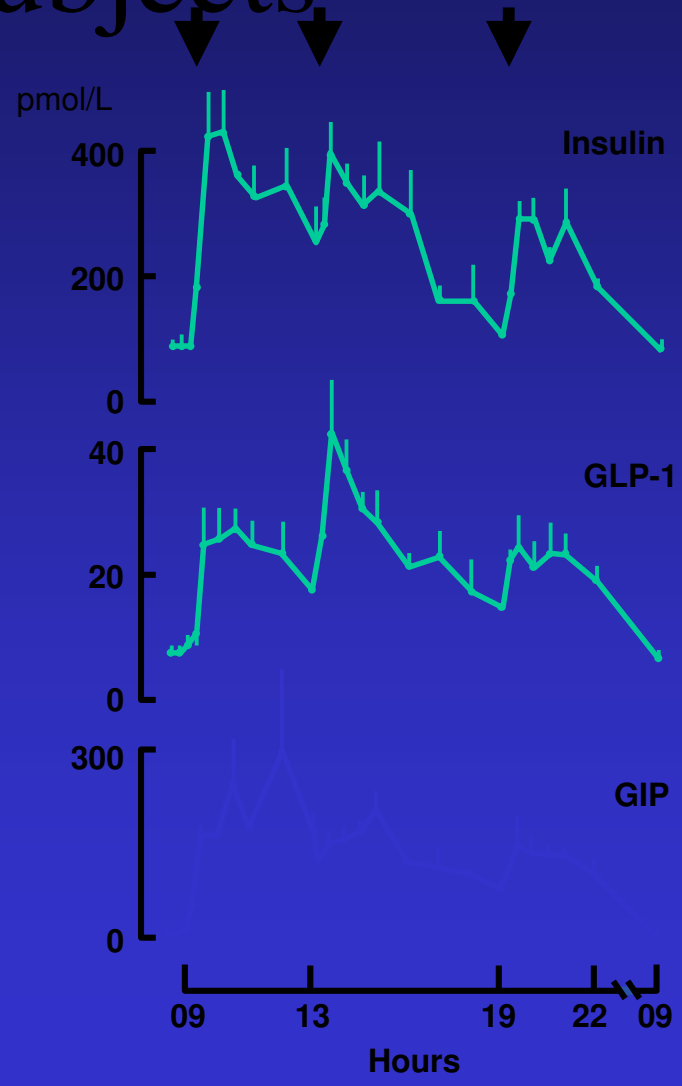
The Incretin Hormones Are Members of the Superfamily of Glucagon-Related Peptides



Plasma Levels of GLP-1, GIP and Insulin in Normal Subjects

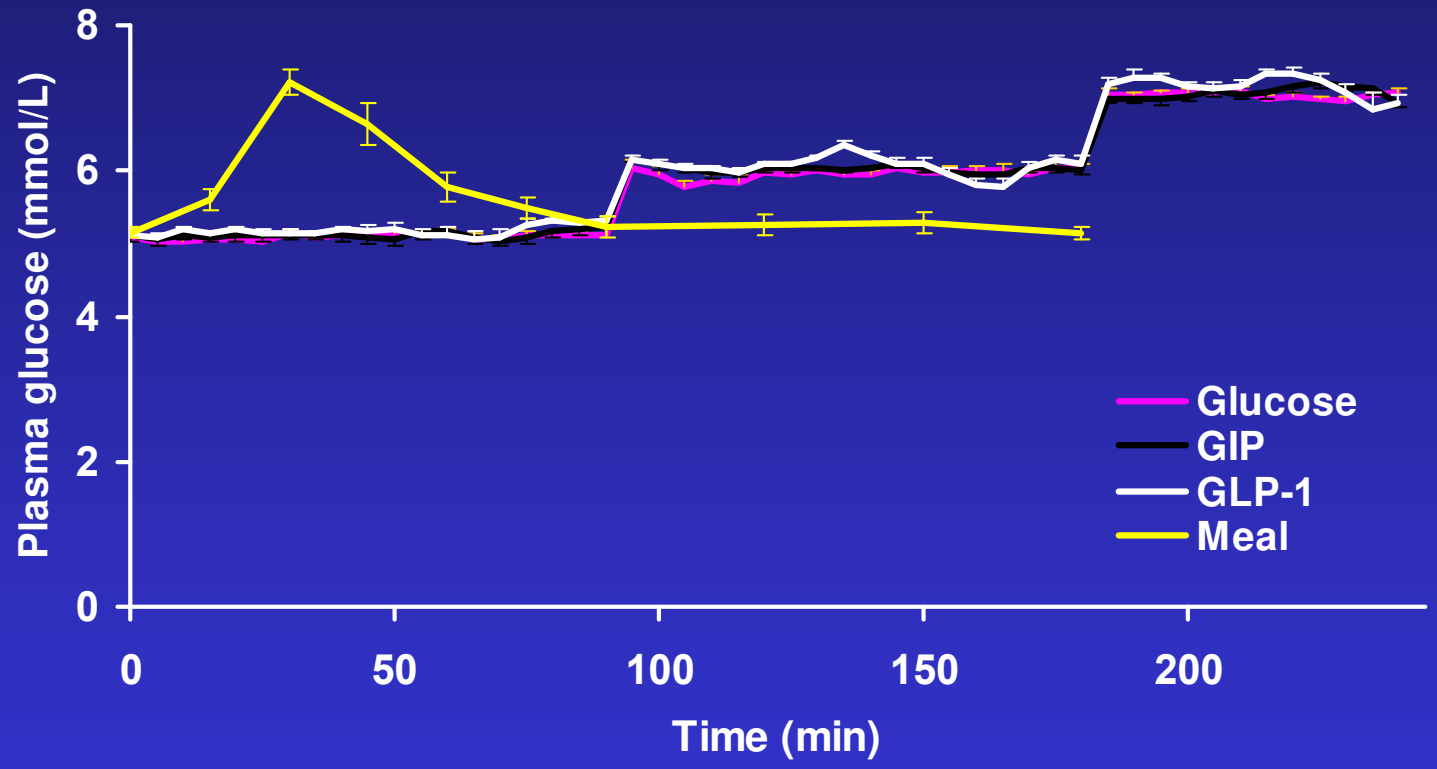
- GLP-1 and GIP are secreted in response to meals (arrows) in normal subjects and correlate to insulin secretion.

- Can the insulinotropic effects of GLP-1 and GIP



Reprinted from Ørskov C et al. *Scand J Gastroenterol.* 1996;31:665–670.

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.

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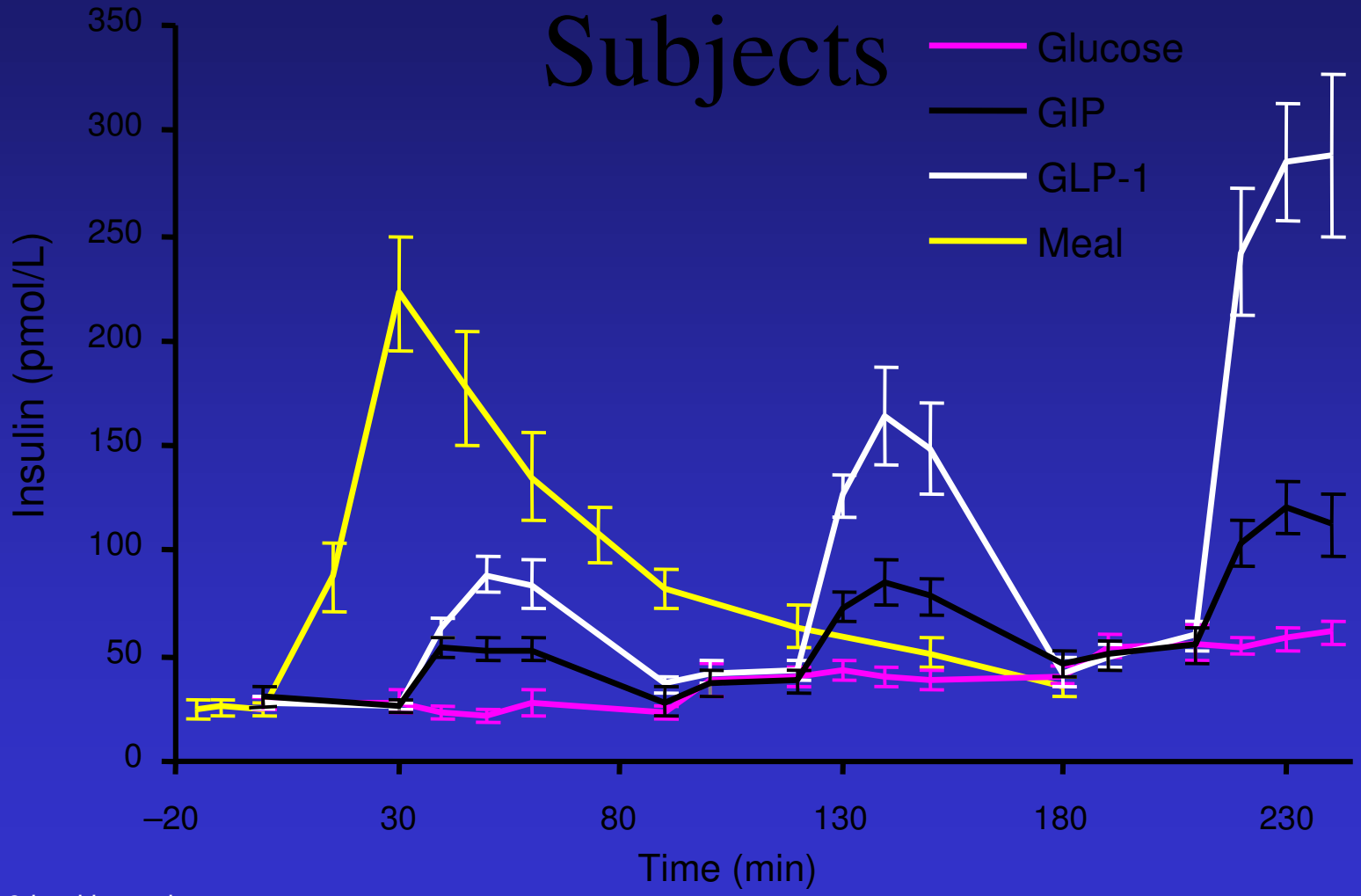
During Glucose Clamps in Healthy Subjects



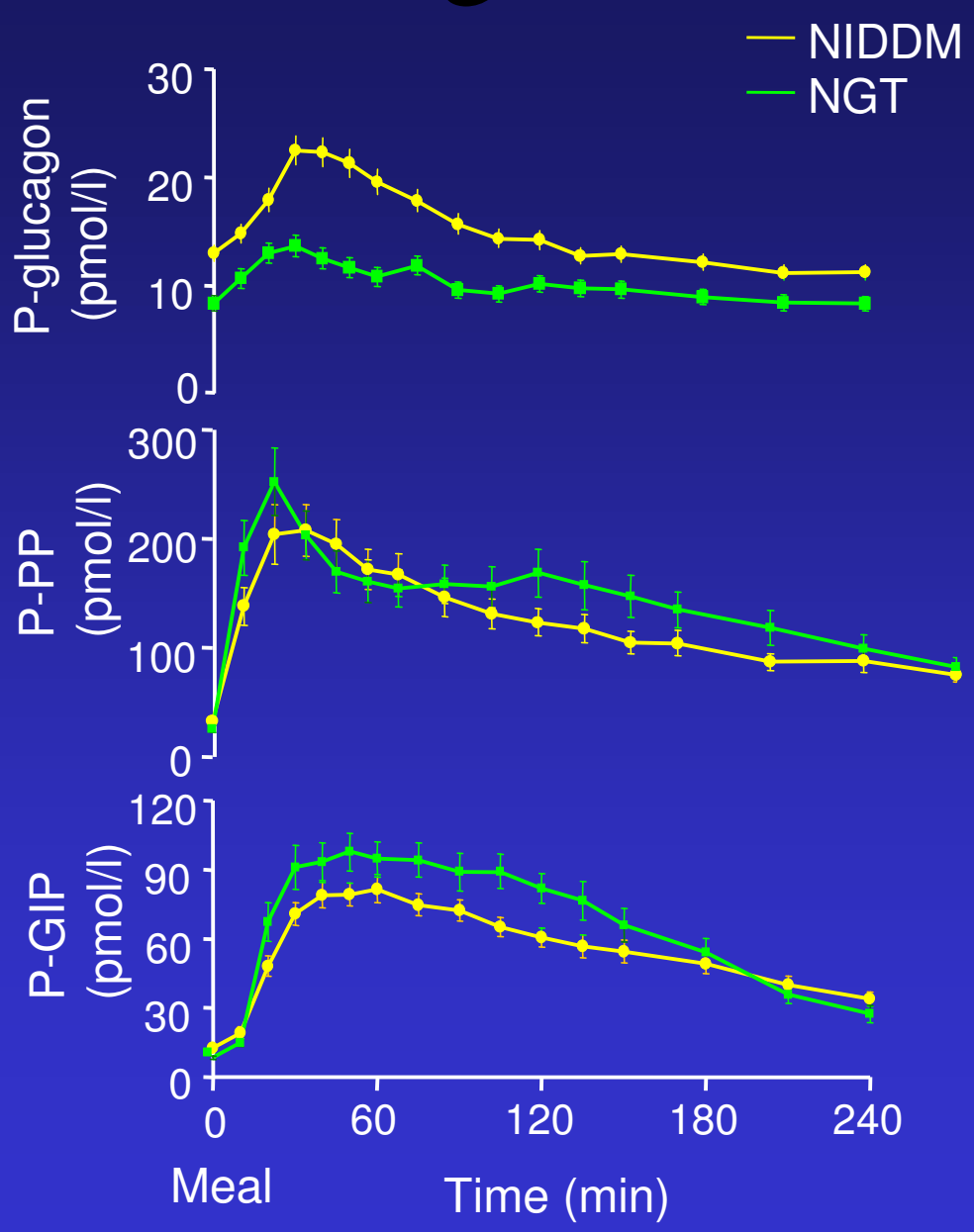
N=8 healthy males.

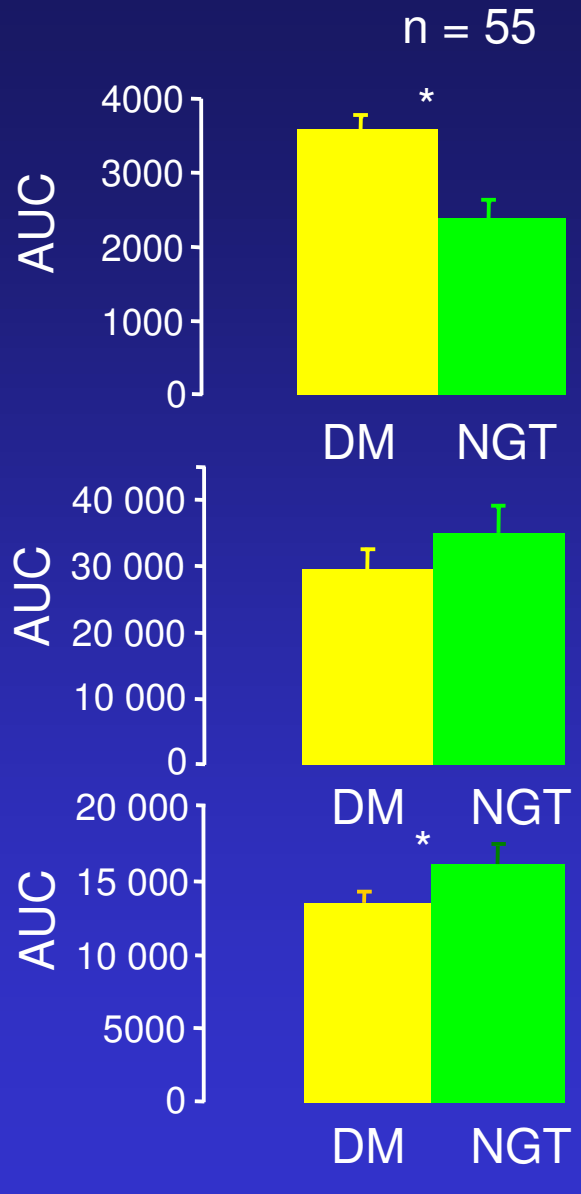
Adapted from Vilsbøll T et al. *Regul Pep*. 2003;114:115–121.

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?

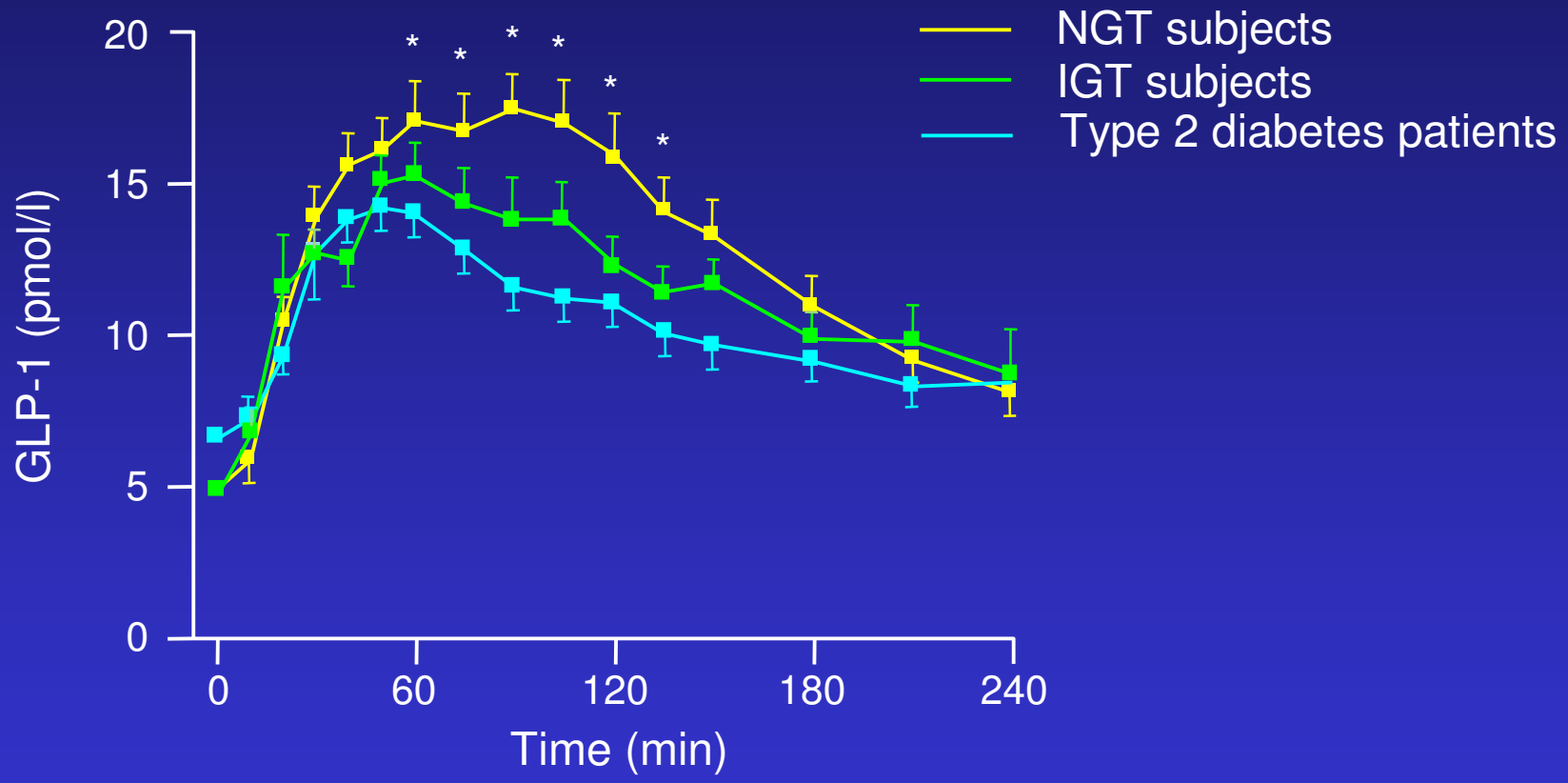
Glucagon, PP and GIP





Toft-Nielsen et al. 2001

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

Toft-Nielsen et al. J Clin Endocrinol Metab 2001;86:3717–23

Summary of the Study Toft-Nielsen et al 2001

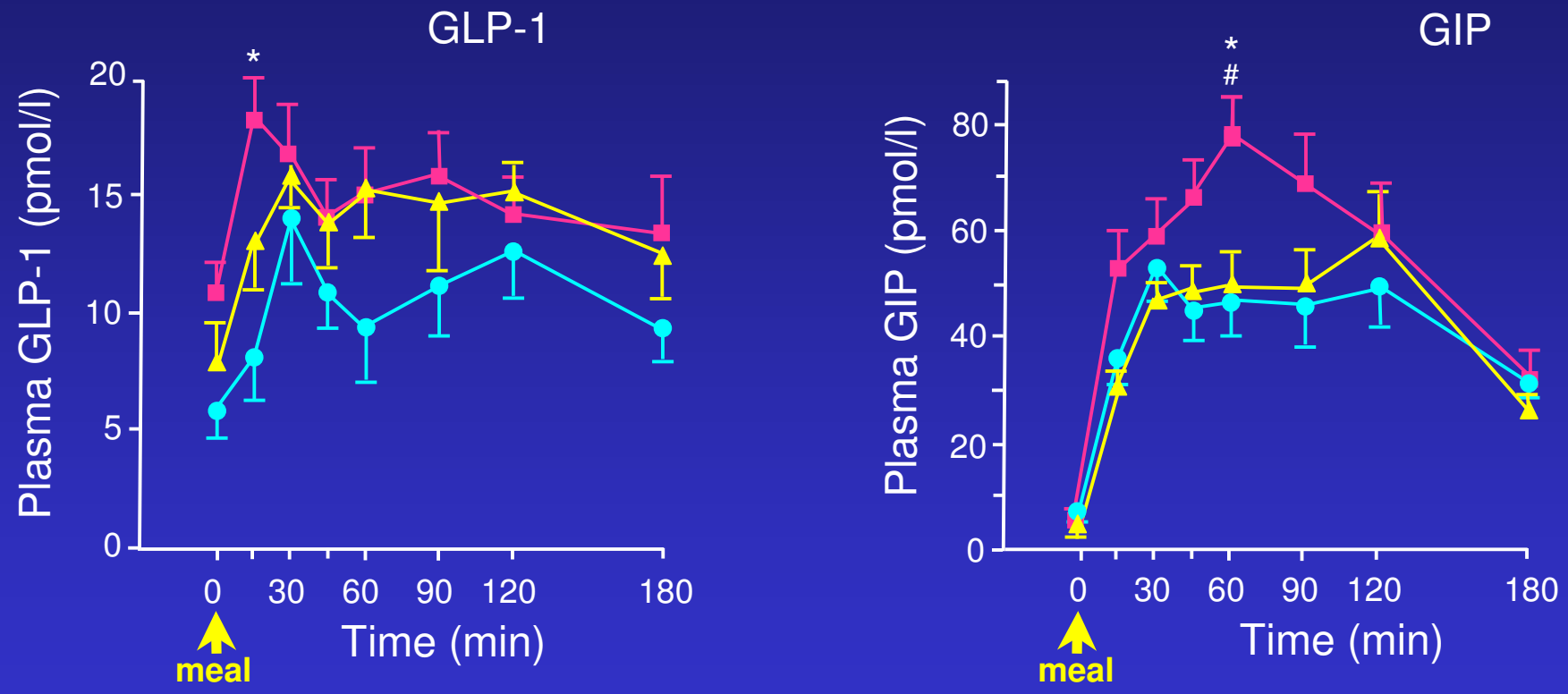
The meal-induced secretion of GLP-1:

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.

Toft-Nielsen M-B et al. *J Clin Endocrinol Metab*. 2001; 86:3717–3723.

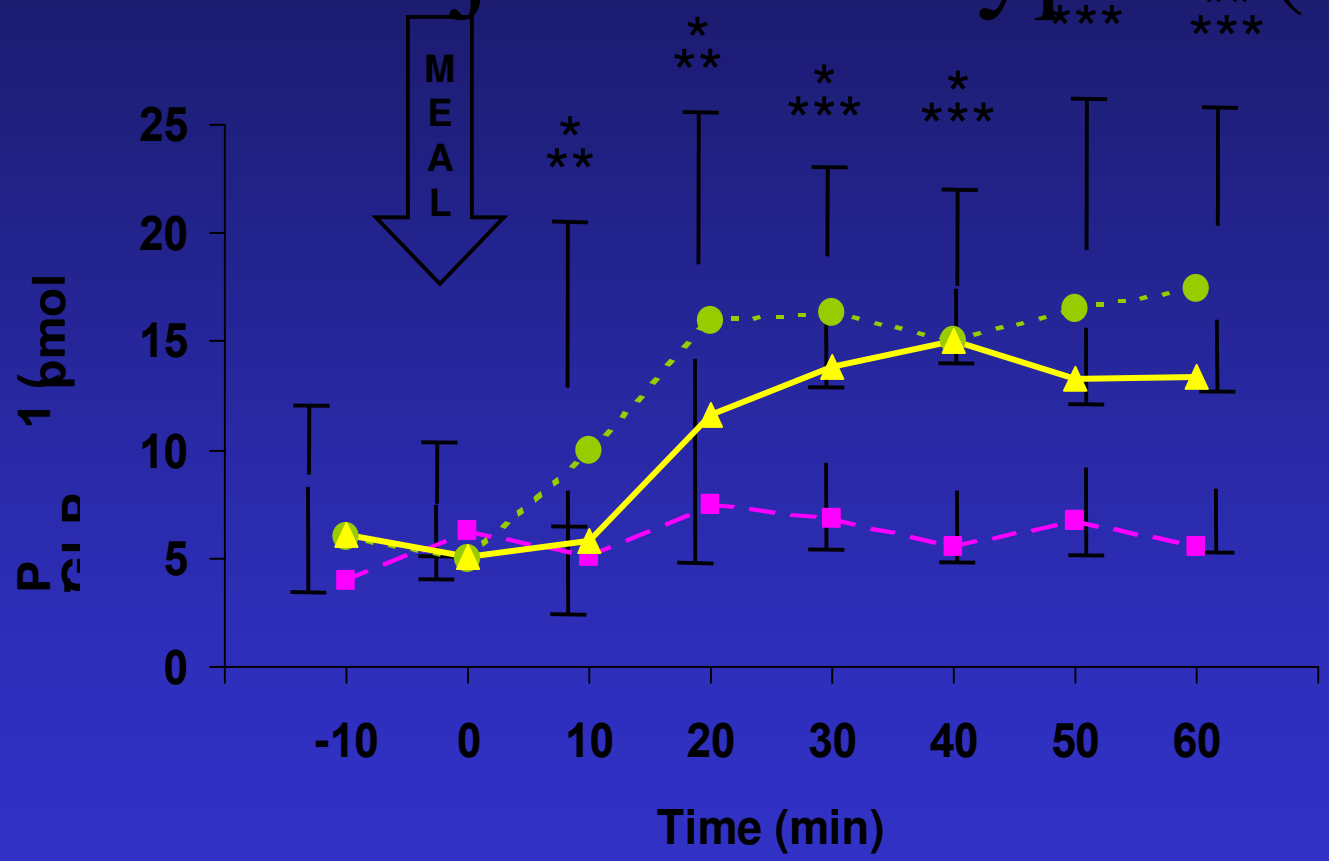
Meal-Stimulated Incretin Hormone Concentrations are Positively Correlated with Insulin Sensitivity in Non-Diabetic Men



Rask et al. Diabetes Care (2001)

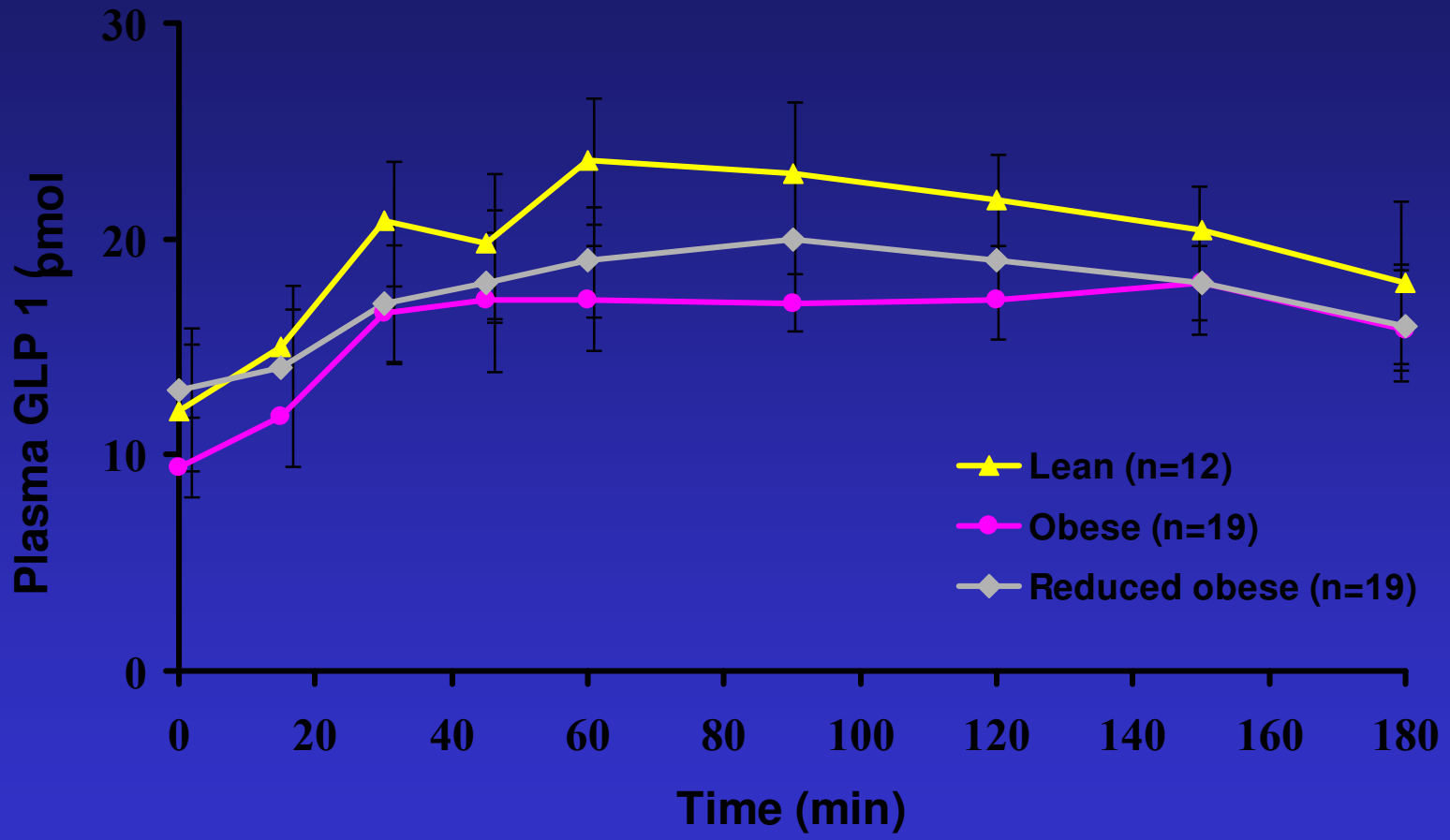
GLP-1 Secretion in Morbid Obesity

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.
Reprinted from Näslund E et al. *Obes Surg*. 1998;8:253–260.

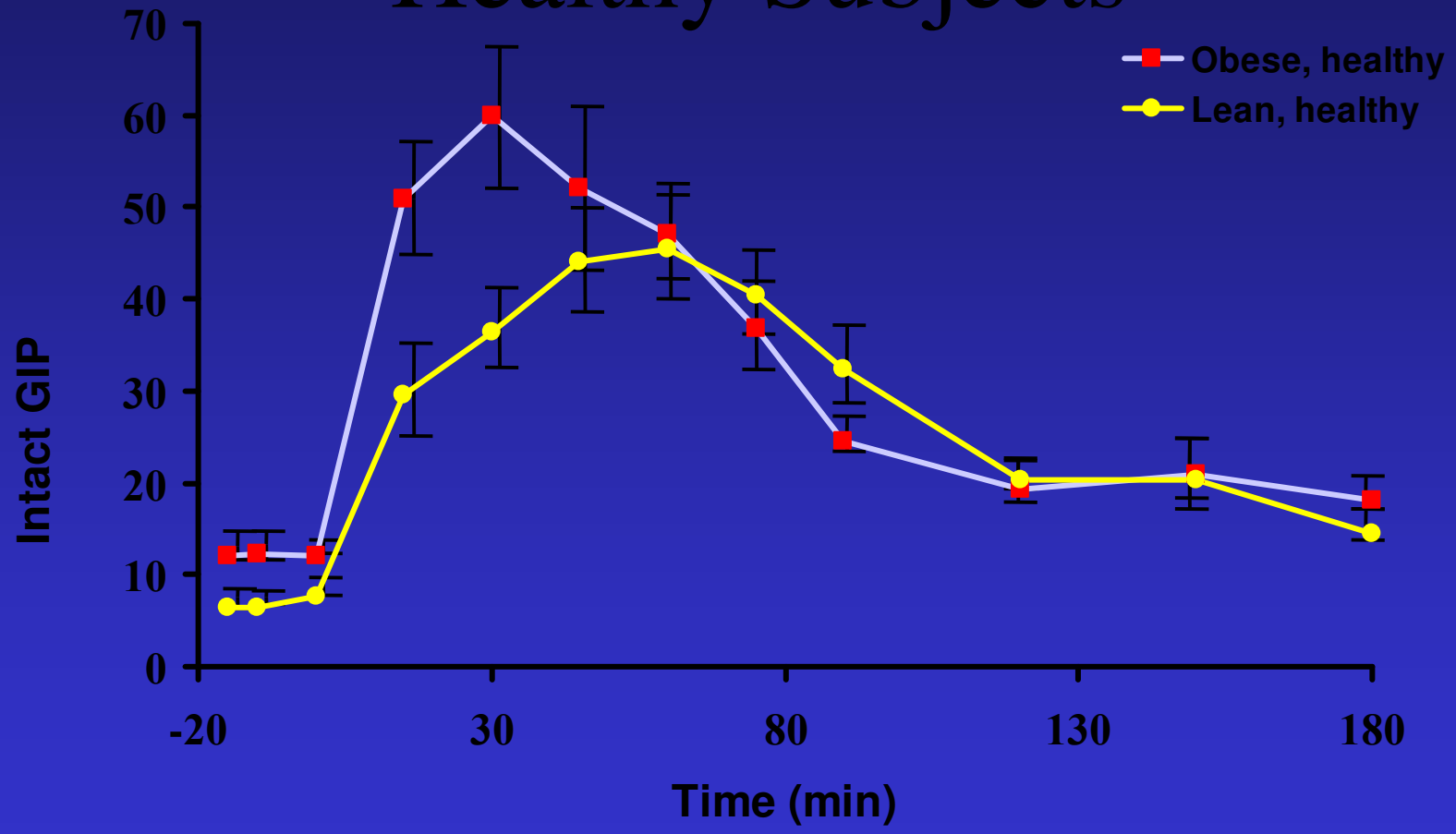
GLP-1 Response Following a 2.5 MJ* Test Meal



*Unit of energy, megajoules.

Reprinted from Verdich C et al. *Int J Obes*. 2001;25:1206–1214.

GIP: Obese, Healthy vs Lean, Healthy Subjects



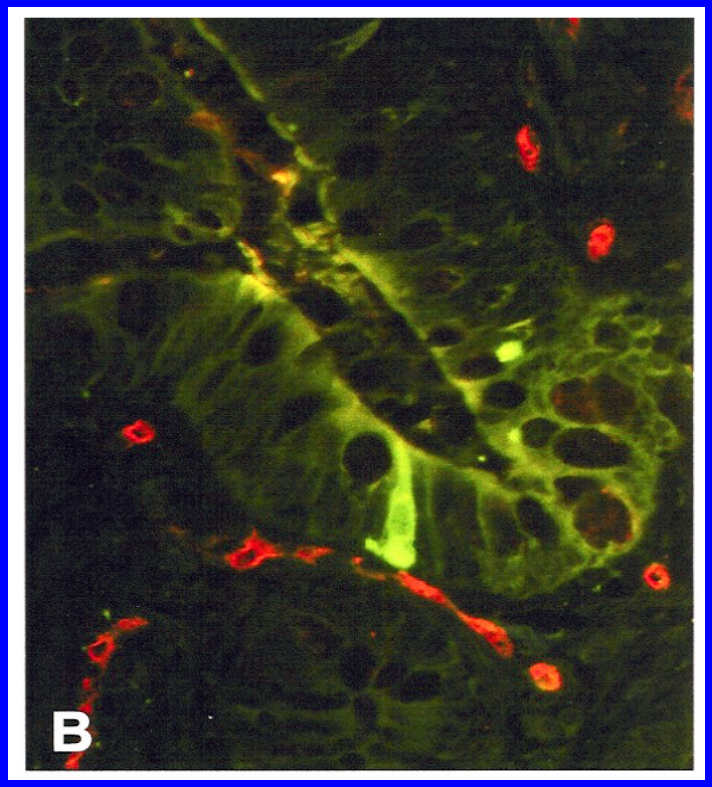
Adapted from Vilsbøll T et al. *J Clin Endocrinol Metab*. 2003;88:2706–2713.

Native GLP-1 is Rapidly Degraded by DPP IV

Plasma $T_{½}$ =1-2 minutes (i.v.)
MCR = 5-10 l/min

MCR=metabolic clearance rate.

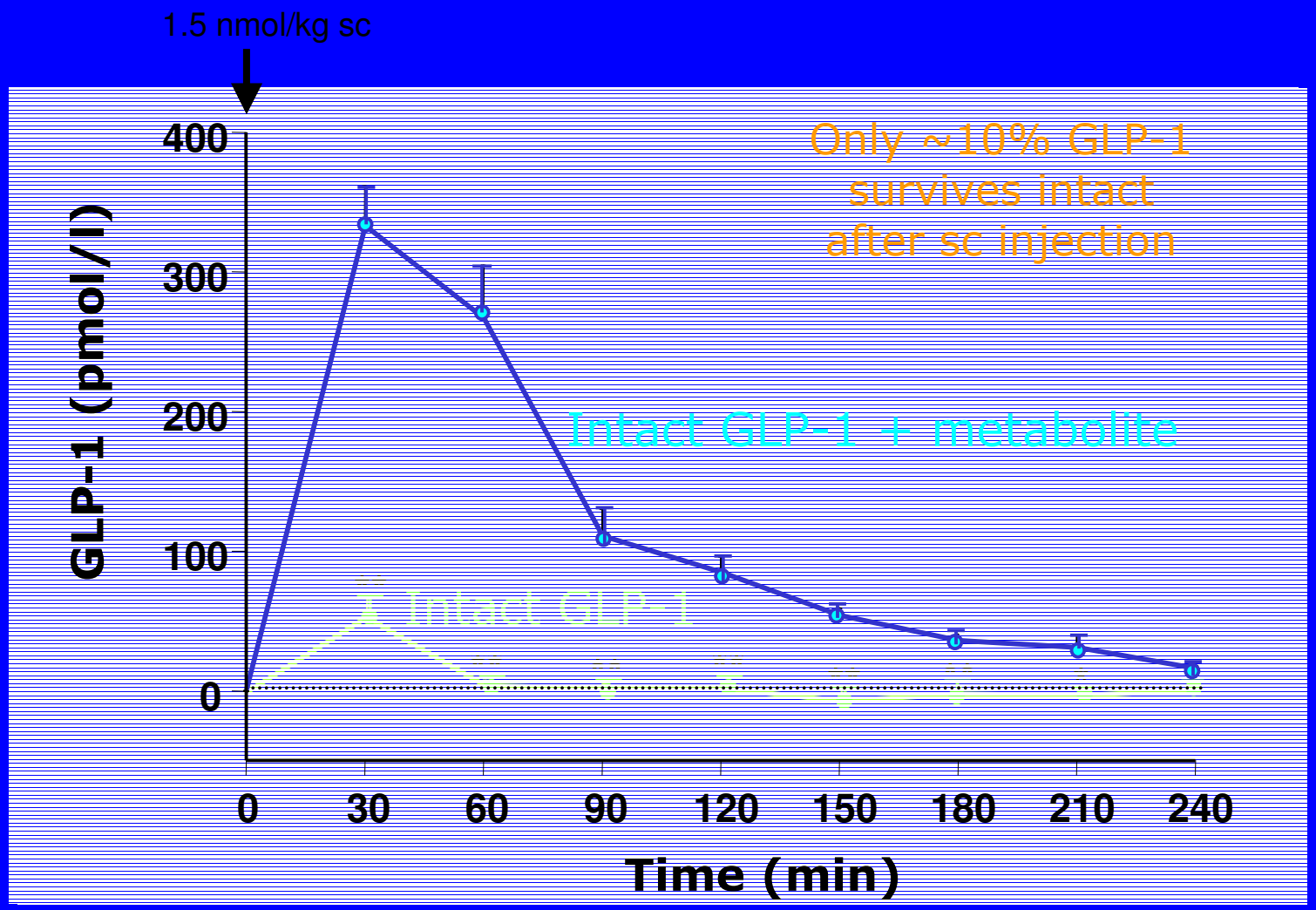
Vilsbøll T et al. *J Clin Endocrinol Metab*. 2003;88:220–224.



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

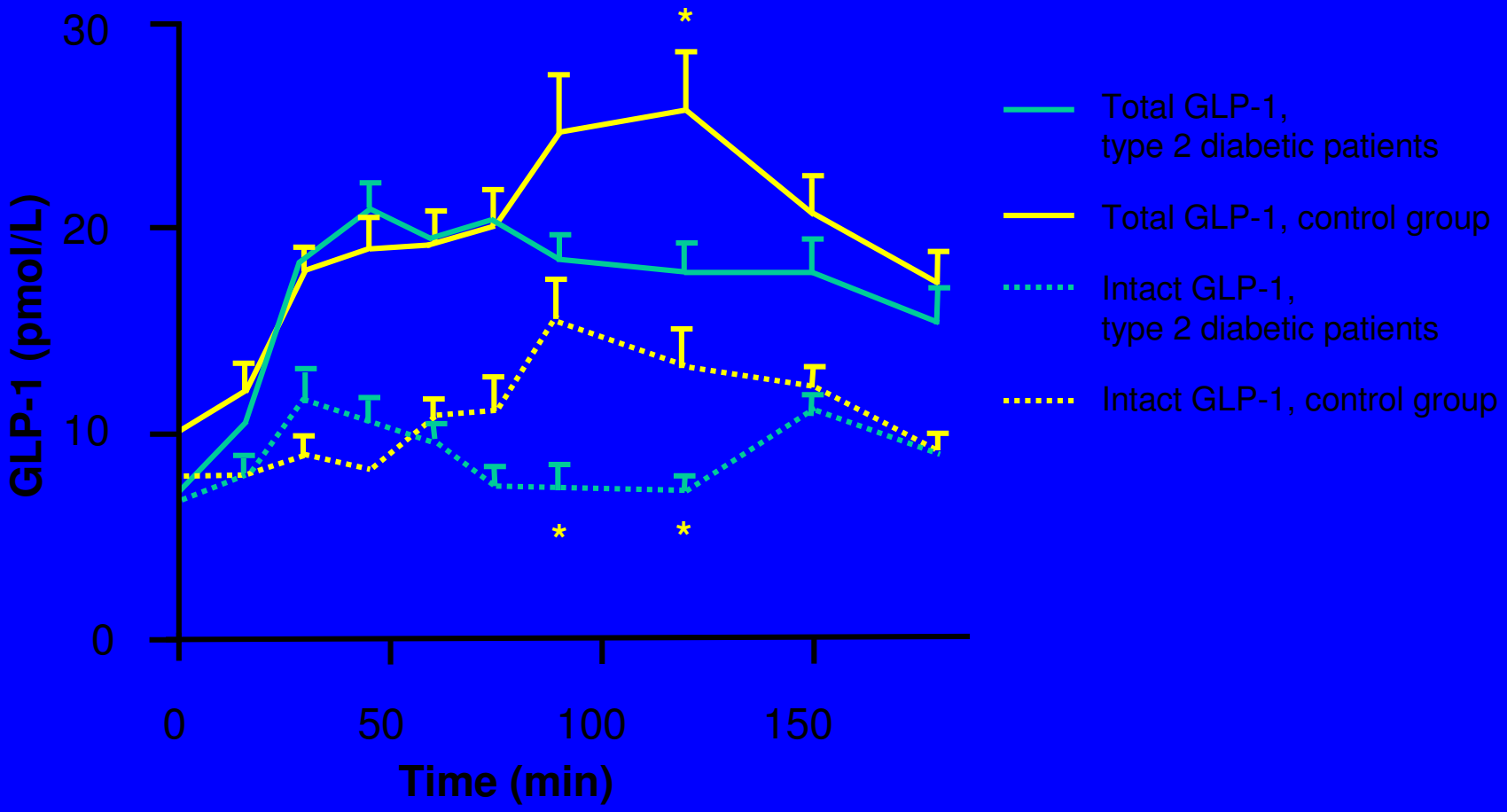
DPP IV=dipeptidyl peptidase IV
Hansen et al, *Endocrinology* 1999; 140:5356-5363

Survival of sc GLP-1 in Type 2 Diabetes



Deacon et al, Diabetes 1995; 44:1126-1131

Plasma Concentrations of Active GLP-1 Are Decreased in Type 2 Diabetes



*p<0.05

Adapted from Vilsbøll T et al. *Diabetes*. 2001;50:609–613.

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

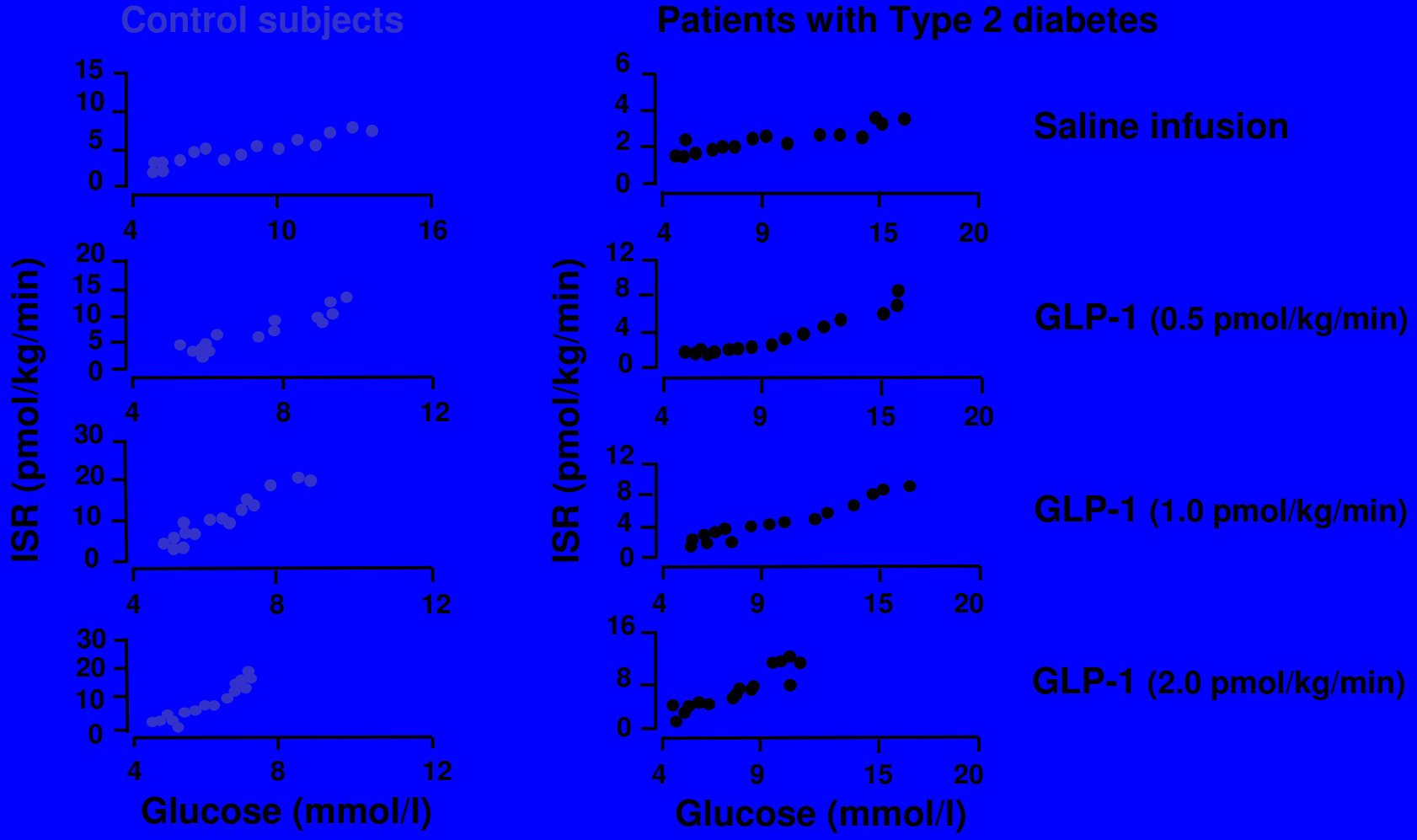
- Vaag et al, 1996: In identical twins discordant for type 2 diabetes, GLP-1 was decreased in the diabetic twin only
- Nyholm et al, 1999: 24-hour plasma profiles of GLP-1 were normal in healthy offspring of parents with type 2 diabetes
- Meier et al, 2005: Incretin hormone

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

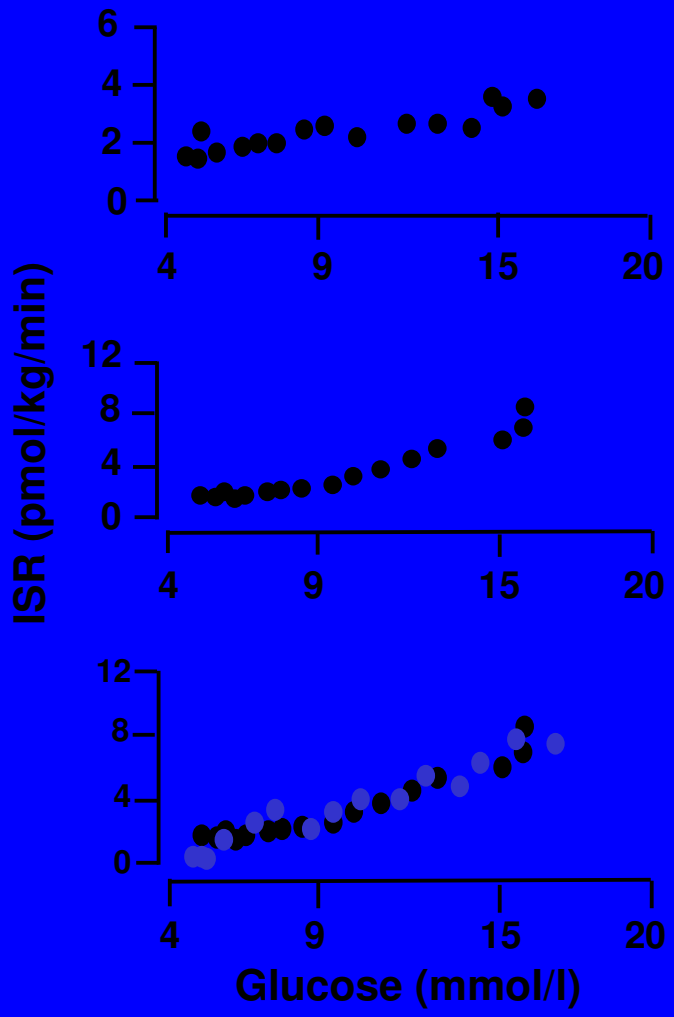
Relationship between average glucose concentrations and ISR in



ISR=insulin secretion rate.

Reprinted from Kjems LL et al. *Diabetes*. 2003;52:380–386.

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



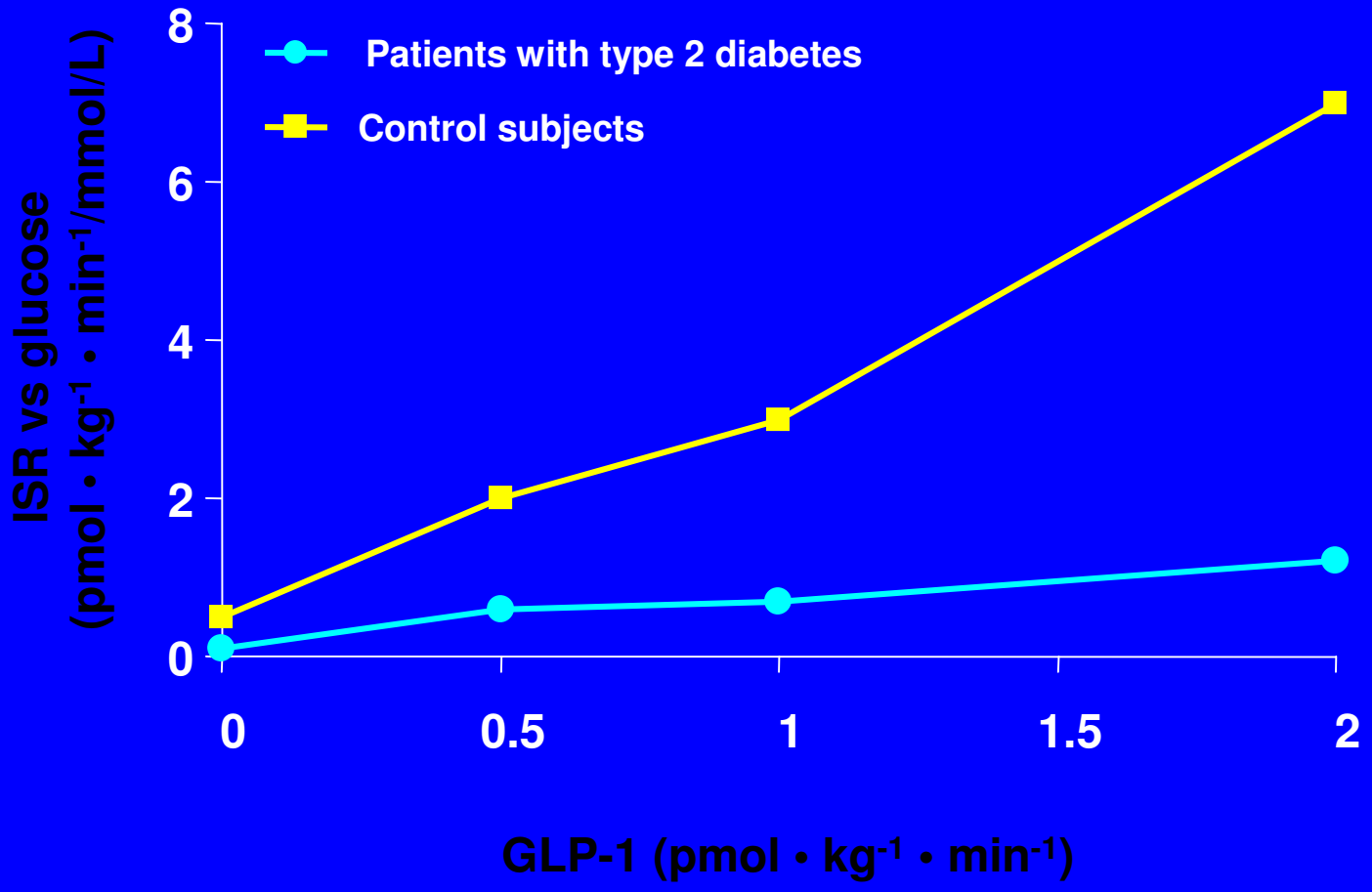
Type 2 diabetic: Saline infusion

Type 2 diabetic: GLP-1 (0.5 pmol/kg/min)

Type 2 diabetic: GLP-1 (0.5 pmol/kg/min)
+
Controls: Saline infusion

Adapted from Kjems LL et al. *Diabetes.* 2003;52:380–386.

Beta-Cell Responsiveness to Glucose

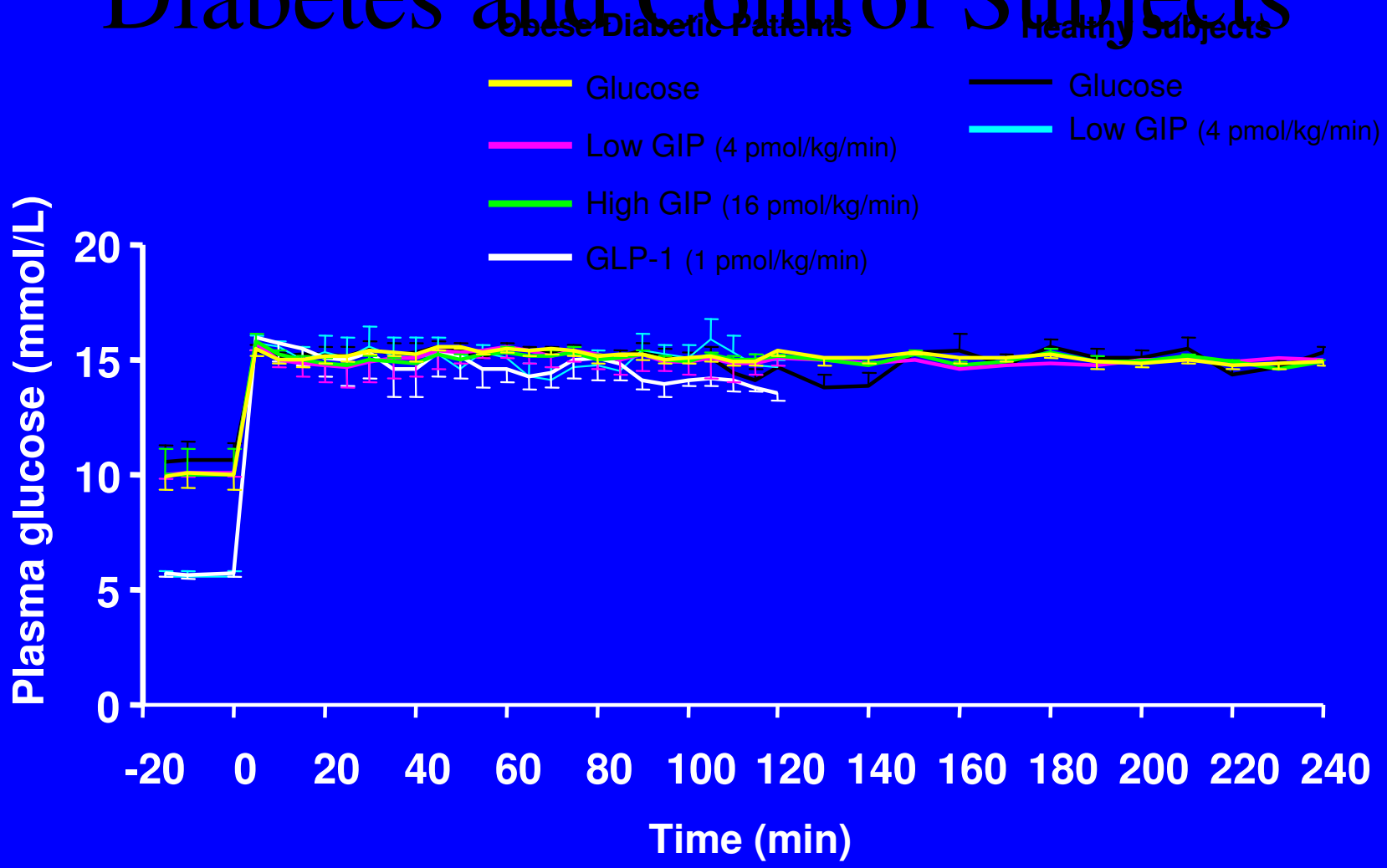


ISR=insulin secretion rate.
Beta-cell responsiveness to glucose expressed as the slope of the linear relation between ISR and glucose concentration.
Reprinted from Kjems LL et al. *Diabetes*. 2003;52:380–386.

Effects of GLP-1 on insulin secretion in patients with 2DM:

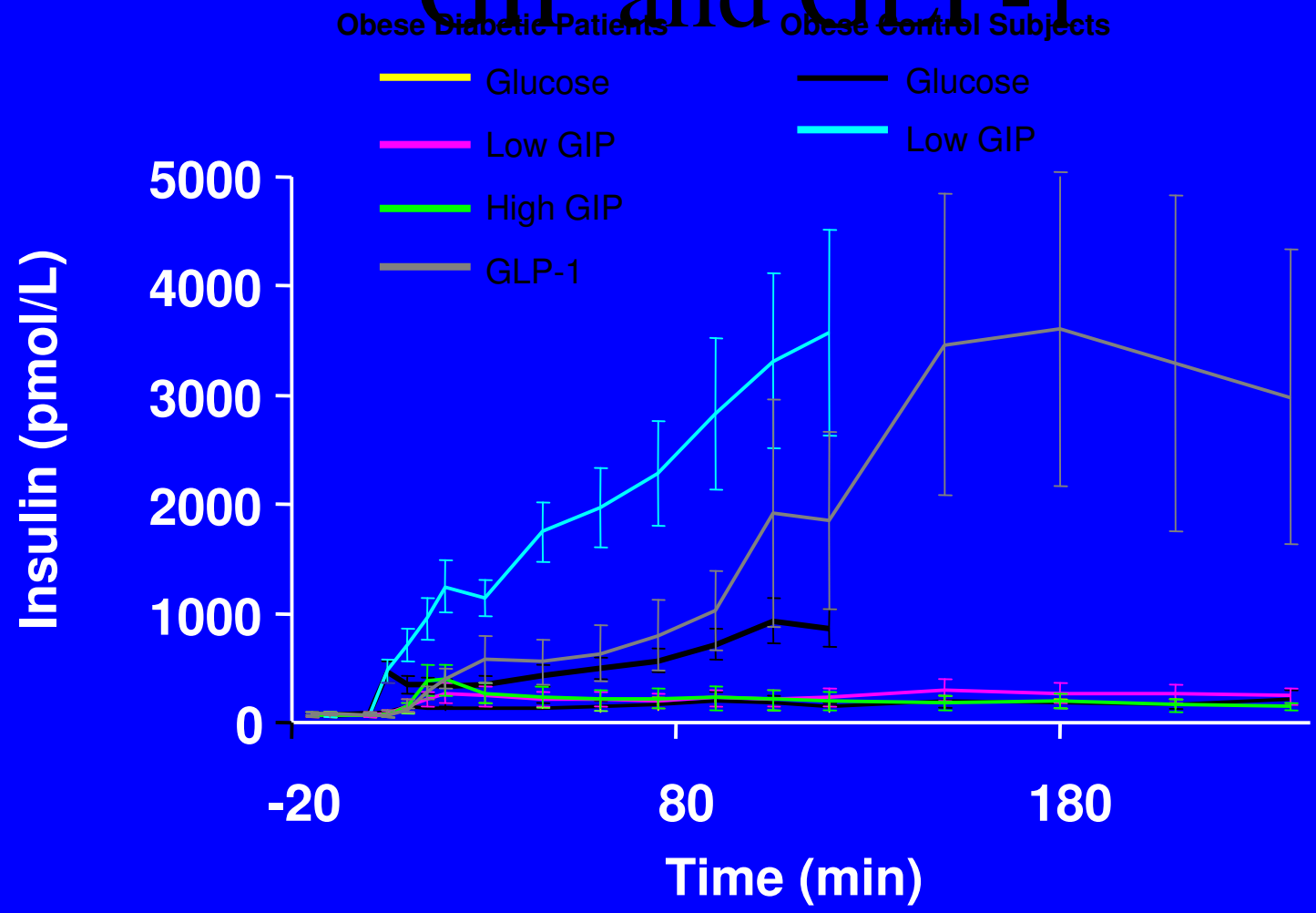
- Glucose-induced insulin secretion may be restored to normal values
- The potency of GLP-1 with respect to enhancing the beta cell responsiveness to glucose is decreased
- This decreased potency can be improved by improved metabolic control

Hyperglycemic Clamp + GLP-1/GIP in Patients With Type 2 Diabetes and Control Subjects



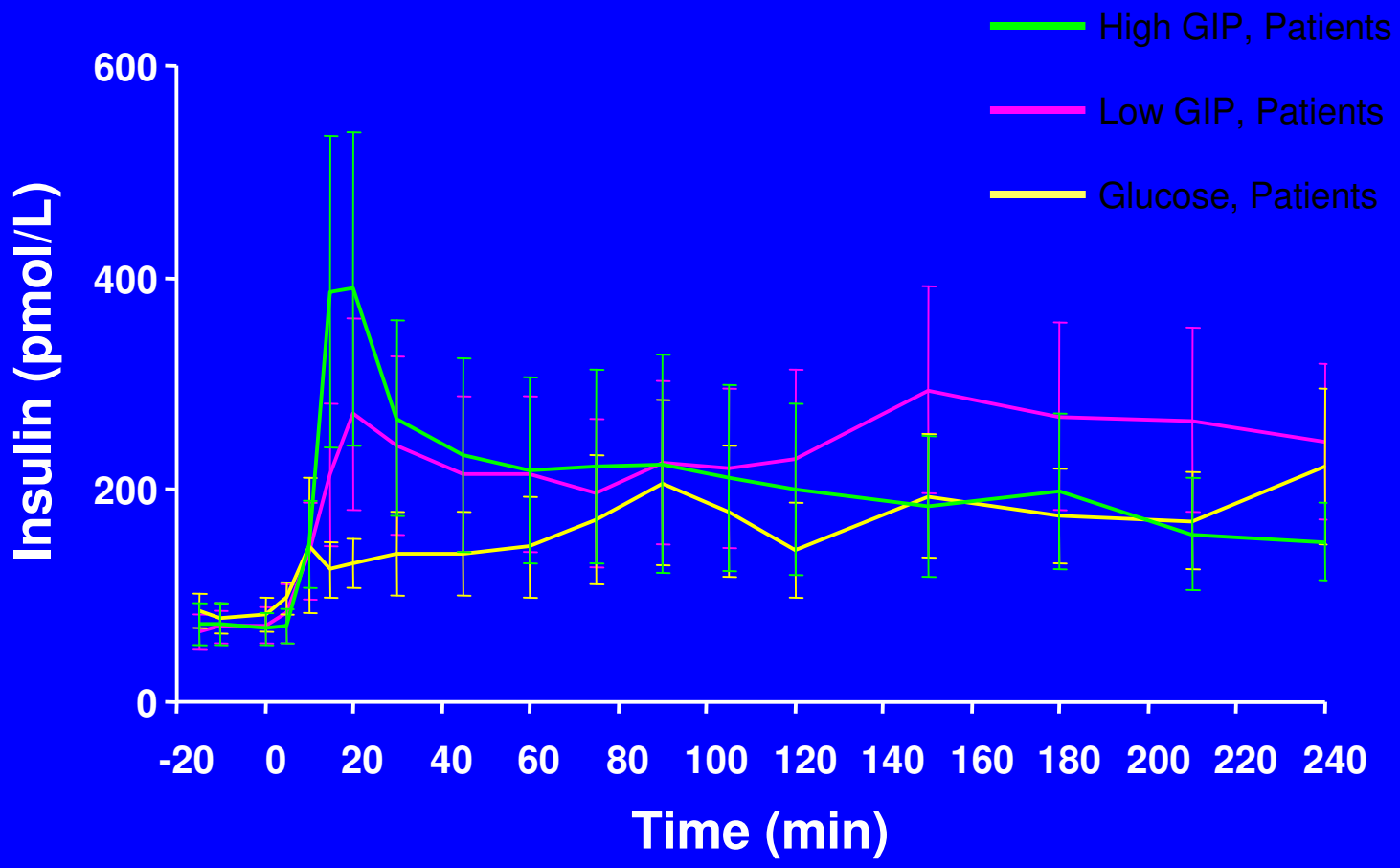
Reprinted from Vilsbøll T et al. *Diabetologia*. 2002;45:1111–1119.

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



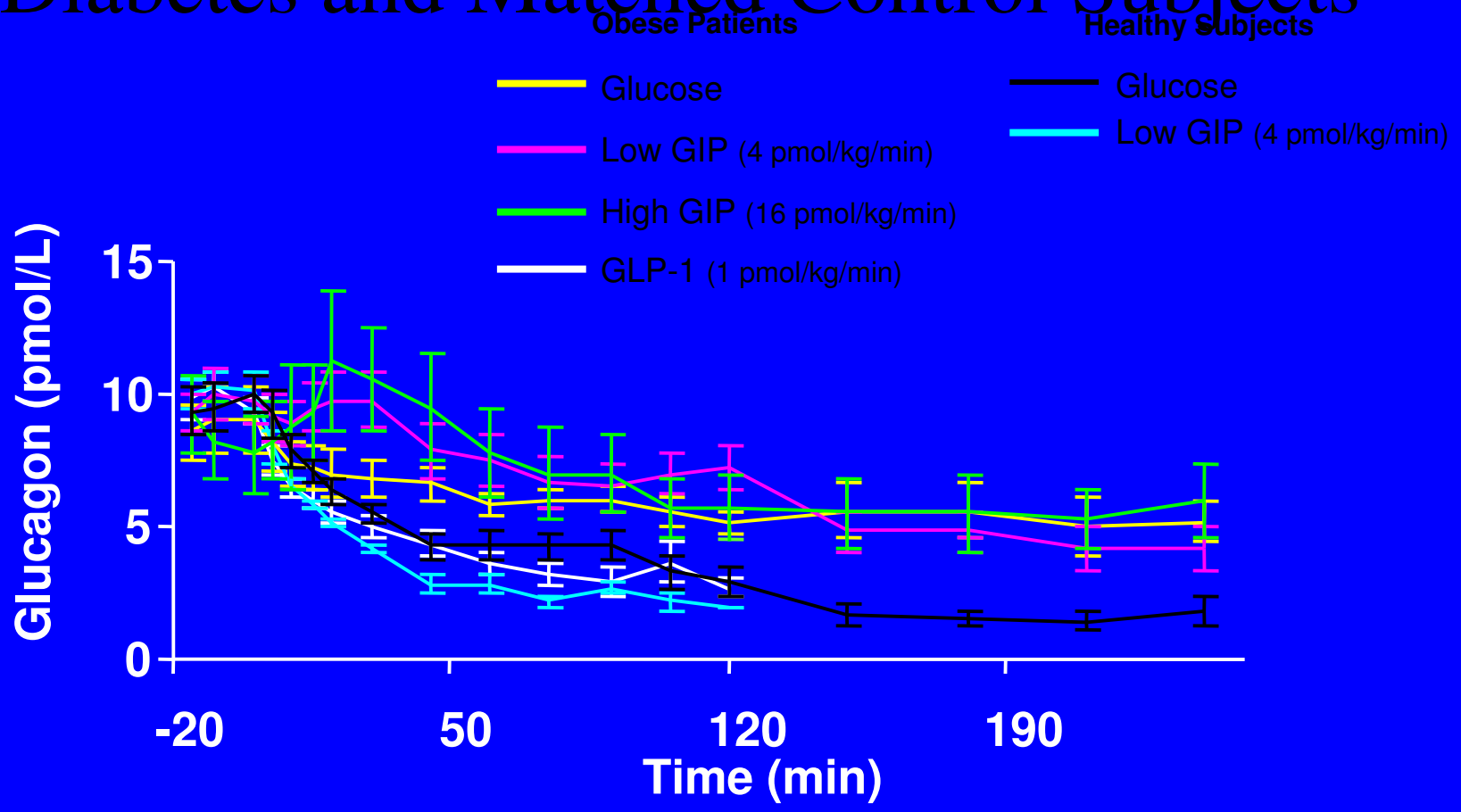
All subjects were obese (BMI 29 kg/m^2); patients with type 2 diabetes (n=8); control subjects (n=6).
IV=intravenous.
Adapted from Vilsbøll TI et al. *Diabetologia*. 2002;45:1111–1119.

Insulin Responses (cont)



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.
Vilsbøll T et al. *Diabetologia*. 2002;45:1111–1119.

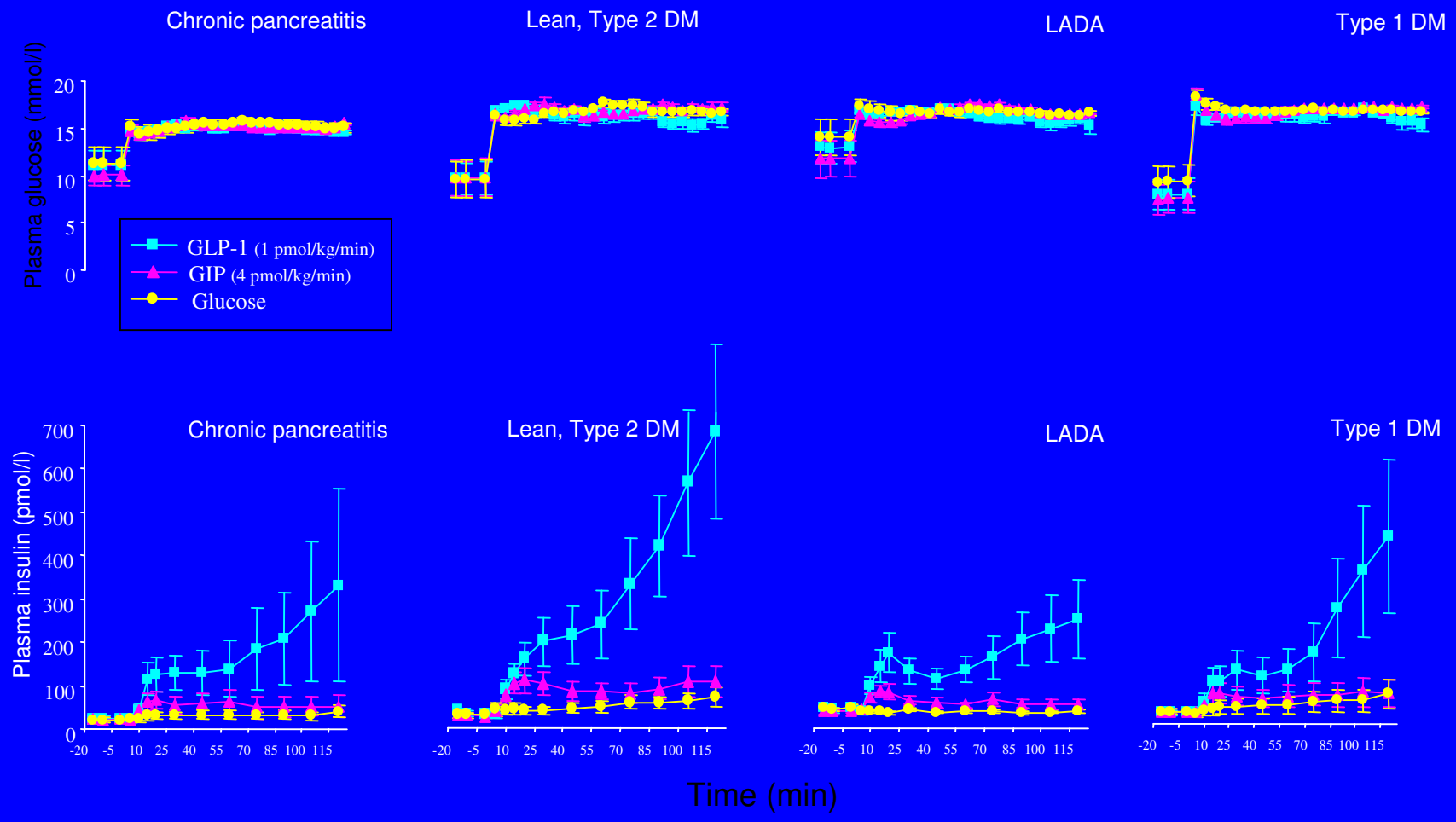
Inhibition of Glucagon Secretion by Glucose + GIP or GLP-1 in Patients With Type 2 Diabetes and Matched Control Subjects



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

Reprinted from Vilsbøll T et al. *Diabetologia*. 2002;45:1111–1119.

GLP-1 in Diabetes of Different Etiology



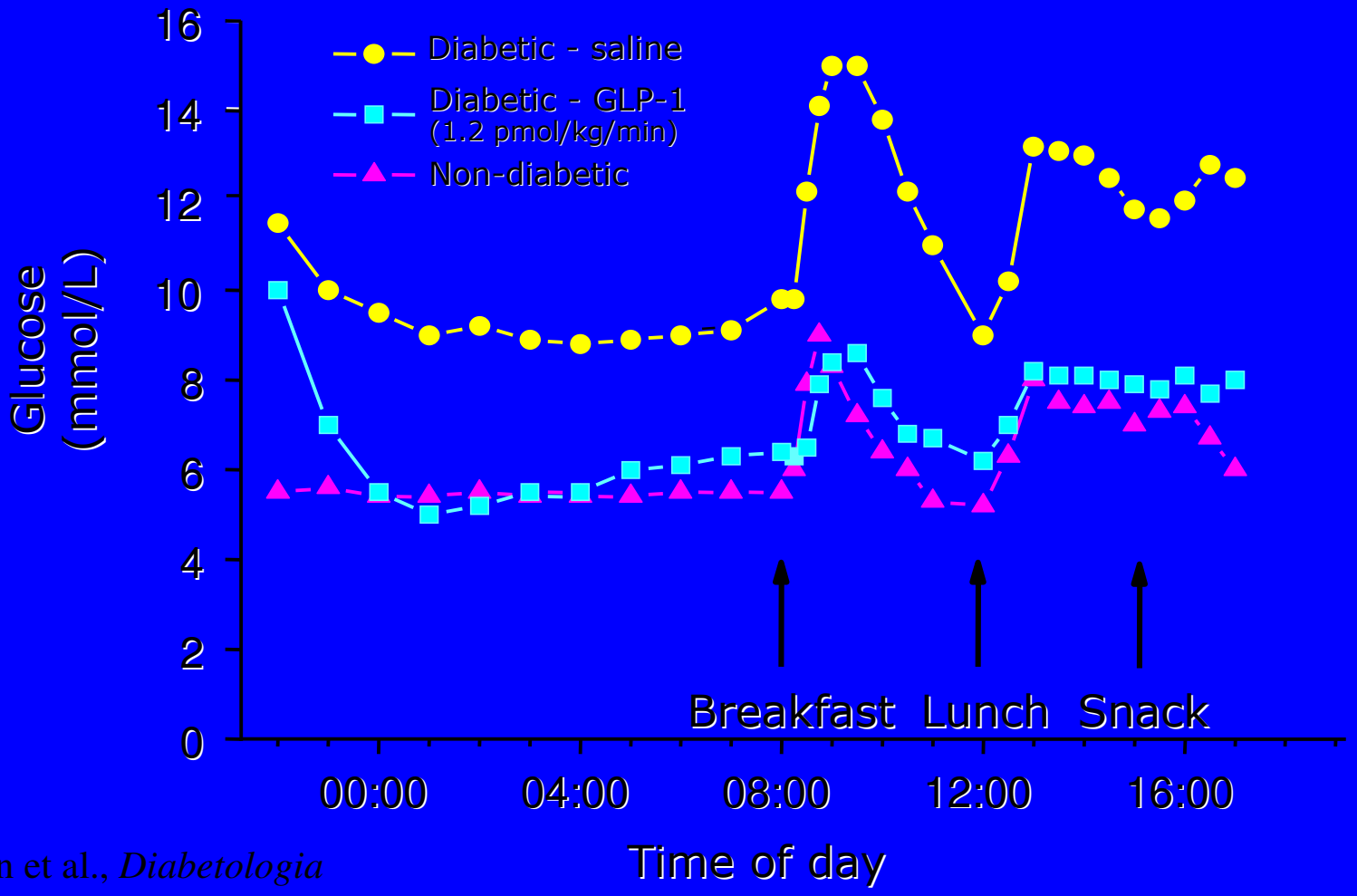
n=6 in each group. Modified from from Vilsbøll T et al. *J Clin Endocrinol Metab*. 2003;88:4897–4903.

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