Incretinas e inhibidores de la DPP-4

Dr. Ramon Gomis

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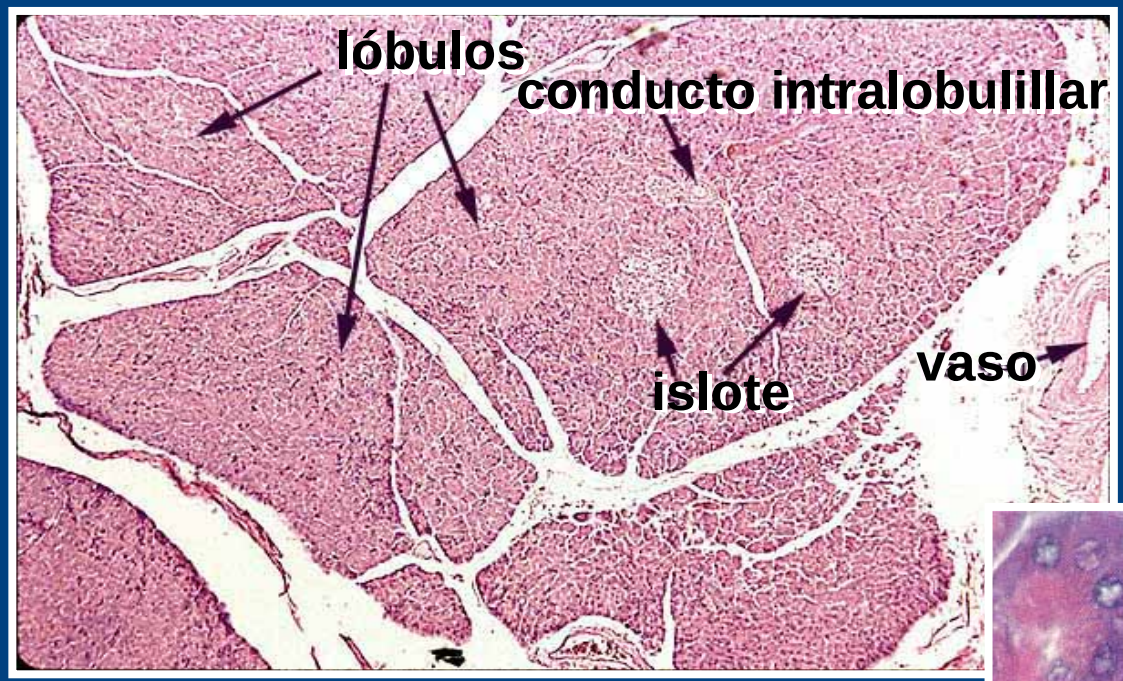
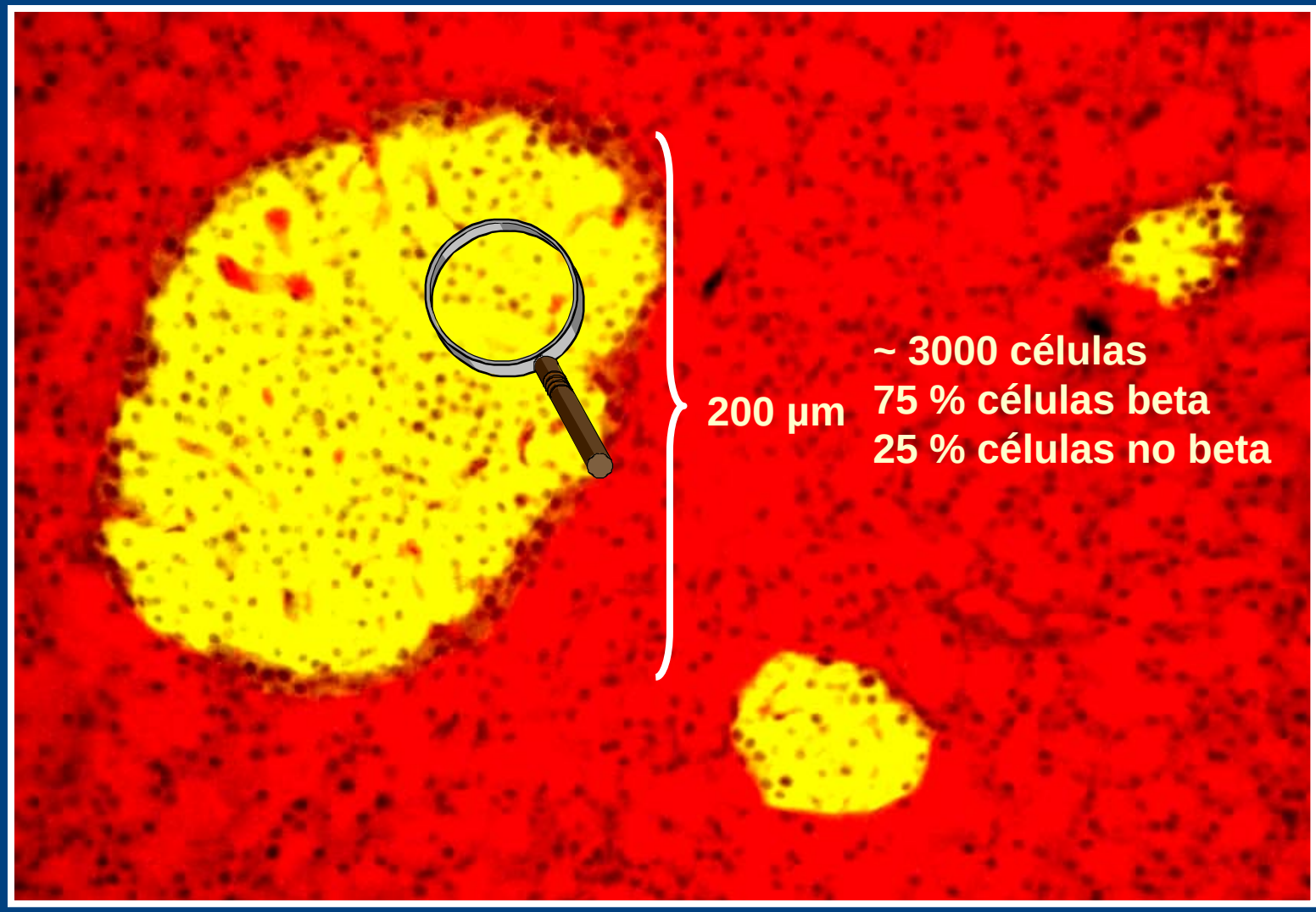
Barcelona

El páncreas normal y el islote de Langerhans



Adaptado de y disponible en: http://pathologyoutlines.com/pancreas.html. Acceso el 28 de febrero de 2006.

El islote de Langerhans



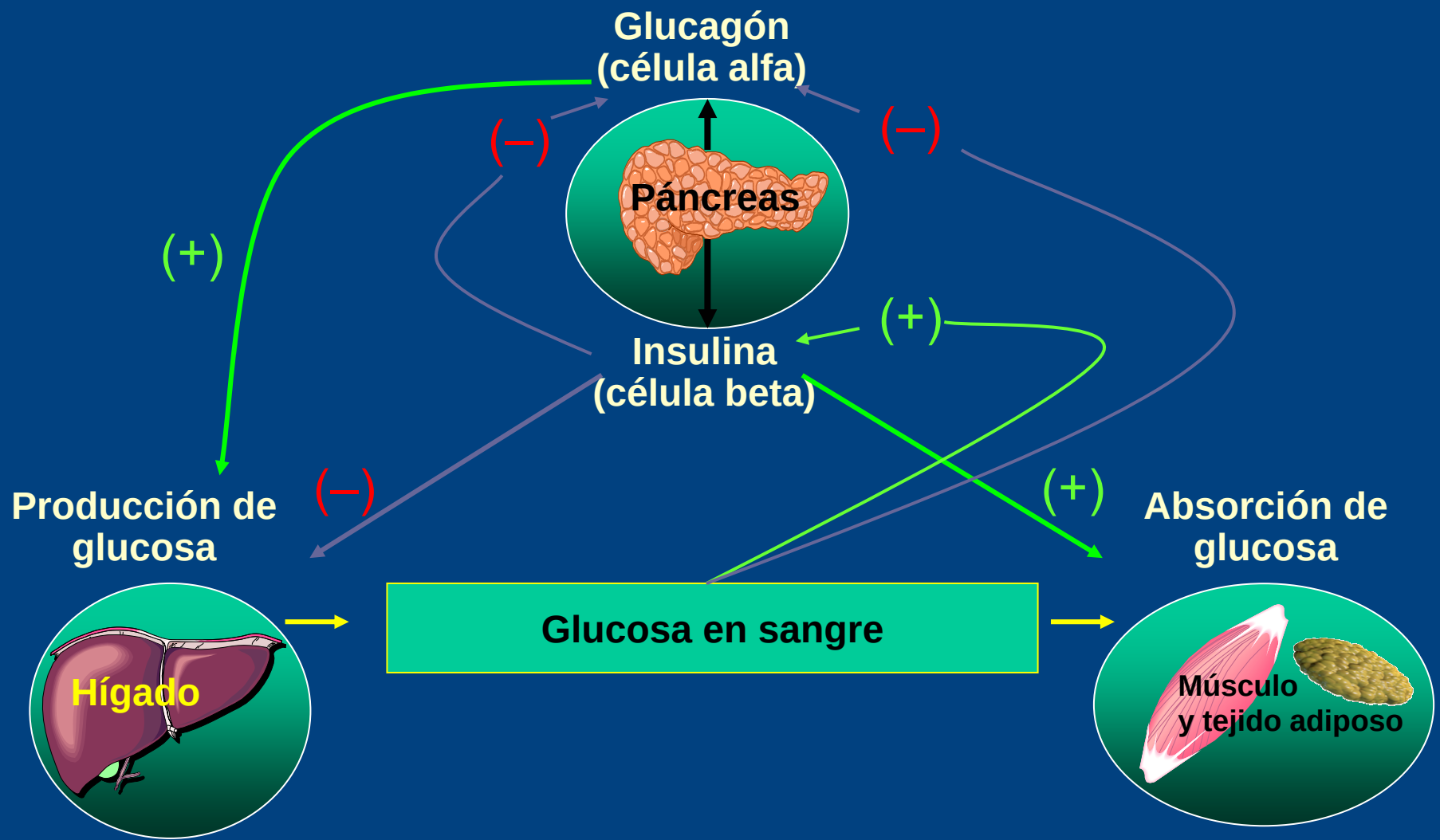
Micrografía: Lelio Orci, Ginebra

Las células beta y alfa en el páncreas de las personas sanas

Células beta	Células alfa
• Constituyen alrededor del 50 % de la masa endocrina del páncreas[1]	• Constituyen alrededor del 35 % de la masa endocrina del páncreas[1]
• Producen insulina y amilina[2]	• Producen glucagón[2]
• La insulina se secreta en respuesta a una glucemia alta[2]	• El glucagón se secreta en respuesta a una glucemia baja[2]

1. Cabrera O et al. PNAS. 2006;103:2334–2339.
2. Cleaver O et al. In: Joslin's Diabetes Mellitus. Lippincott Williams & Wilkins; 2005:21–39.

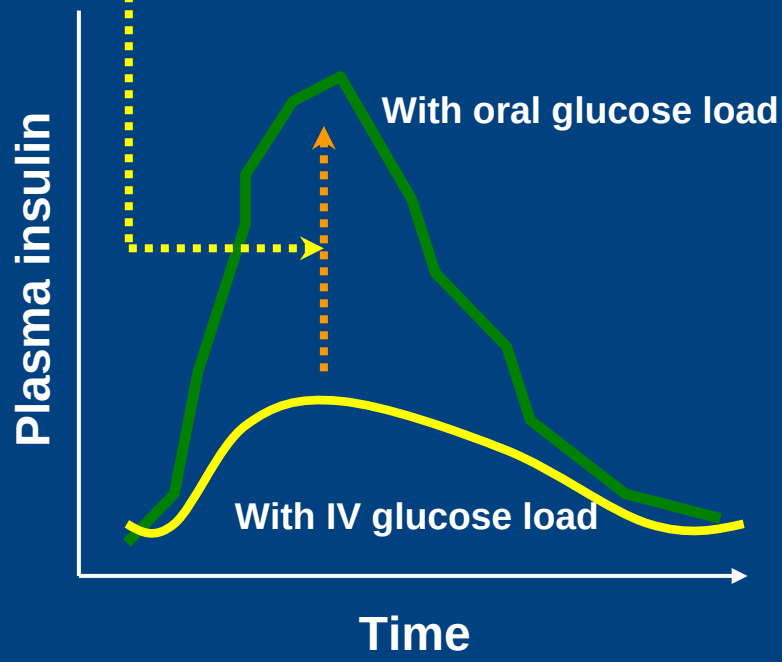
La insulina y el glucagón regulan la homeostasis normal de la glucosa



Porte D Jr et al. Clin Invest Med. 1995;18:247–254.
Adaptado de Kahn CR, Saltiel AR. Joslin's Diabetes Mellitus. 14th ed. Lippincott Williams & Wilkins; 2005:145–168.

Physiologic Explanation of the Incretin Response

Incretins
- **GLP-1**
- GIP
- ? Other incretins



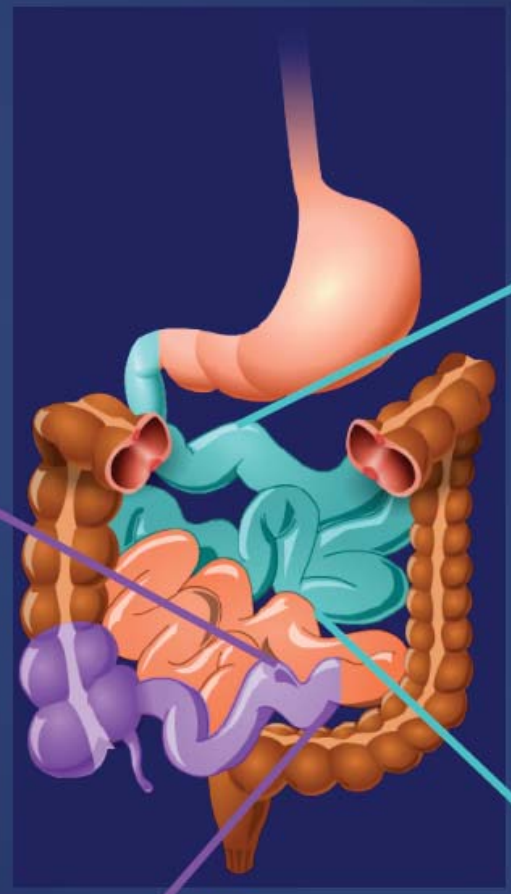
IV=intravenous

Adapted from Vilsbøll T, Holst JJ *Diabetologia* 2004;47:357–366; Brubaker PL, Drucker DJ *Endocrinology* 2004;145:2653–2659.

GLP-1

- “Incretin” hormone secreted by jejunal and ileal L cells in response to a meal
- Stimulates insulin secretion
- Decreases glucagon secretion
- Slows gastric emptying
- Reduces fuel intake (increases satiety)
- Improves insulin sensitivity
- Increases β-cell mass and improves β-cell function (animal studies)

Synthesis and Secretion of GLP-1 and GIP



K-Cell
(jejunum)

ProGIP

GIP [1-42]

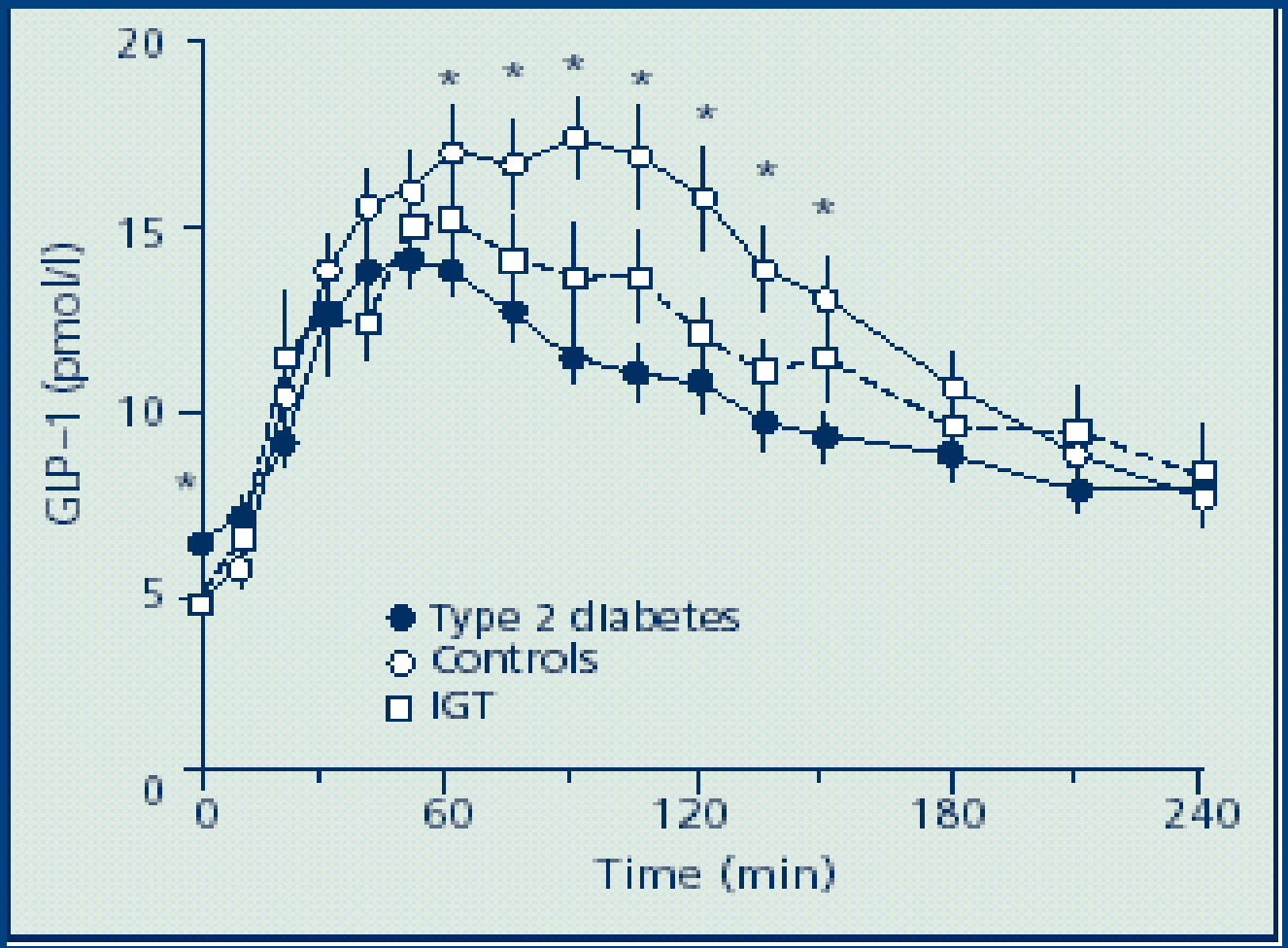
L-Cell
(ileum+ colon)

Proglucagon

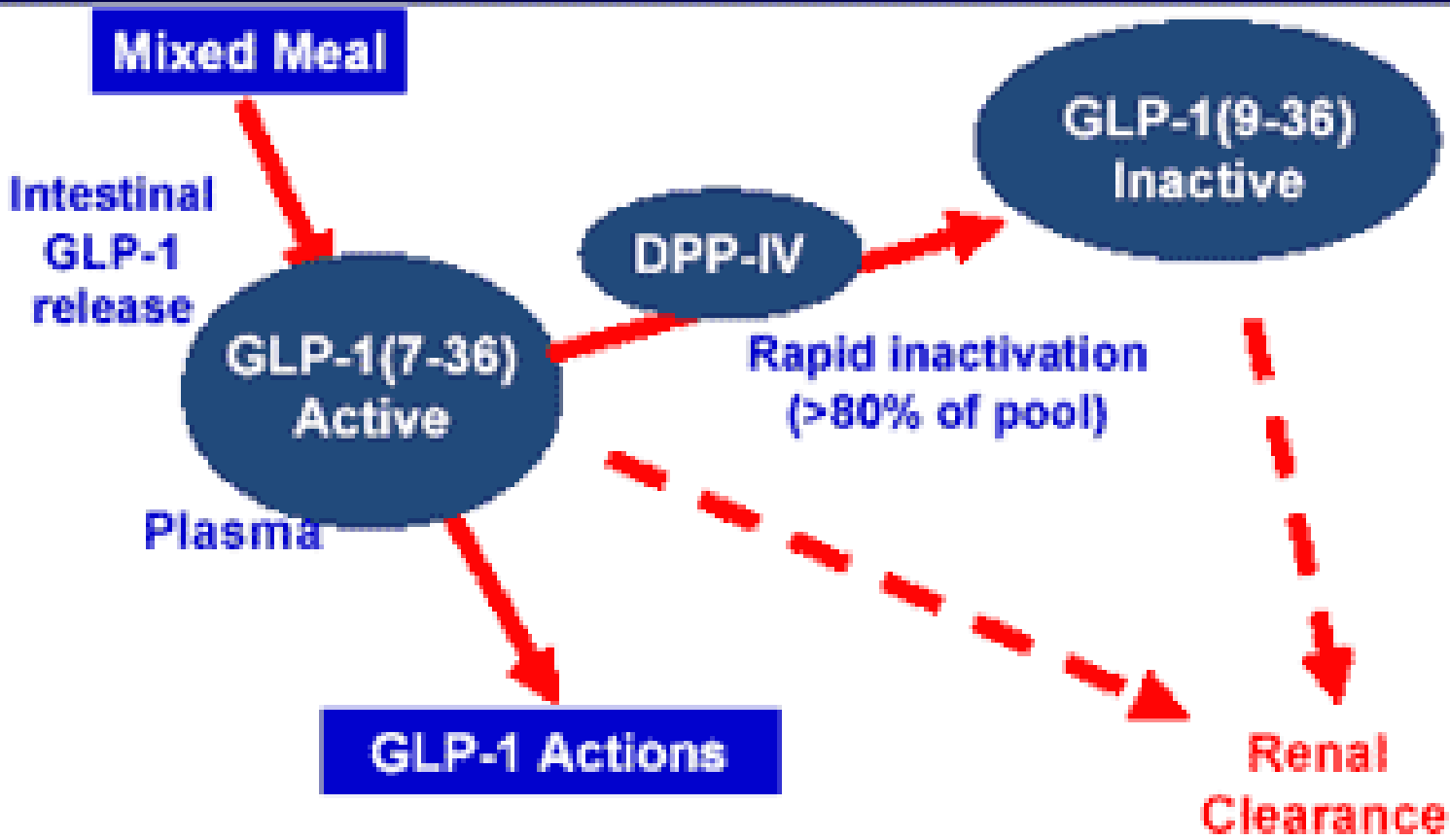
GLP-1 [7-37]

GLP-1 [7-36NH_2]

GLP-1 release following meal: comparison of control, T2DM & IGT



GLP-1 Secretion and Metabolism



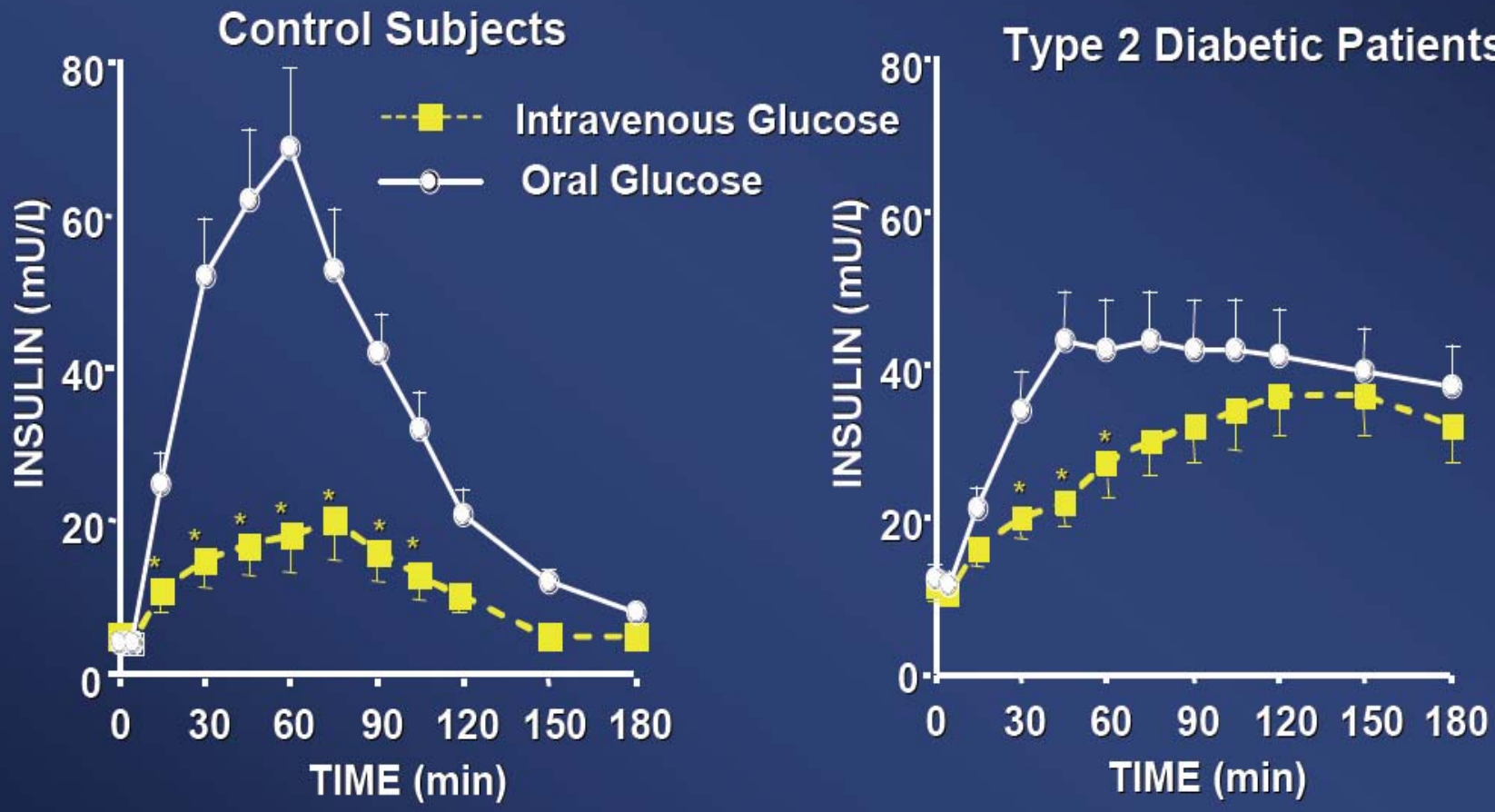
Kieffer TJ, et al. *Endocr Rev.* 1995;20:876-913.
Deacon CF et al. *Diabetes.* 1995;44:1126-1131.

Type 2
Diabetes Pathophysiology

Type 2 Diabetes is a Multi-Hormonal Disease

- Pancreatic hormones
  - Insulin (β-cell)
  - Glucagon (α-cell)
  - Amylin (β-cell)
- Intestinal Hormones (Incretins)
  - GLP-1 (L-cells)
  - GIP (K-cells)

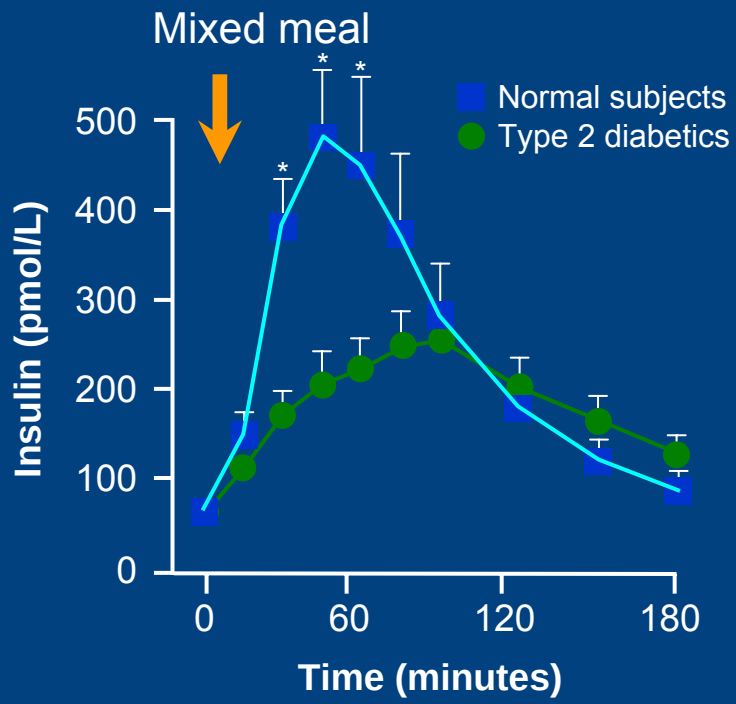
Reduced Incretin Effect in Type 2 Diabetic patients



Nauck M. et al. *Diabetologia*. 1986;29:46-52.

Abnormal Beta-Cell Function in Type 2 Diabetes

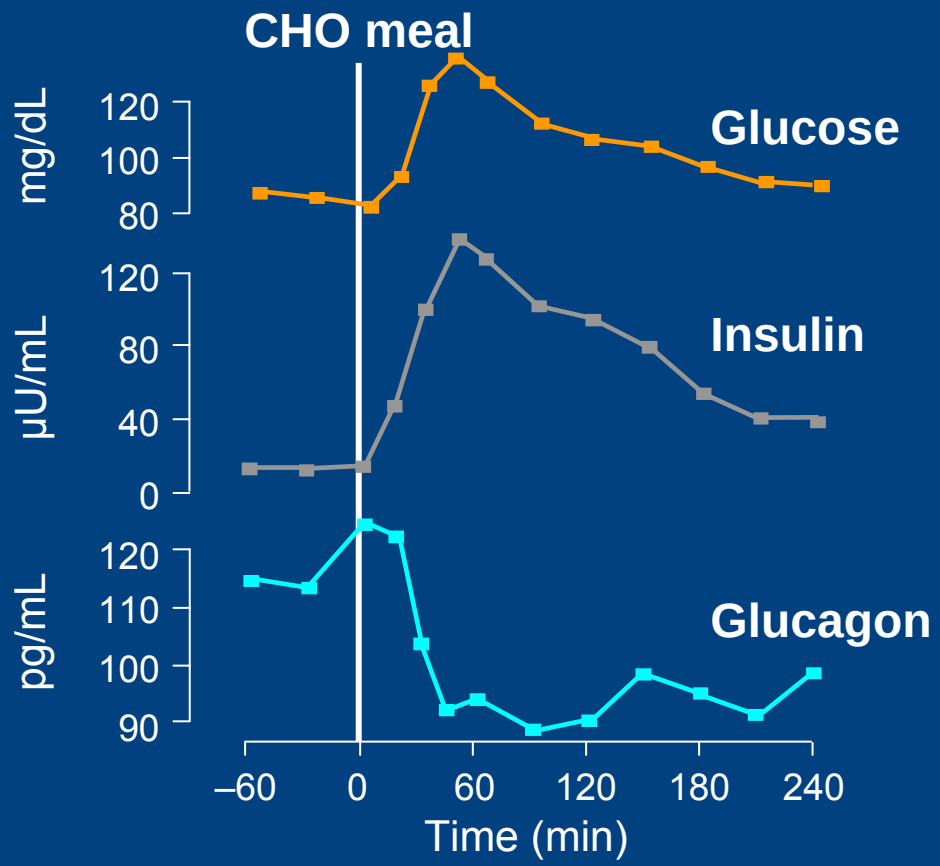
- A range of functional abnormalities is present
- Abnormal oscillatory insulin release
- Increased proinsulin levels
- Loss of 1st-phase insulin release
- Abnormal 2nd-phase insulin release
- Progressive loss of beta-cell functional mass

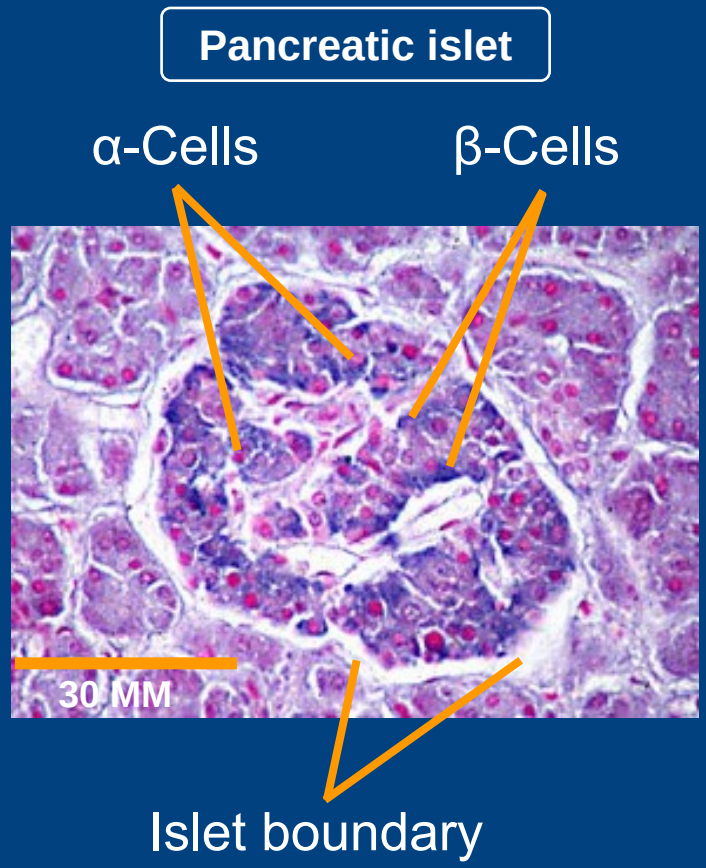


*p<0.05 between groups

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

Reciprocal Response of Insulin and Glucagon in Postprandial Period in Persons Without Diabetes



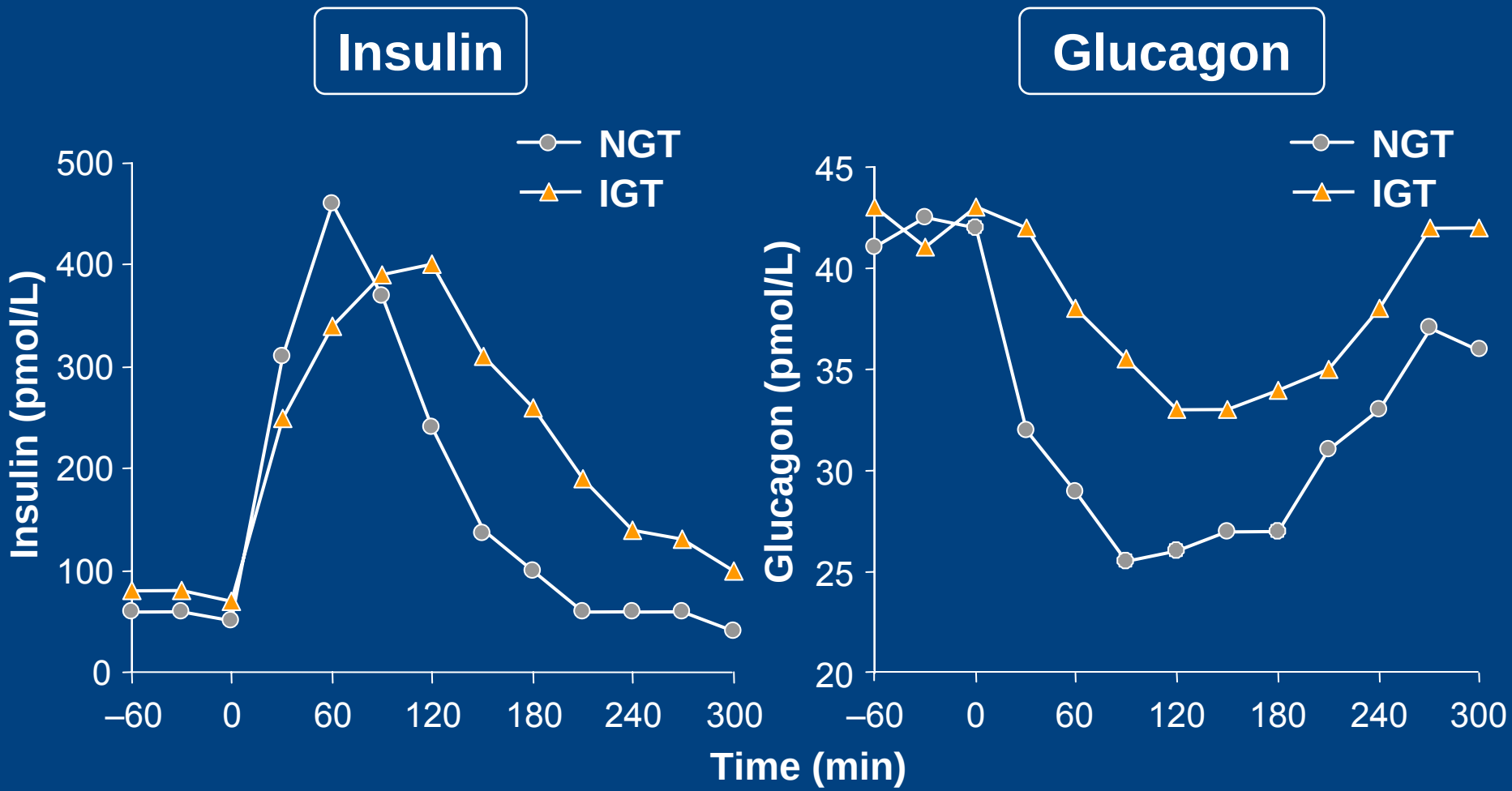


Photomicrograph courtesy of Michael Sarras, PhD, Rosalind Franklin University of Medicine and Science.

CHO = carbohydrate

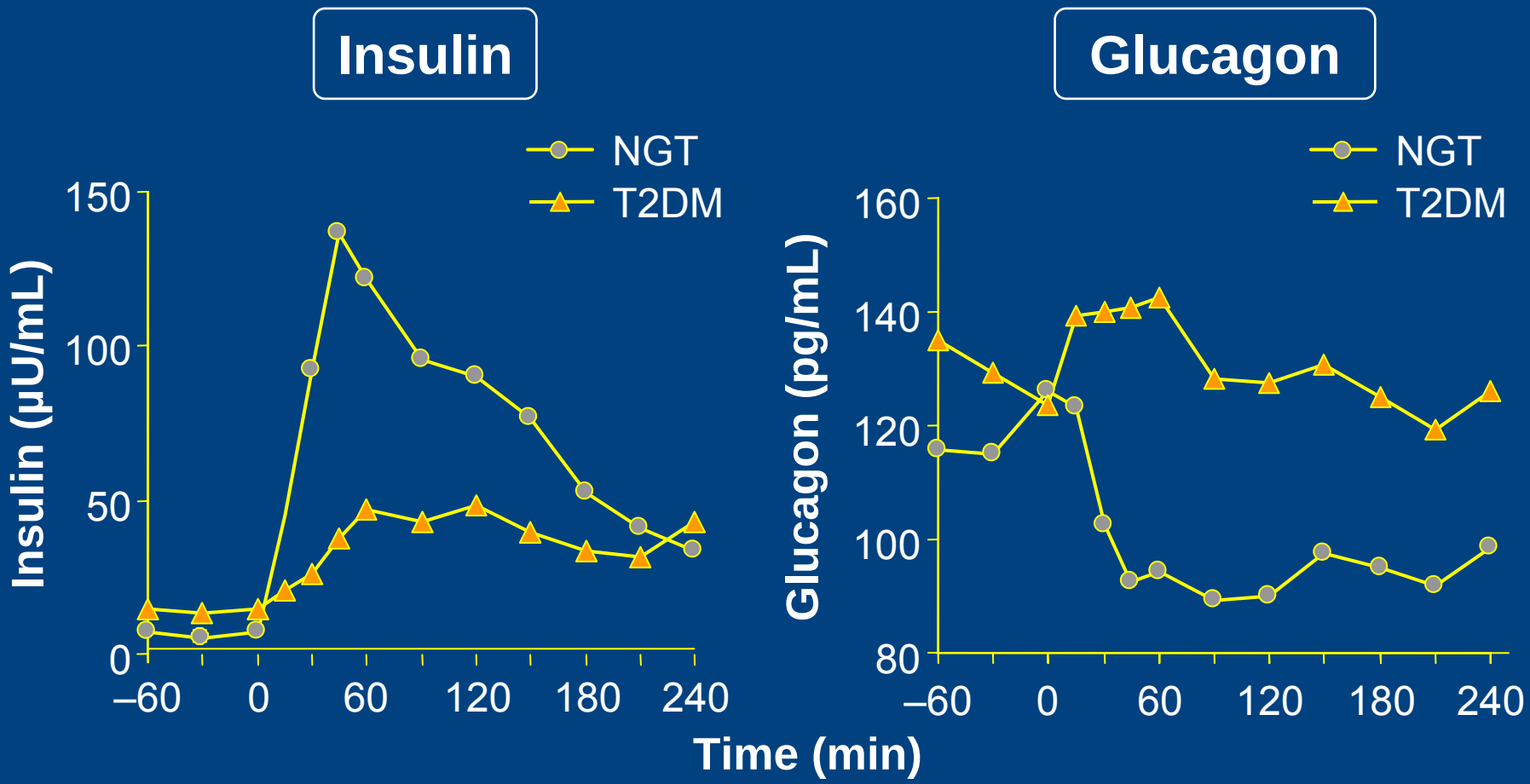
Unger RH. *N Engl J Med.* 1971;285:443-449.

Inappropriate Insulin and Glucagon Responses to Glucose in Individuals With IGT



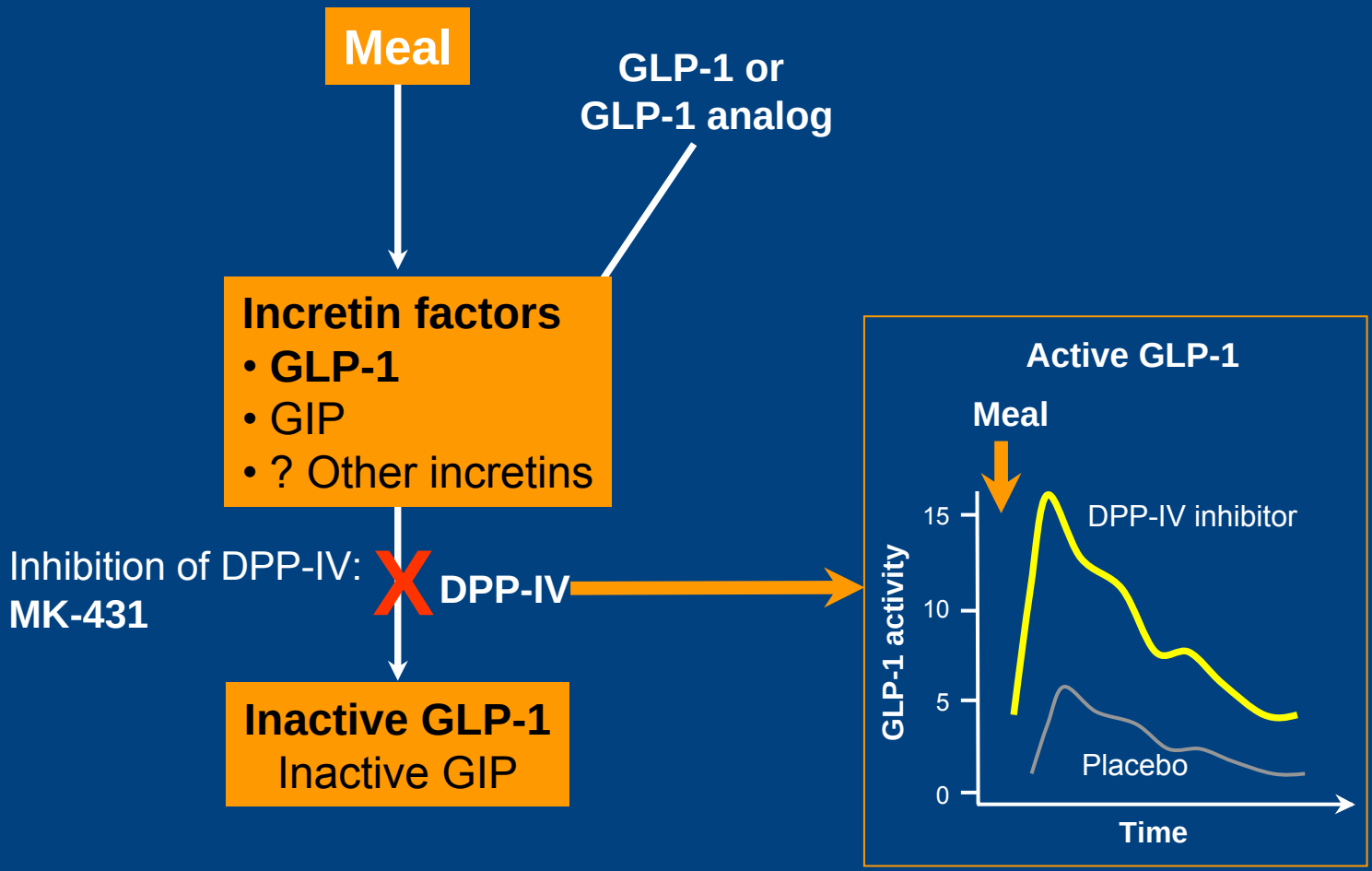
Mitrakou A, et al. *N Engl J Med*. 1992;326:22-29.

Inappropriate Insulin and Glucagon Responses to Glucose in Patients With T2DM



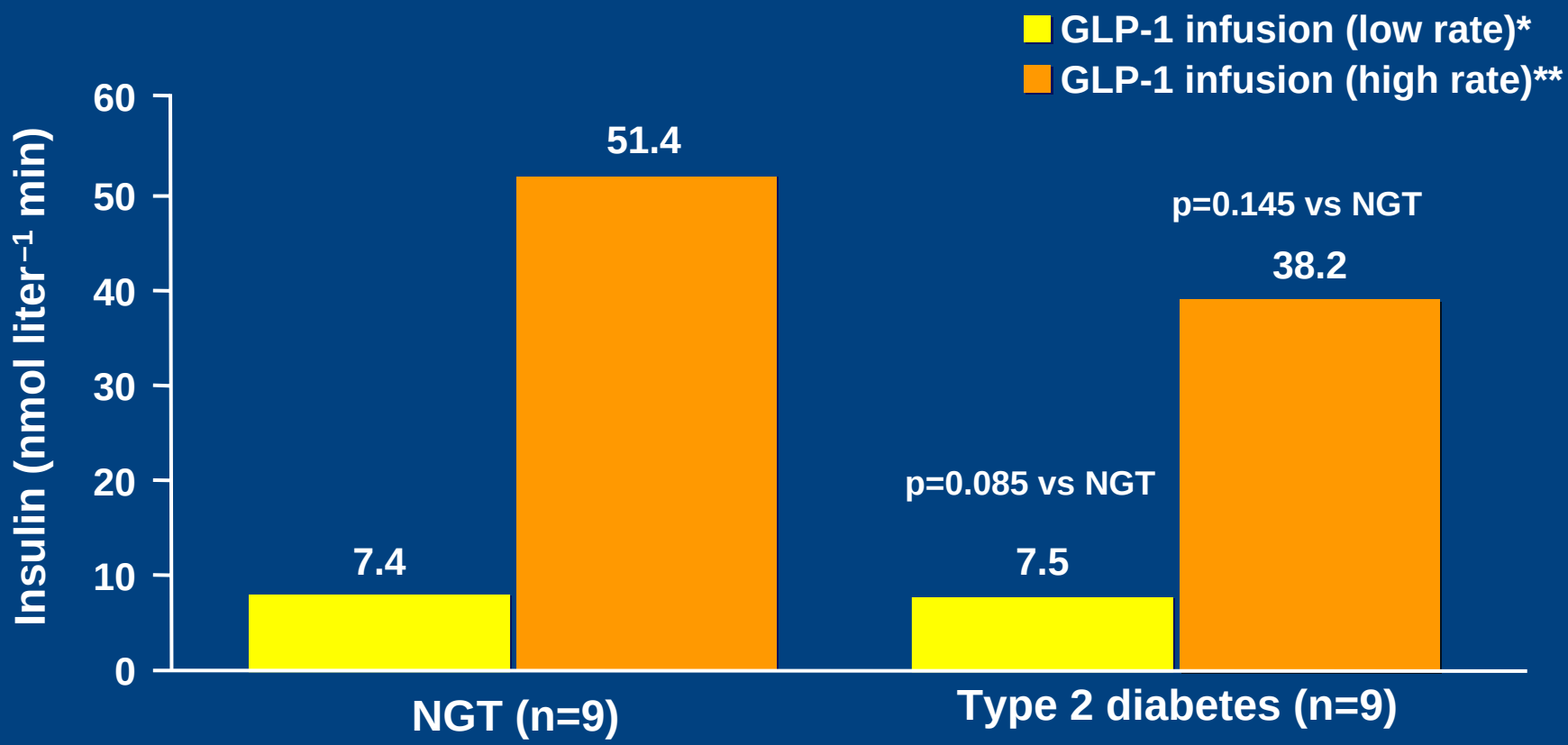
Muller WA, et al. *N Engl J Med*. 1970;283:109-115.

Incretin Axis: Potential Therapeutic Intervention



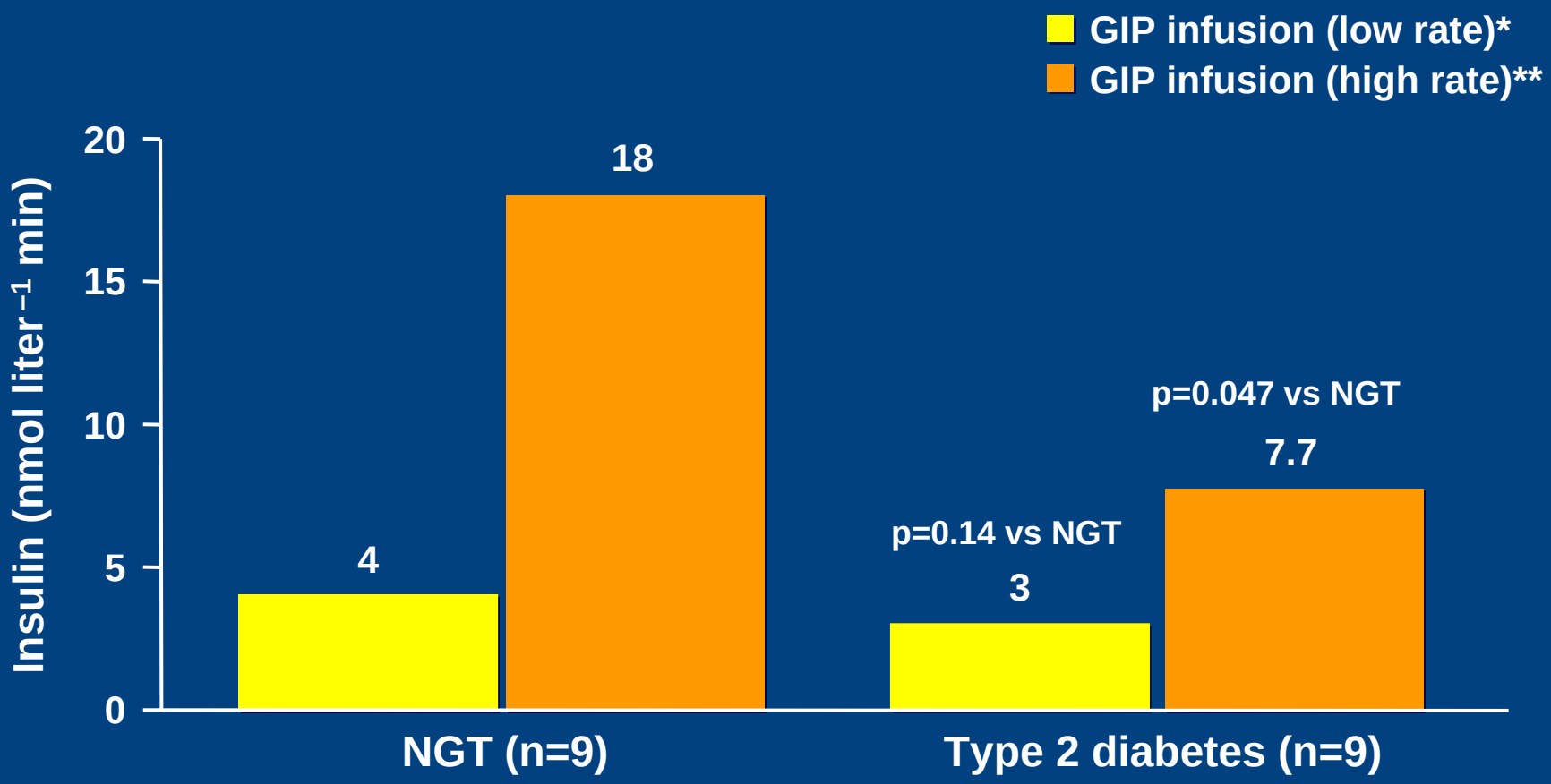
Adapted from Weber A *J Med Chem* 2004;47:4135–4141; Ahrén B *Curr Diabetes Rep* 2003;3:365–372; Drucker DJ *Diabetes Care* 2003;26:2929–2940; Holz GG, Chepurny OG *Curr Med Chem* 2003;10:2471–2483; Deacon CF et al *J Clin Endocrinol Metab* 1995;80:952–957; Drucker DJ *Curr Pharm Des* 2001;7:1399–1412.

GLP-1 Action Is Preserved in Type 2 Diabetes



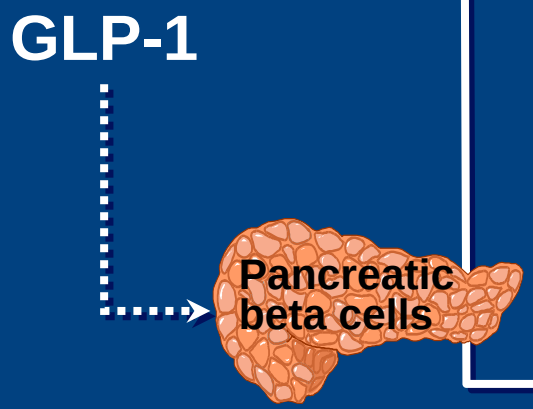
*Low rate=0.4 pmol kg^{-1} min^{-1}.
**High rate=1.2 pmol kg^{-1} min^{-1}.
NGT=normal glucose tolerance.
Nauck MA et al. *J Clin Invest*. 1993;91:301–307.

GIP Action Decreases in Type 2 Diabetes But Is Not Absent



*Low rate=0.8 pmol kg^{-1} min^{-1}.
**High rate=2.4 pmol kg^{-1} min^{-1}.
Nauck MA et al. *J Clin Invest*. 1993;91:301–307.

GLP-1 Improves Multiple Aspects of Beta-Cell Function and Turnover



Functional improvements in beta cell

- Stimulates glucose-dependent insulin release*
- Enhances insulin biosynthesis and stimulates insulin gene transcription**
- Improves beta-cell responsiveness to glucose**
  - By increasing expression of mRNA for glucose transporter-2 and glucokinase

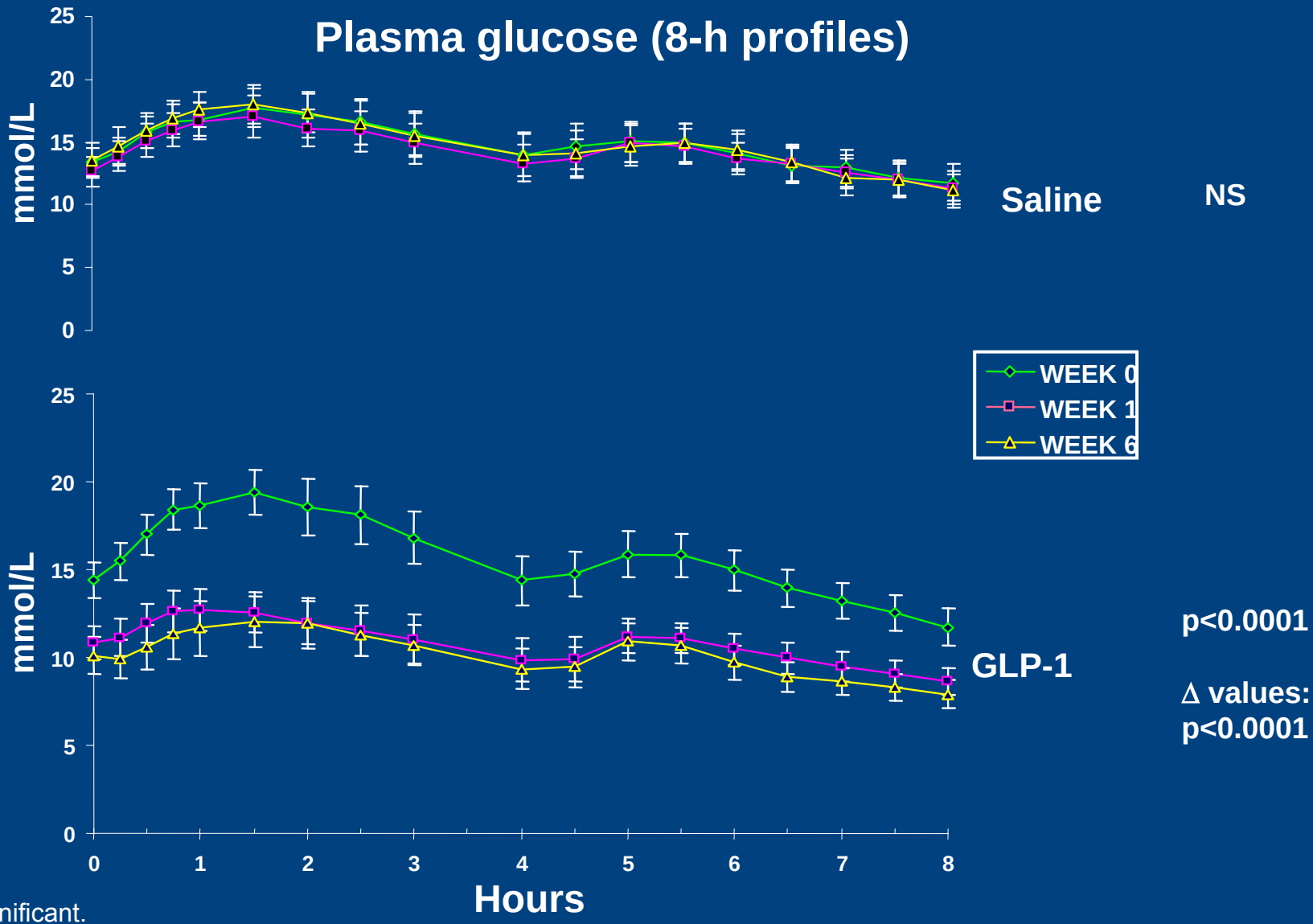
Effects on beta-cell turnover

- Promotes beta-cell proliferation***
- Decreases beta-cell apoptosis**,***

*Studies in patients with type 2 diabetes.
**In vitro studies.
***In vitro and ex vivo studies in rodent models.

Quddusi S et al. *Diabetes Care*. 2003;26:791–798; Drucker DJ. *Mol Endocrinol*. 2003;17:161–171; Holz GG, Chepurny OG. *Curr Med Chem*. 2003;10:2471–2483; Zhou J et al. *Diabetes*. 1999;48:2358–2366; Farilla L et al. *Endocrinology*. 2002;143:4397–4408; Tourrel C et al. *Diabetes*. 2001;50:1562–1570.

Six Weeks of Native GLP-1 Infusion in Human Subjects With Type 2 Diabetes

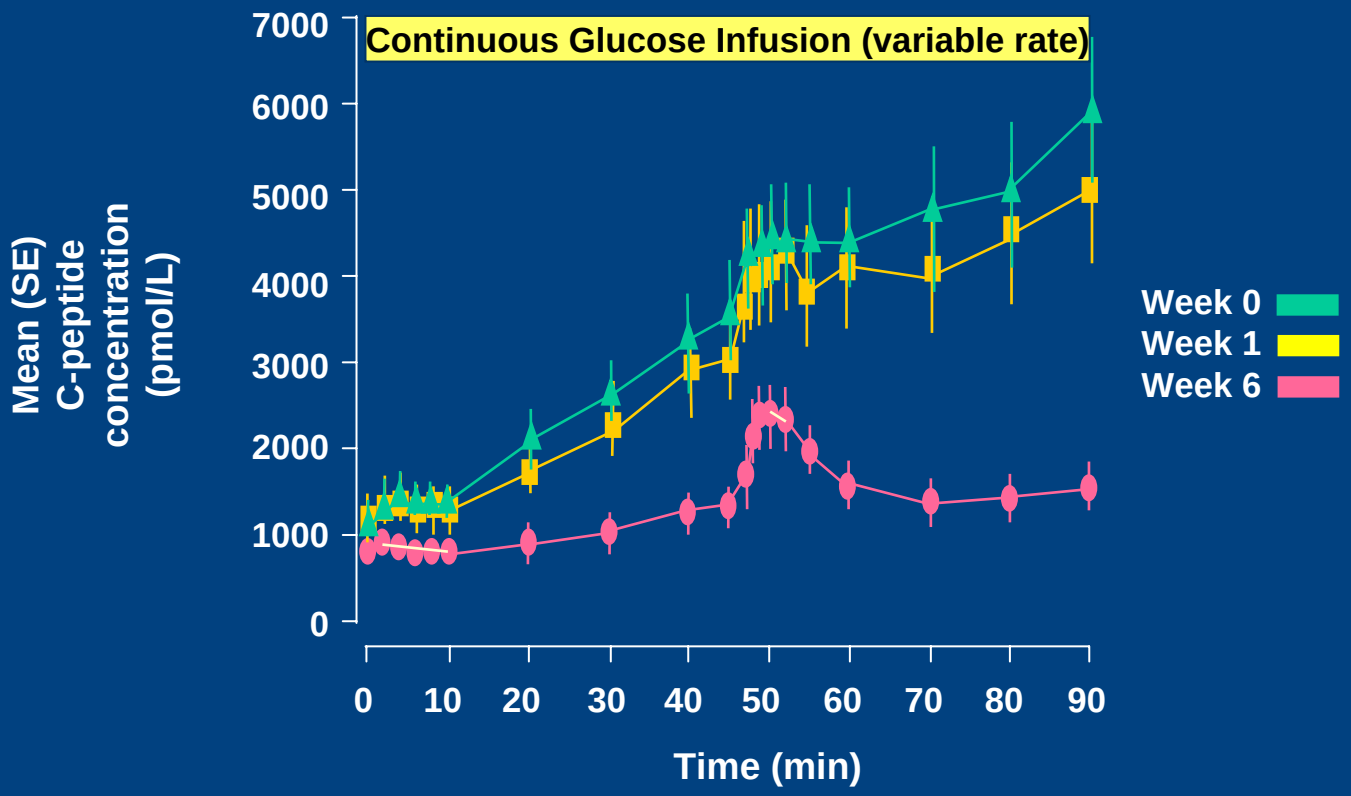


NS=not significant.

Reprinted from Zander M et al. *Lancet*. 2002;359:824–830.

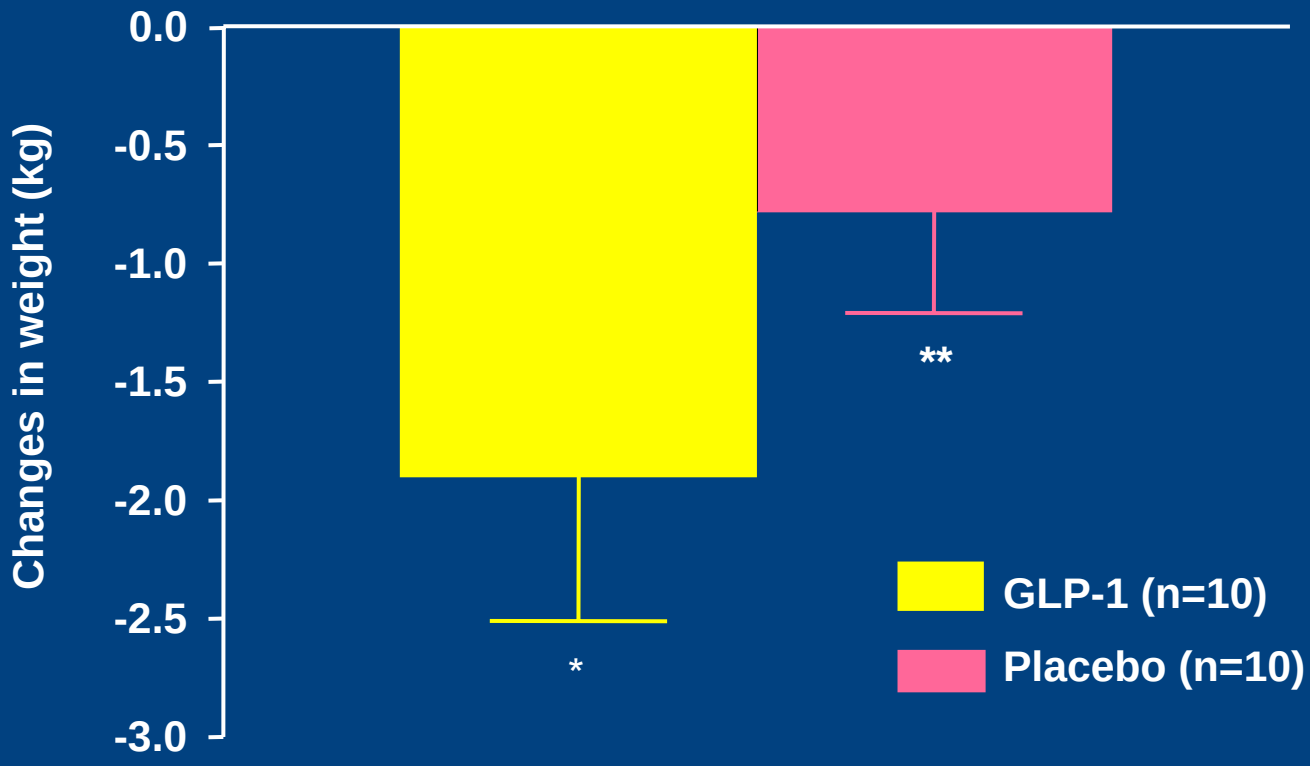
Effect of 6-Week Continuous GLP-1 Infusion on Beta-Cell Function

C-peptide Concentration During 30 mmol/L Hyperglycemic Clamp



5 g L-Arginine intravenous stimulation.
Only data of patients treated with GLP-1 shown.
n=10.
Adapted from Zander M et al. *Lancet*. 2002;359:824–830.

Six Weeks of GLP-1 Infusion Lowers Body Weight in Type 2 Diabetes



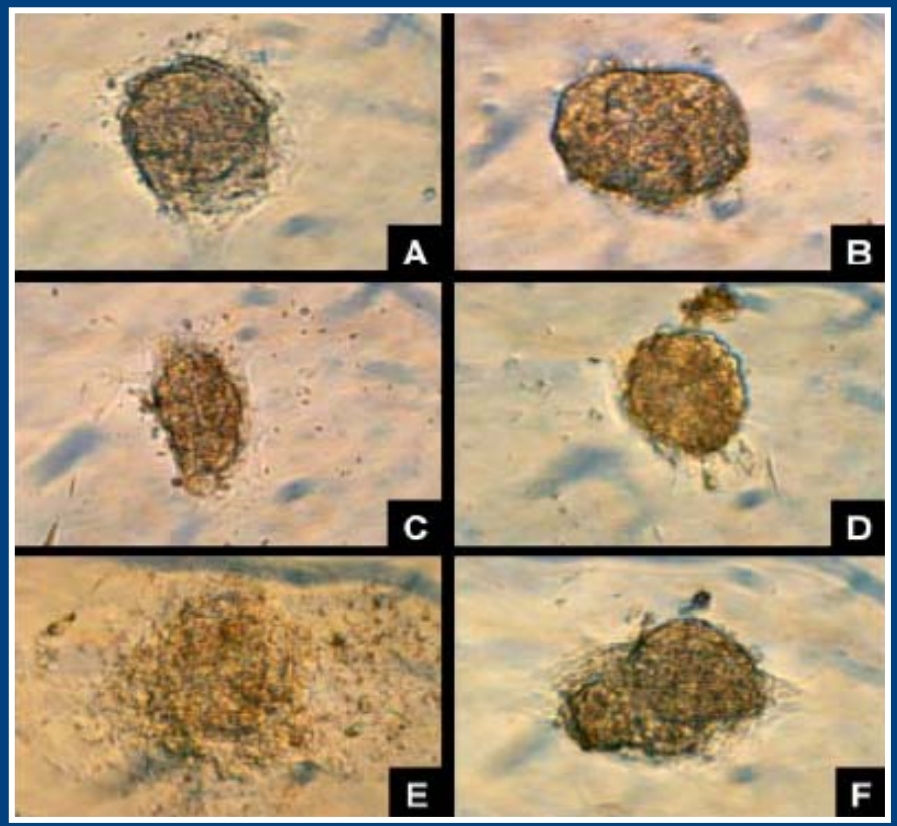
*p=0.02 GLP-1 group.
**p=0.4 saline group.
Difference between groups at Week 6 not significant (p=0.13).
Adapted from Zander M et al. *Lancet*. 2002;359:824–830.

Six Weeks of Native GLP-1 Infusion in Subjects With Type 2 Diabetes

- Reduces fasting and mean plasma glucose by 4.3 and 5.5 mmol/L, respectively
- Reduces HbA1c by 1.3% and normalizes fructosamine
- Results in a weight loss of 1.9 kg presumably because of significantly reduced appetite (range - 4.2 to +1.2)
- Improves insulin sensitivity and enhances beta-cell secretion
- Had no significant side effects

Zander M et al. *Lancet*. 2002;359:824–830.

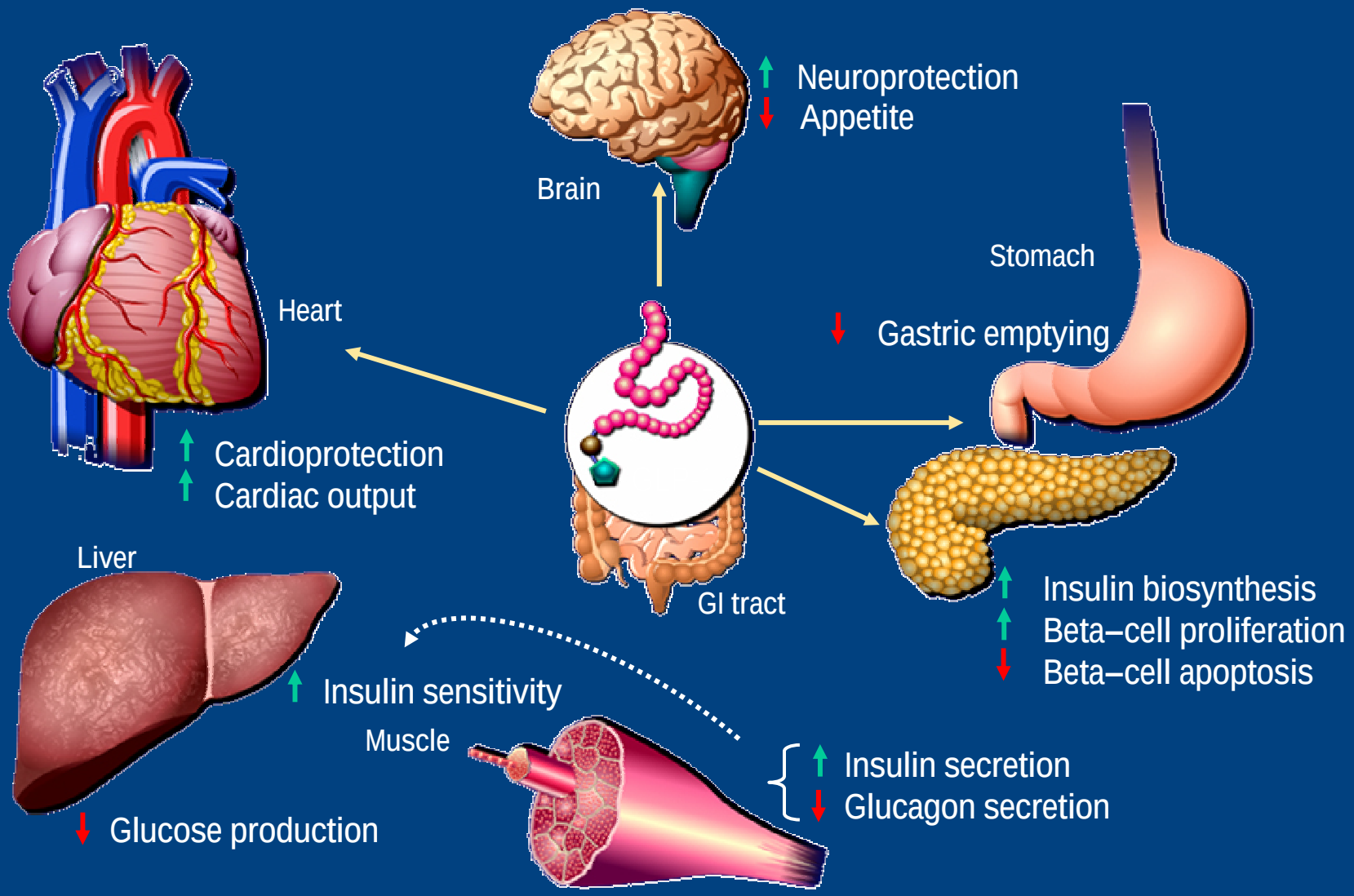
GLP-1 Preserved Morphology of Human Islet Cells In Vitro



Islets treated with GLP-1 in culture were able to maintain their integrity for a longer period of time.

Adapted from Farilla L et al. *Endocrinology*. 2003;144:5149–5158.

Summary of Incretin Actions on Different Target Tissues

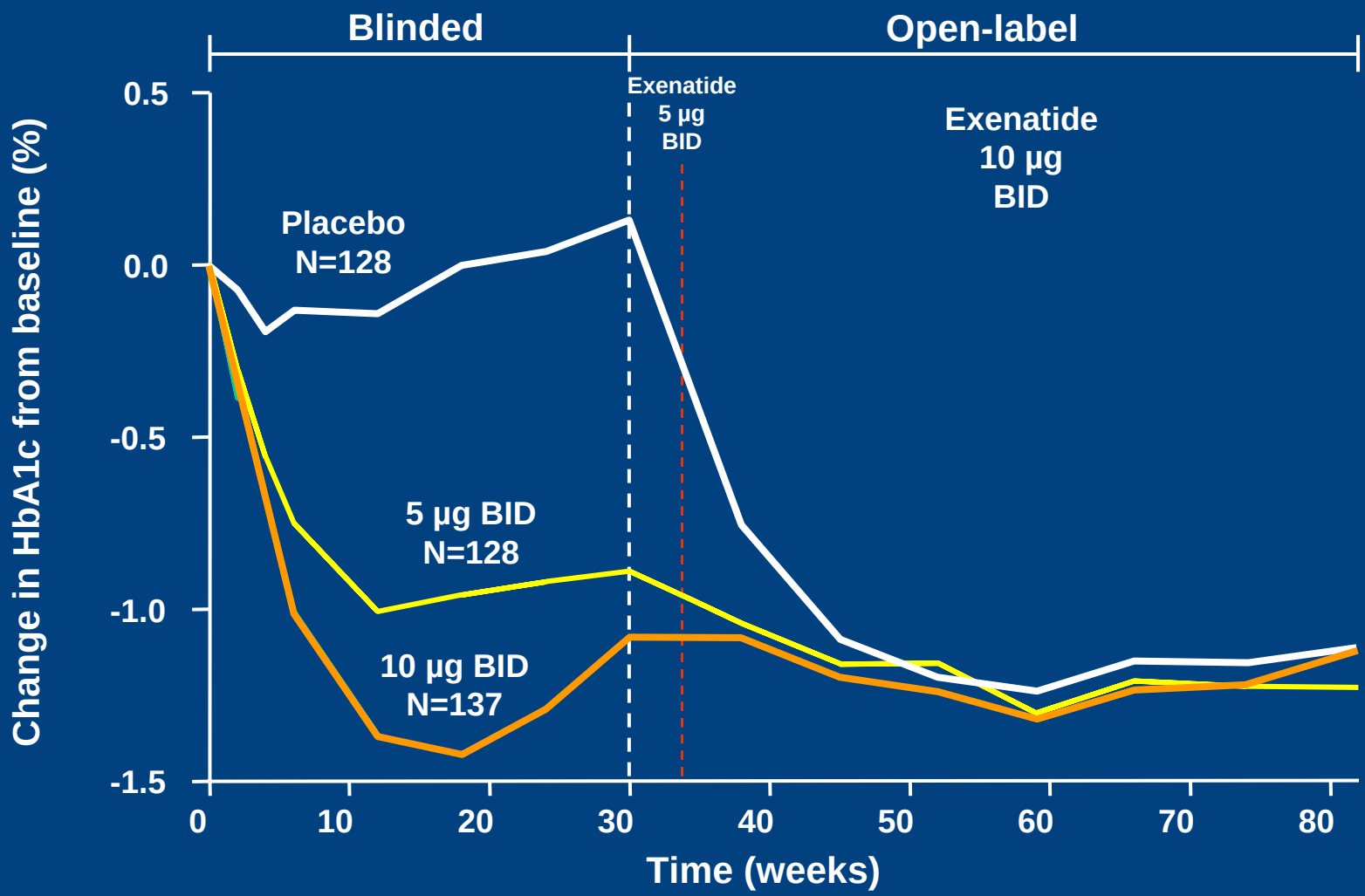


Adapted from Drucker DJ. *Cell Metab*. 2006;3:153–165.

Overview of Incretin-Based Therapies

- Incretin mimetics
  - Compounds that mimic the effect of the endogenous incretin GLP-1
    - ✓ Examples
      - GLP-1R agonists
        - » (ie, Byetta® [exenatide], liraglutide)
  - Subcutaneous injection
- GIP analogs
- Incretin enhancers
  - Compounds that prevent the breakdown of the endogenous incretins GLP-1 and GIP
    - ✓ Examples
      - DPP-4 inhibitors (ie, sitagliptin, vildagliptin)
  - Given orally

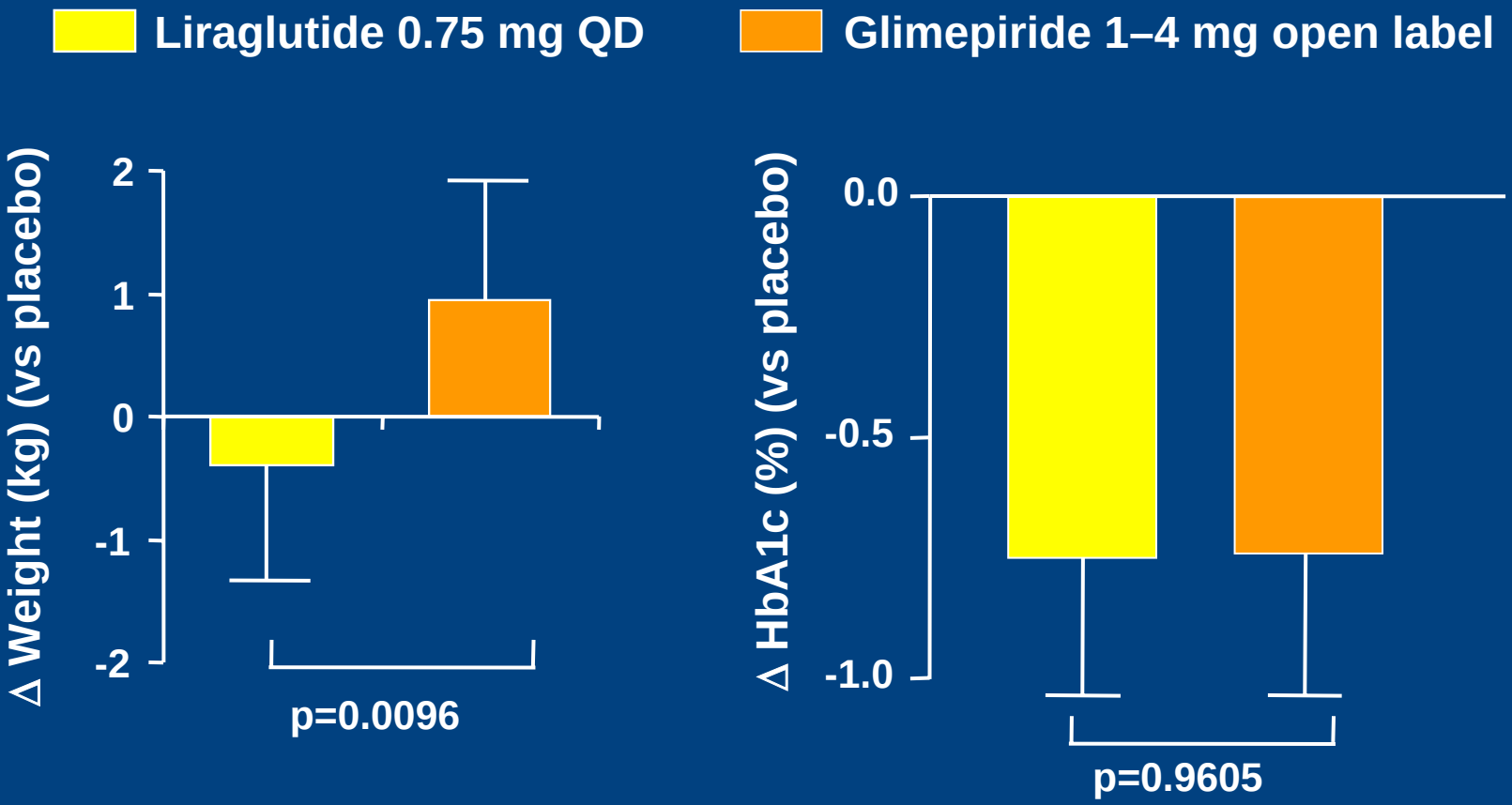
Exenatide Showed Durable Effect on HbA1c



Combined baseline HbA1c=8.3%; Completer population (n=393) at 82 weeks.

Blonde L et al. Poster presented at the 65th Scientific Session of the American Diabetes Association; June 10–14, San Diego, Calif. Abstract 477-P.

Liraglutide Reduces Body Weight and HbA1c in Type 2 Diabetes



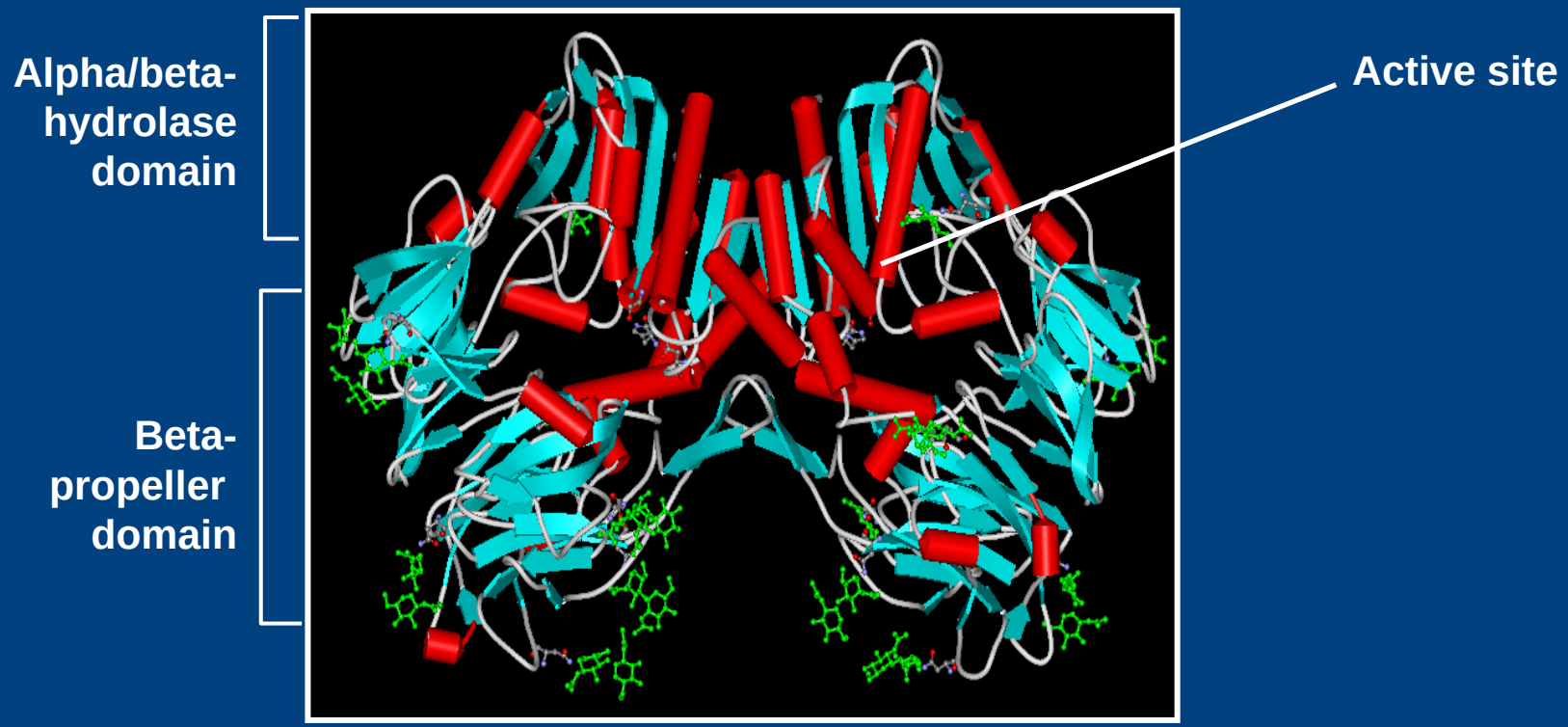
QD=once daily.

Data from Matthews D et al. *Diabetes*. 2002;51(suppl 2):A84.

Long-Acting GLP-1R Agonists

- Exenatide LAR
  - Once-weekly injection
  - 15-week Phase 2 study
  - 2% reduction in HbA1c
  - 50 mg reduction in FPG
  - 9 lbs weight loss
  - 20% nausea rate
  - 12/14 subjects HbA1c <7% after 15 weeks

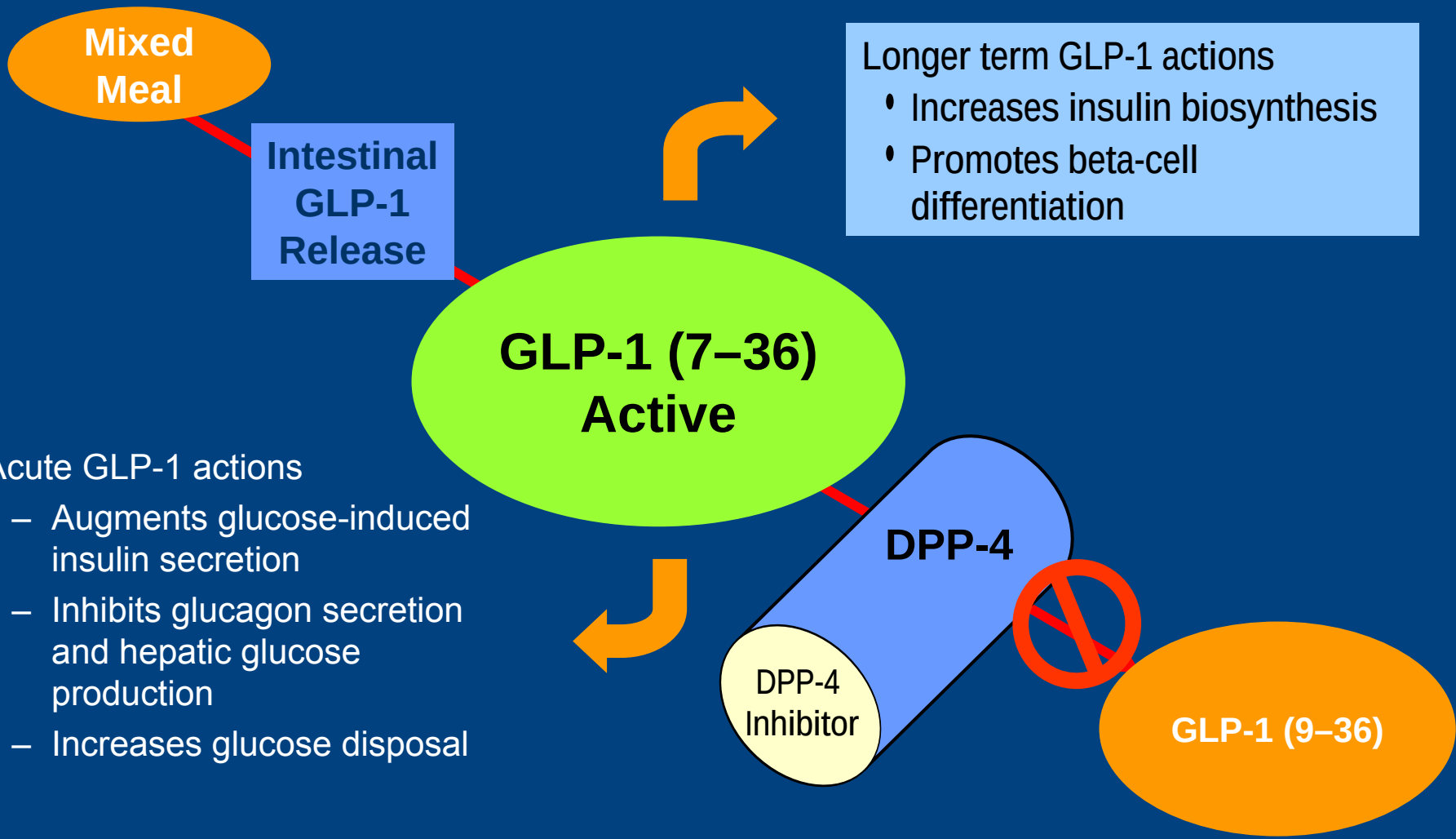
Dipeptidyl Peptidase 4 (DPP-4)



- DPP-4 is a serine protease of the prolyl oligopeptidase enzyme family that exists in 2 forms
  - Membrane-bound
  - Soluble

Evans DM. *I Drugs*. 2002;5:577–585; Drucker DJ. *Expert Opin Investig Drugs*. 2003;12:87–100;
Adapted from Rasmussen HB et al. *Nat Struct Biol*. 2003;10:19–25.

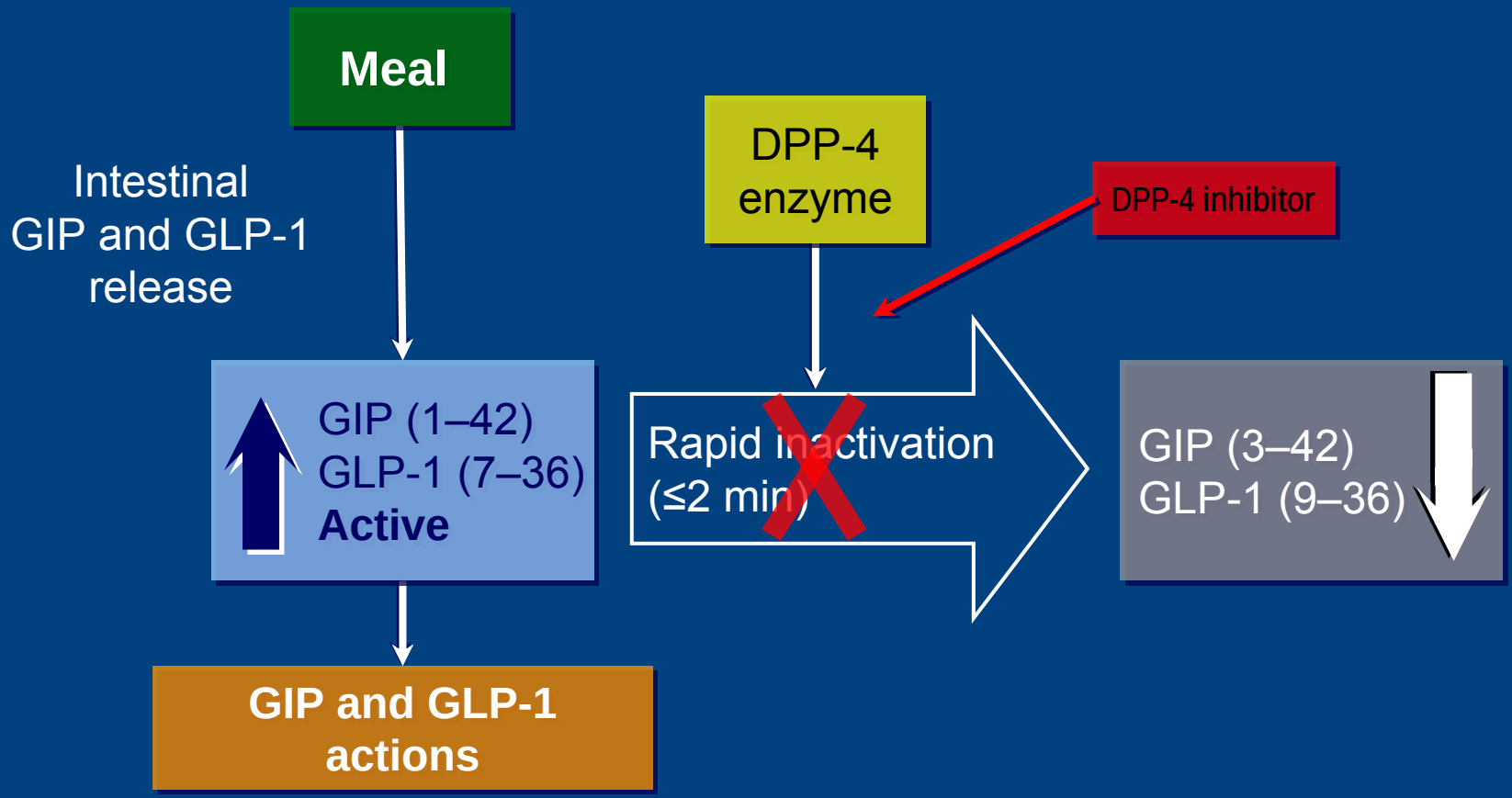
Inhibition of DPP-4 Increases Levels of Intact Biologically Active GLP-1



- Acute GLP-1 actions
  - Augments glucose-induced insulin secretion
  - Inhibits glucagon secretion and hepatic glucose production
  - Increases glucose disposal

Drucker DJ. *Diabetes Care*. 2003;26:2929–2940.

DPP-4 Inhibition Increases Levels of Biologically Active GLP-1 and GIP



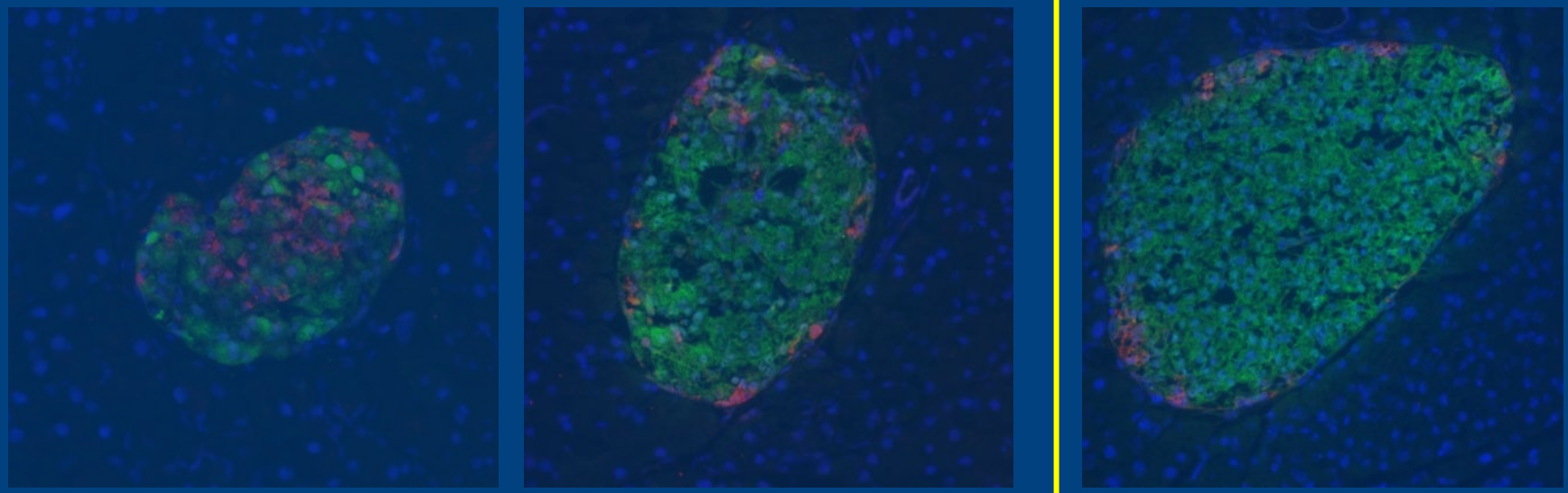
Deacon CF et al. *Diabetes*. 1995;44:1126–1131; Kieffer TJ et al. *Endocrinology*. 1995;136:3585–3596; Ahrén B. *Curr Diab Rep*. 2003;3:365–372; Deacon CF et al. *J Clin Endocrinol Metab*. 1995;80:952–957; Weber AE. *J Med Chem*. 2004;47:4135–4141.

DPP-4 Inhibitor Restored Pancreatic Islet Beta Cells in Diabetic Mice

Diabetic mouse

Diabetic mouse + DPP-4 inhibitor

Lean control mouse

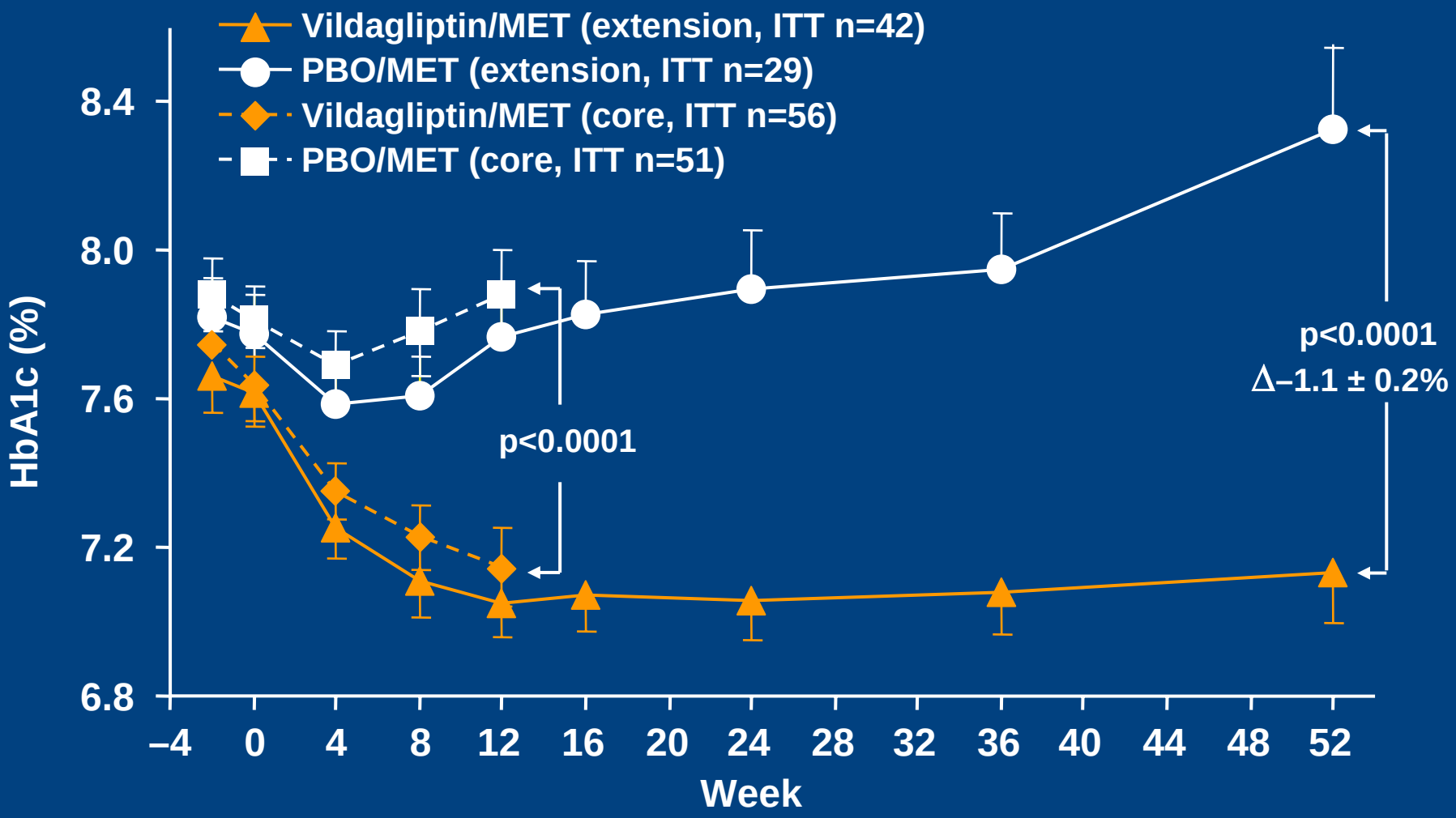


Green: Insulin-producing beta cell

Red: Glucagon-producing alpha cell

Zhang BB et al. Poster presented at the 64th Scientific Session of the American Diabetes Association, Orlando, Florida. June 2004.

Vildagliptin Therapy Significantly Lowered HbA1c Over the Course of 1 Year

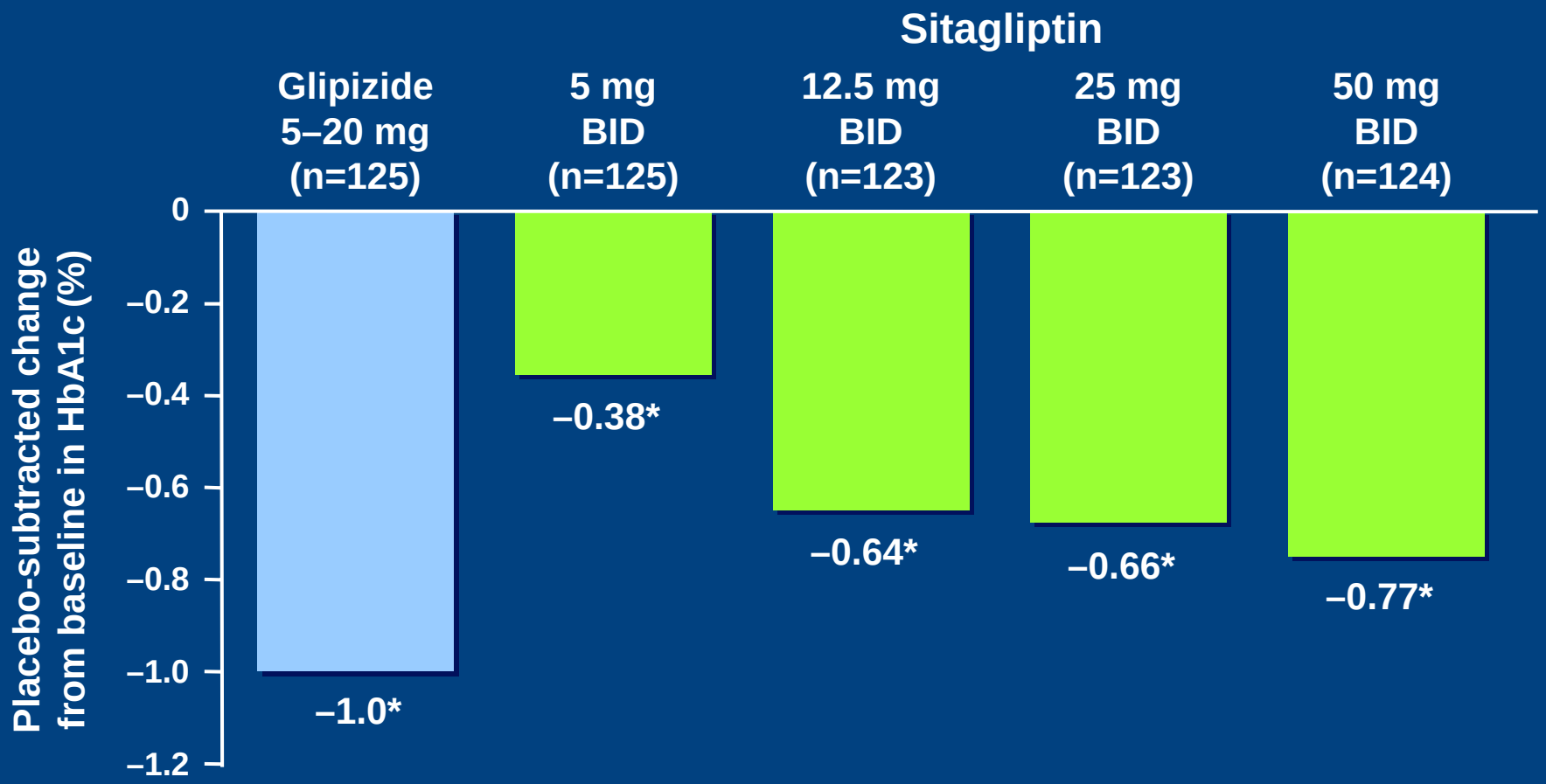


MET=metformin; PBO=placebo; ITT=intent to treat.

Adapted from Ahrén B et al. *Diabetes Care*. 2004; 27:2874–2880.

BID Dose-Range Finding Study

Sitagliptin Significantly Reduced HbA1c in 12-Week Study of Patients With Type 2 Diabetes



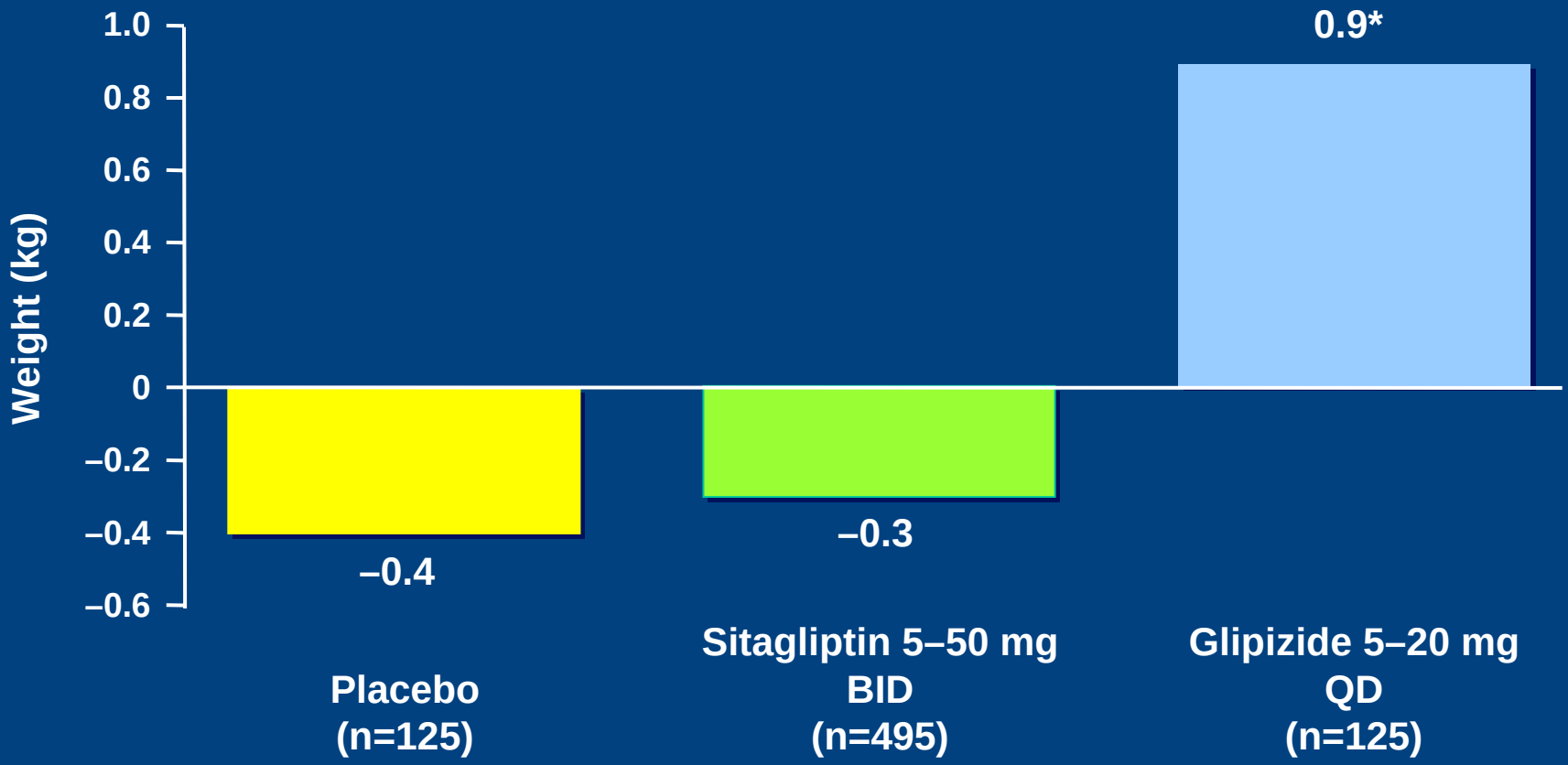
*p<0.001 vs placebo.

Adapted from Scott RS et al. Poster presented at the 41st Annual Meeting of the European Association for the Study of Diabetes (EASD); September 12–15, 2005; Athens, Greece.

BID Dose-Range Finding Study

Sitagliptin Had Neutral Effect on Body Weight

Week 12 change in body weight



QD=once daily.

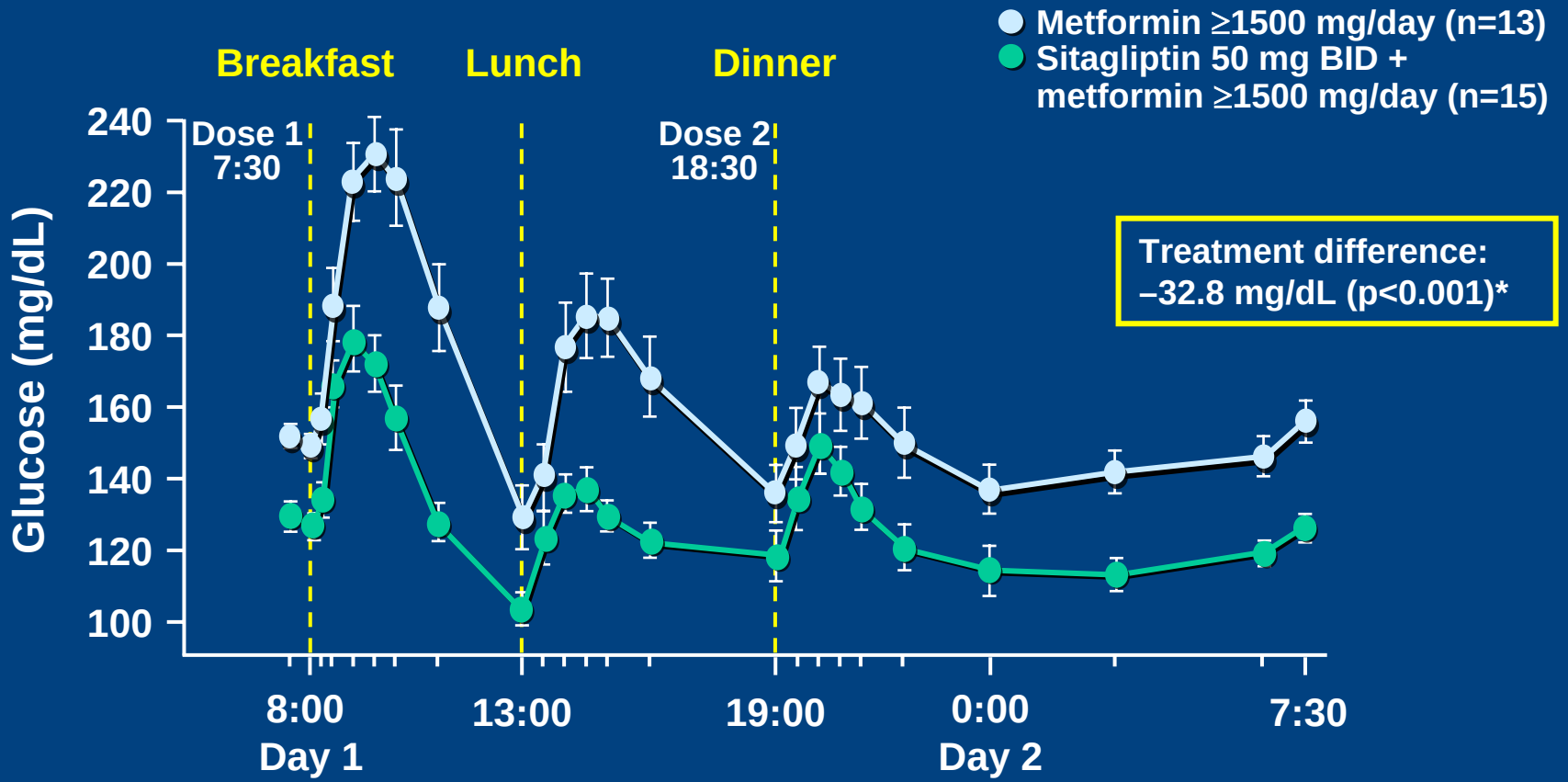
*p<0.001 vs placebo and sitagliptin groups.

Adapted from Scott RS et al. Poster presented at the 41st Annual Meeting of the European Association for the Study of Diabetes (EASD); September 12–15, 2005; Athens, Greece.

Add-On Therapy to Metformin Study

Sitagliptin Improved 24-Hour Glucose Profile vs Metformin Alone

Period 1 Results



*Least-squares mean difference in weighted mean glucose.

Adapted from Brazg RL et al. Poster presented at the 65th Annual Scientific Sessions of the American Diabetes Association; June 10–14, 2005; San Diego, Calif.

GLP-1R Agonists vs DPP-4 Inhibitors

	GLP-1R Agonists	DPP-4 Inhibitors
Administration	Injection	Orally Available
GLP-1 concentrations	Pharmacological	Physiological
Mechanisms of action	GLP-1	GLP-1 + GIP
Activation of portal glucose sensor	No	Yes
↑ Insulin secretion	+++	+
↓ Glucagon secretion	++	++
Gastric emptying	Inhibited	+/-
Weight loss	Yes	No
Expansion of beta-cell mass		
In preclinical studies	Yes	Yes
Nausea and vomiting	Yes	No
Potential immunogenicity	Yes	No