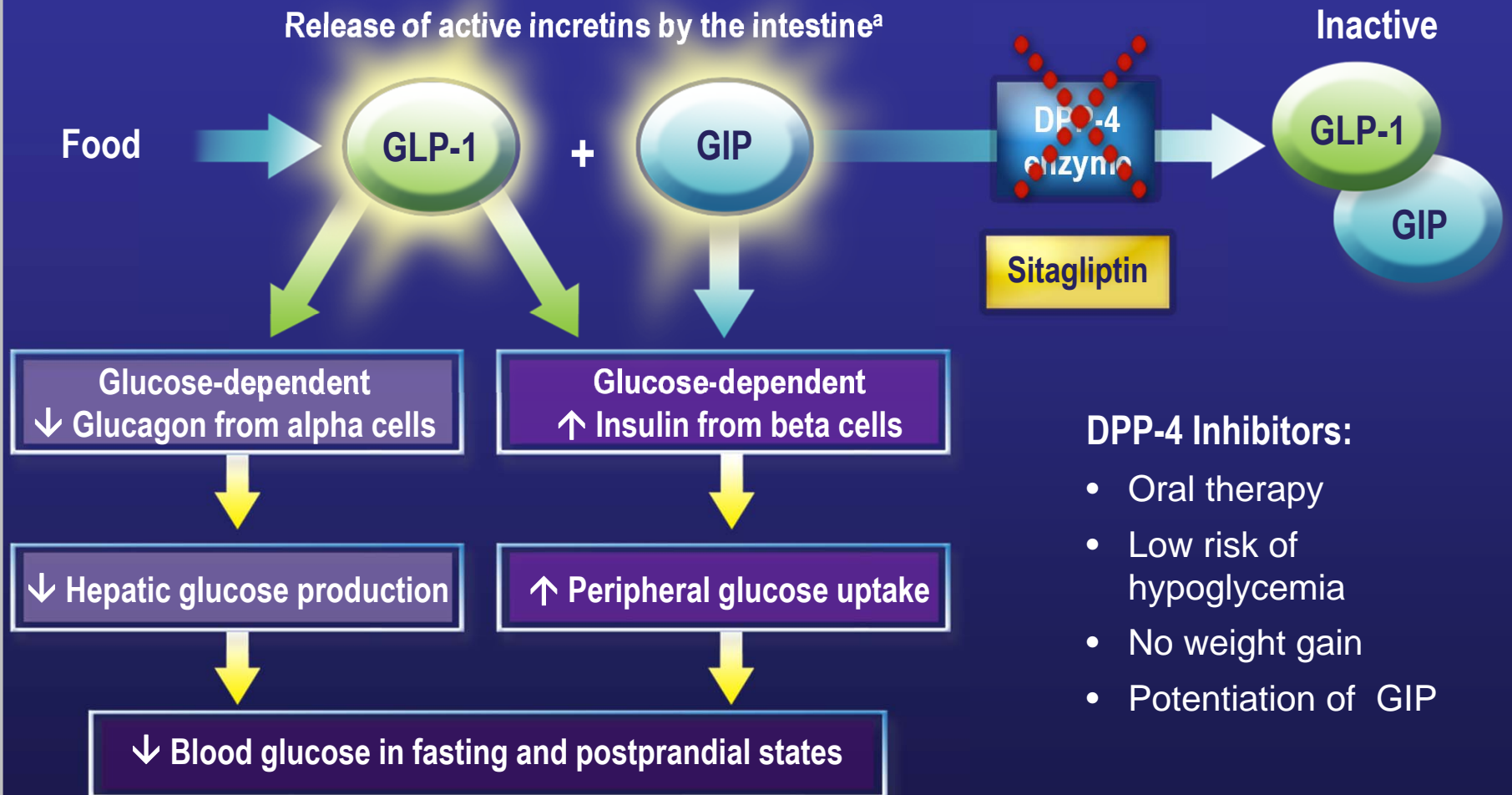


Design and Development of the Selective DPP-4 Inhibitor Sitagliptin

Incretin-Based Therapies: A Glucose-Dependent Mechanism for Diabetes Therapy¹⁻⁴

Release of active incretins by the intestine^a



DPP-4 Inhibitors:

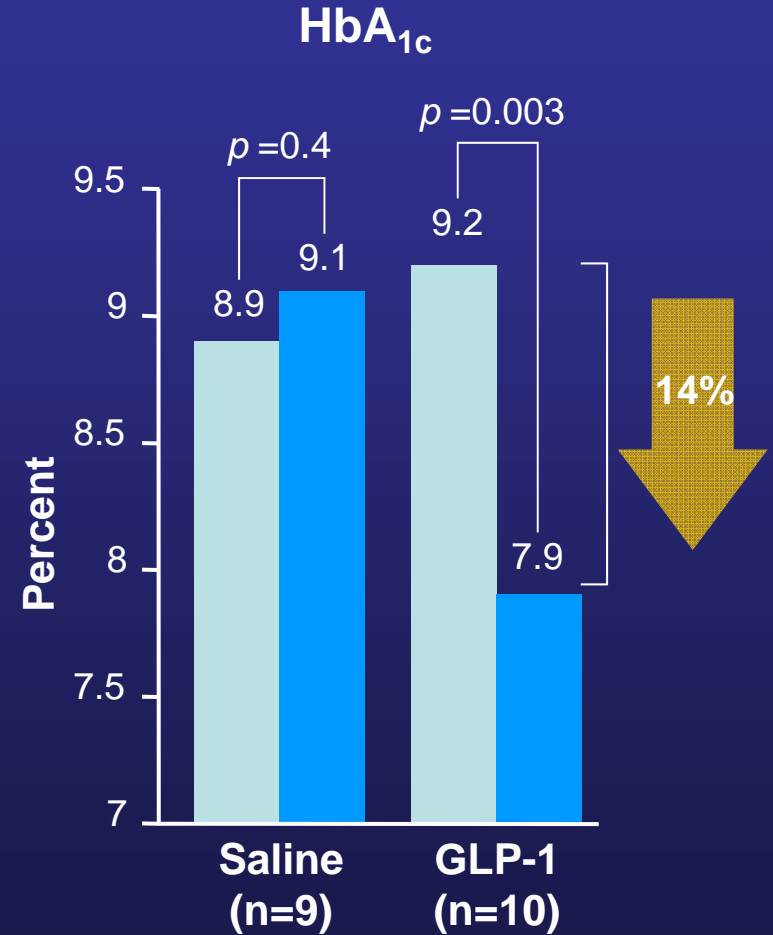
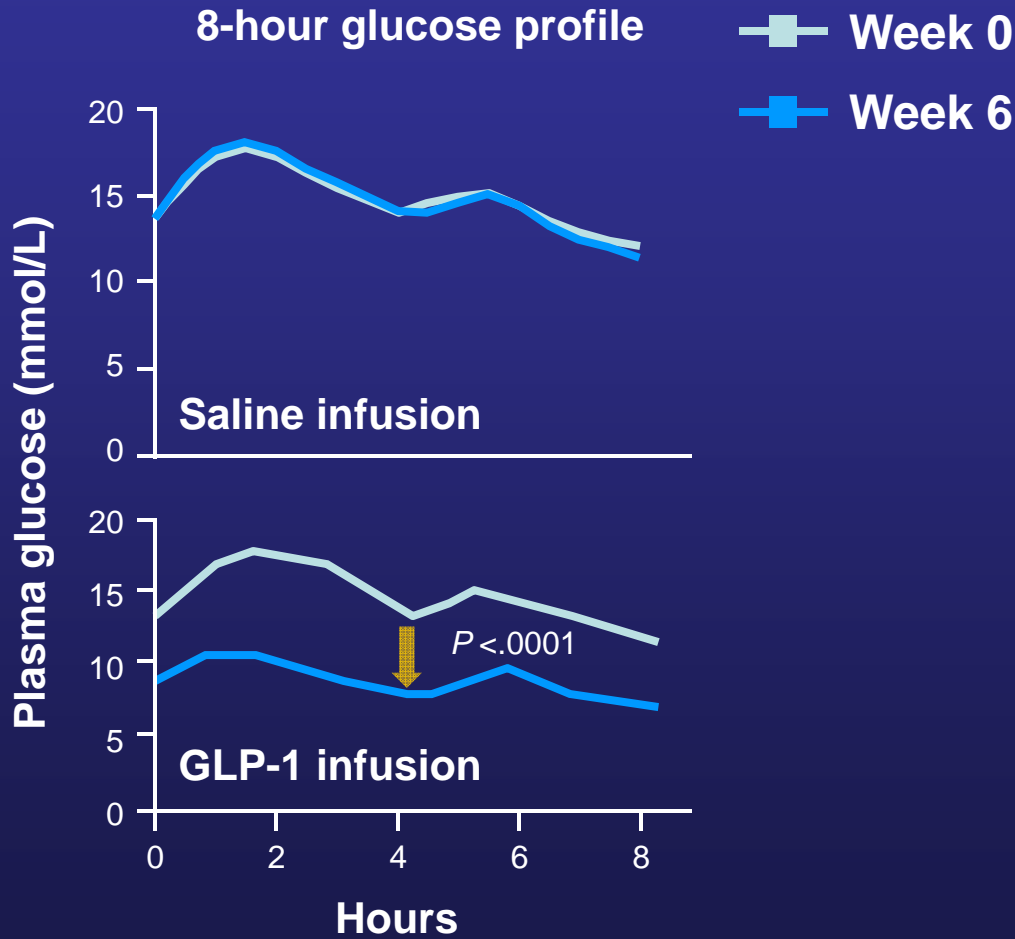
- Oral therapy
- Low risk of hypoglycemia
- No weight gain
- Potentiation of GIP

DPP-4=dipeptidyl peptidase-4; GIP=glucose-dependent insulinotropic peptide; GLP-1=glucagon-like peptide-1.

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

1. Kieffer TJ et al. *Endocr Rev.* 1999;20(6):876–913. 2. Ahrén B. *Curr Diab Rep.* 2003;3(5):365–372. 3. Drucker DJ. *Diabetes Care.* 2003;26(10):2929–2940. 4. Holst JJ. *Diabetes Metab Res Rev.* 2002;18(6):430–441.

6-Week Infusion of GLP-1 in Subjects With Type 2 Diabetes¹



¹GLP-1=glucagon-like peptide-1.

Patients with inadequately controlled type 2 diabetes treated with continuous subcutaneous infusion of saline (n=10) or GLP-1 (n=10) for 6 weeks.

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

GLP-1 Is Rapidly Degraded and Has Limited Clinical Use

Exendin-4 (Exenatide/*Byetta*): A GLP-1 Mimetic With Enhanced Stability

Amino Acid Sequences¹

GLP-1(7-36)amide HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR-NH₂

Exendin-4 HEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS

- Exendin-4 shares 53% amino acid identity with GLP-1²
- Exendin-4 and GLP-1 have similar binding affinity at the GLP-1 receptor³
- Exendin-4 is resistant to proteolytic cleavage⁴



Gila Monster (*H. suspectum*)

¹GLP-1=glucagon-like peptide-1.

²Chen Y et al. *J Biol Chem.* 1997;272:4108-4115.

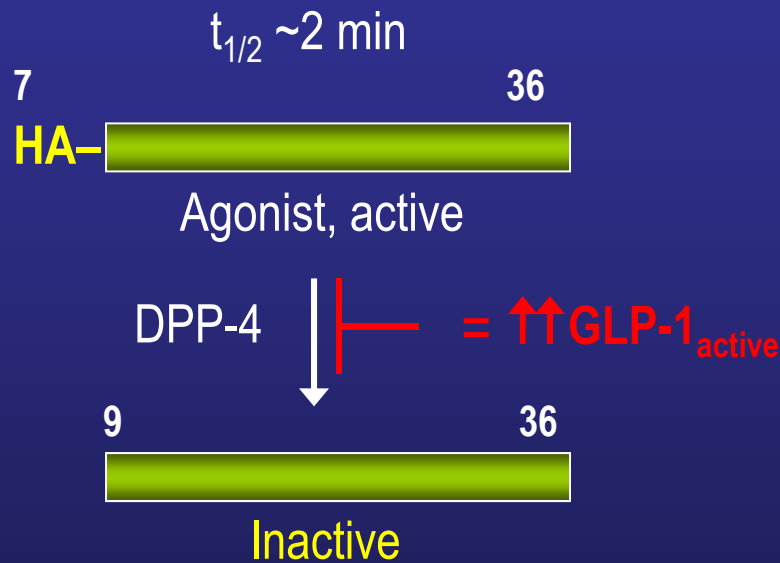
³Ng J et al. *J Biol Chem.* 1992;267:7402-7405.

⁴Booke R et al. *J. Biol. Chem.* 1993;268:19650-19655.

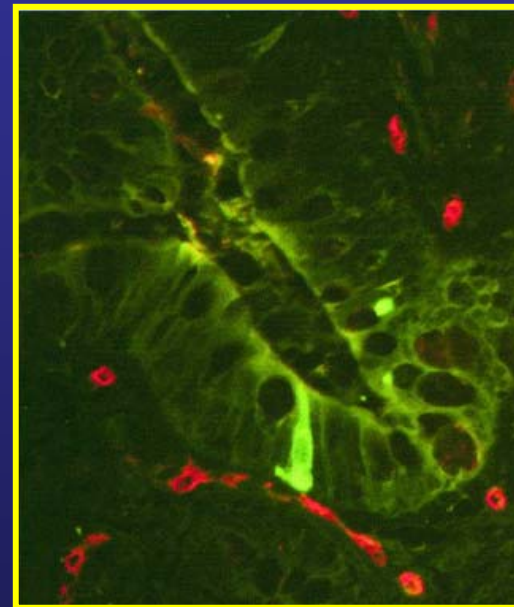
⁵Trucker D. *Diabetes Care.* 2003; 26:2929-2940.

DPP-4 Inactivates GLP-1 and GIP

DPP-4 cleavage of GLP-1¹



Double staining for DPP-4 and GLP-1 in the human ileum²



Red:
DPP-4-positive capillaries

Green:
GLP-1-positive L cell

- DPP-4 inhibitors provide an oral approach to incretin-based therapy.³

¹DPP-4=dipeptidyl peptidase-4; GIP=glucose-dependent insulinotropic peptide; GLP-1=glucagon-like peptide-1.
 Trucker DJ. *Diabetes Care*. 2003; 26:2929–2940.
 Hansen L et al. *Endocrinology*. 1999;140:5356–5363.
 Heacon CF et al. *Diabetes*. 1995;44:1126–1131.

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