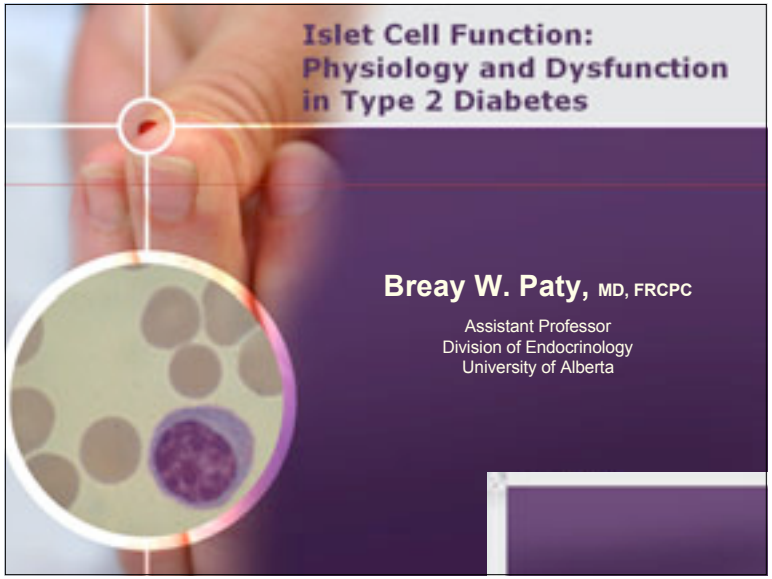
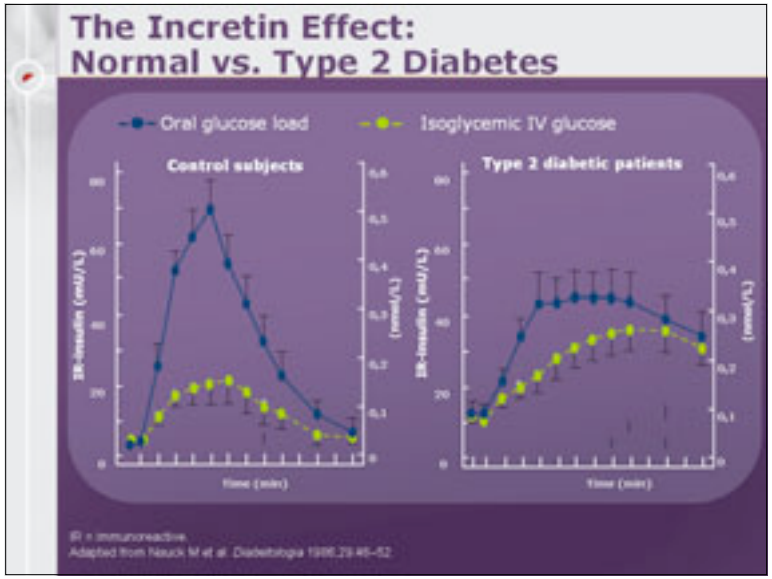
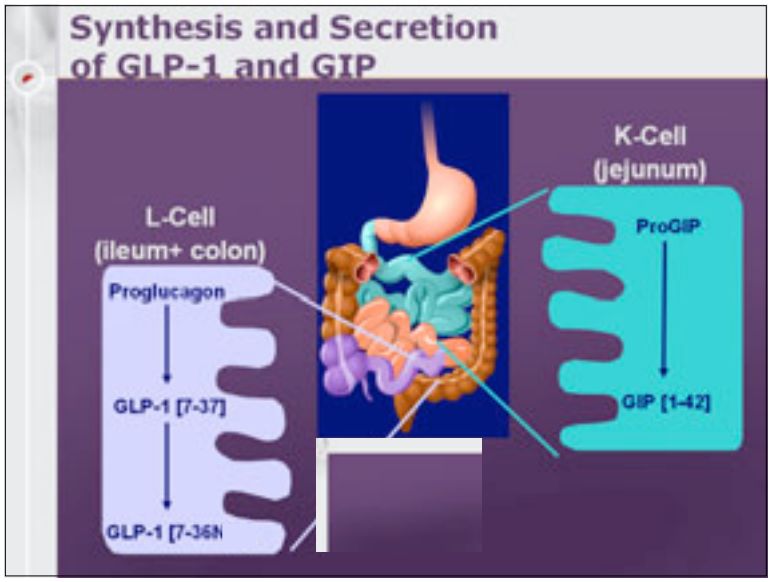
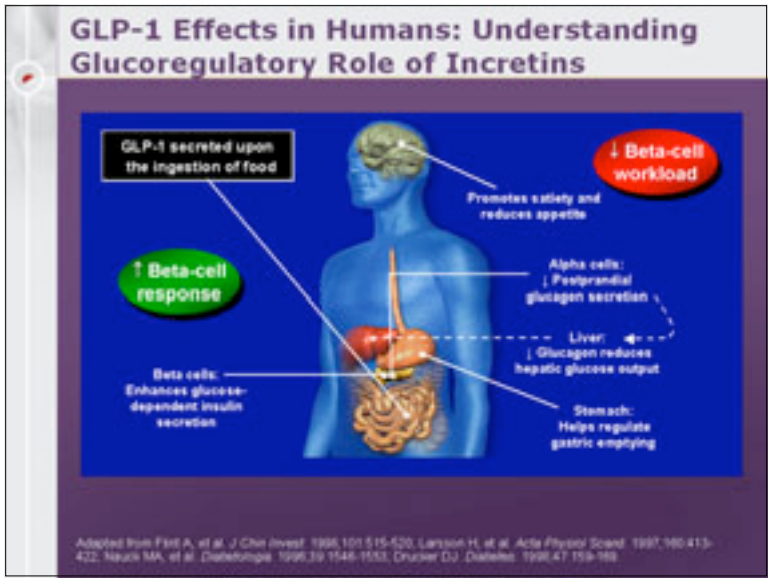
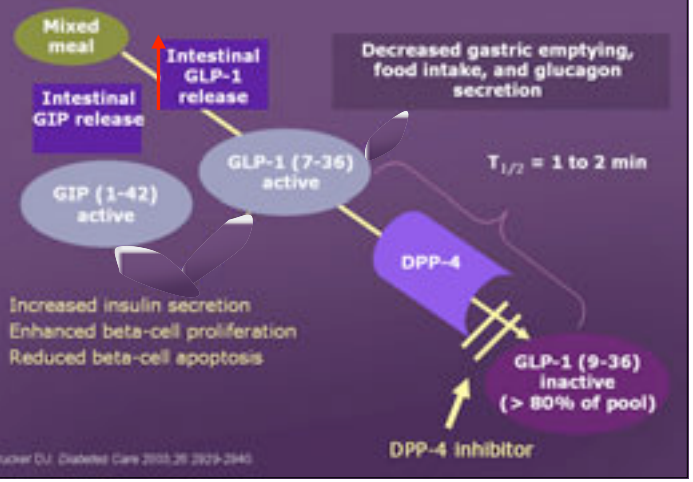

Islet Cell Function:
Physiology and Dysfunction
in Type 2 Diabetes
Breay W. Paty, MD, FRCPC
Assistant Professor
Division of Endocrinology
University of Alberta


The Incretin Effect:
Normal vs. Type 2 Diabetes
Oral glucose load
Isoglycemic IV glucose
Control subjects
Type 2 diabetic patients
IR = immunoreactive
Adapted from Nauck M et al. Diabetologia 1986;29:46–52

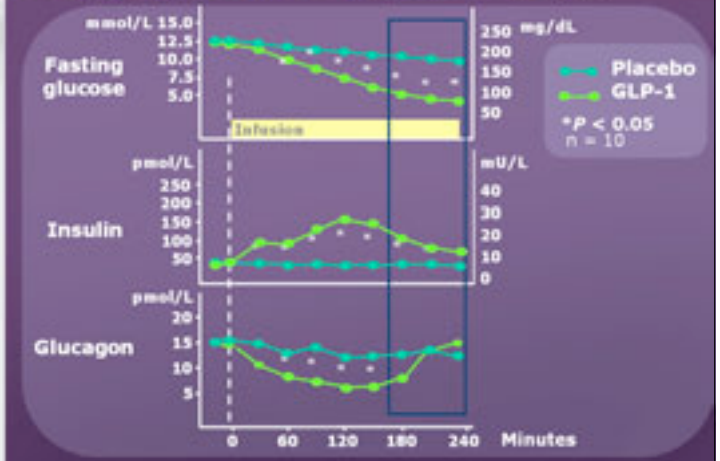

Synthesis and Secretion
of GLP-1 and GIP
L-Cell
(ileum+ colon)
Proglucagon
GLP-1 [7-37]
GLP-1 [7-36]
K-Cell
(jejunum)
ProGIP
GIP [1-42]


GLP-1 Effects in Humans: Understanding
Glucoregulatory Role of Incretins
GLP-1 secreted upon
the ingestion of food
↓ Beta-cell
workload
Promotes satiety and
reduces appetite
↑ Beta-cell
response
Alpha cells:
↓ Postprandial
glucagon secretion
Liver:
↓ Glucagon reduces
hepatic glucose output
Beta cells:
Enhances glucose-
dependent insulin
secretion
Stomach:
Helps regulate
gastric emptying

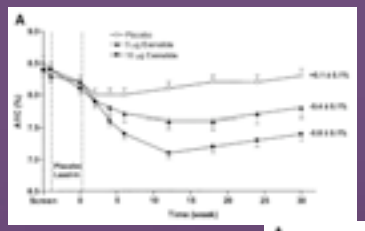
Incretin Secretion and DPP-4–Mediated Inactivation



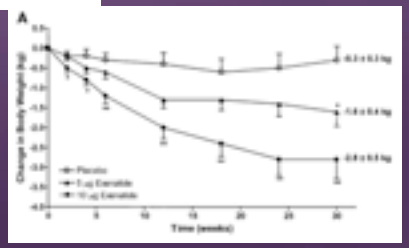
GLP-1 Actions Glucose-Dependent in Patients with Type 2 Diabetes



Exenatide (Byetta®) with Metformin vs. Placebo



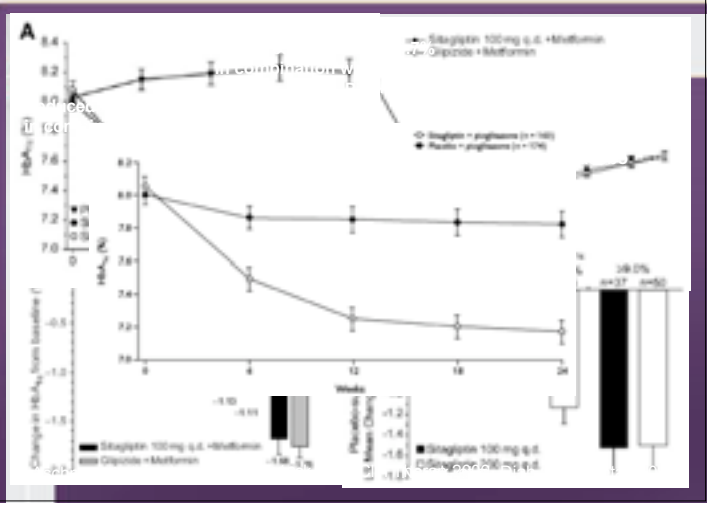
Dose dependent reduction in A1c



Dose-dependent reduction in body weight

DeFronzo, et al Diabetes Care 2005

Sitagliptin (Januvia®)



Incretin-Modifying Therapies

	GLP-1 analogues		DPP-4 Inhibitors	
	Exenatide (Byetta™)	Liraglutide (NN2211)	Vildagliptin (Galvus®)	Sitagliptin (Januvia™)
Administration	Injection		Tablet	
Half-life	2-4 hours (LAR 1 week)	12-14 hours	2.5 hours	12-14 hours
Dosing	b.i.d.	q.d.	b.i.d.	q.d.
Dose	5-10 µg b.i.d. (LAR 2 mg/wk)	Up to 2 mg	50 mg b.i.d.	100 mg

LAR: long-acting release formulation

Incretin-Modifying Therapies (2)

	GLP-1 analogues		DPP-4 Inhibitors	
Insulin secretion	**Increased**		**Increased**	
Glucagon secretion	**Decreased**		**Decreased**	
A_{1c} reduction	**-0.8% to 2.0%**	**-0.8% to 2.0%**	**-0.5% to -1.5%**	**-0.5% to -1.5%**
FPG reduction	**↓ (LAR better)**	**↓↓↓**	**↓**	**↓**

Incretin-Modifying Therapies (3)

	GLP-1 analogues		DPP-4 Inhibitors	
	Exenatide (Byetta™)	Liraglutide (NN2211)	Vildagliptin (Galvus®)	Sitagliptin (Januvia™)
Body weight reduction	**Yes (3-5 kg)**	**Yes (3-5 kg)**	**No**	**No**
Hypoglycemia	**No**	**No**	**No**	**No**
Nausea	**Yes**	**Less**	**None**	**None**
Antibody production	**Yes (45%)**	**No**	**None**	**None**
β cell mass	**Probable**		**Possible**	

Key Points

Incretin-modifying therapies

- New treatment strategy in T2 Diabetes
- Reduces hyperglycemia, A1C levels
- No hypoglycemia or weight gain
- Possible beta cell preservation
- Incretin mimetics - higher levels of GLP-1
  - weight loss, nausea
- DPP-4 inhibitors - oral administration
  - little/no nausea