



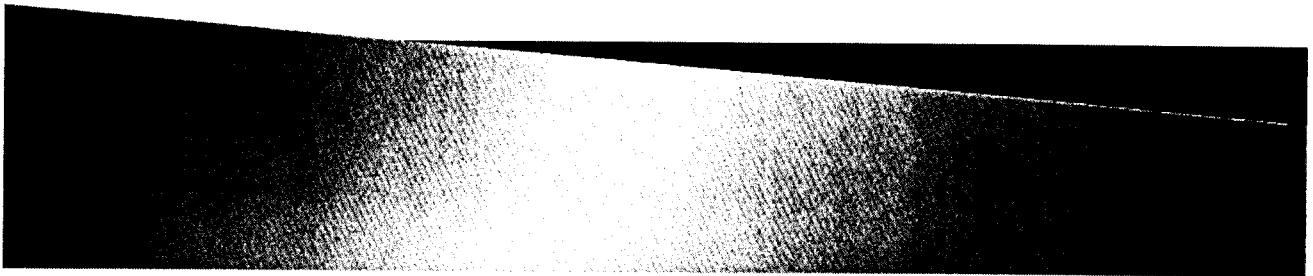
السنة الثالثة

تأثير الأدوية 2

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8م

Drugs for Diabetes



Pharmacotherapy

- Insulin
- Pramlinitide
- Exenatide

- Sulfonylureas
- Meglitinides
- Biguanides
- Thiazolidinediones (TZDs)
- DPP-IV inhibitors
- α -glucosidase inhibitors
- SGLT₂ inhibitors

Insulin

- Anabolic & anticatabolic hormone
- Necessary for carbohydrate, protein & fat metabolism
- Required for all type 1 DM patients
- Recommended for type 2 DM patients that do not achieve glycemic control with oral antidiabetic agents
- Insulin strengths in the US
 - 100 units/mL (U-100)
 - 500 units/mL (U-500)
 - only available in regular insulin

Insulin

- Originally derived from bovine & porcine pancreas
- All human insulin in the US now made exclusively by recombinant DNA (rDNA) technology
- Recombinant insulin analogs also available via modification of human insulin molecules
 - synthesized to overcome problems of human insulin
 - onset of action
 - duration of action
 - absorption



Fast-acting analogues

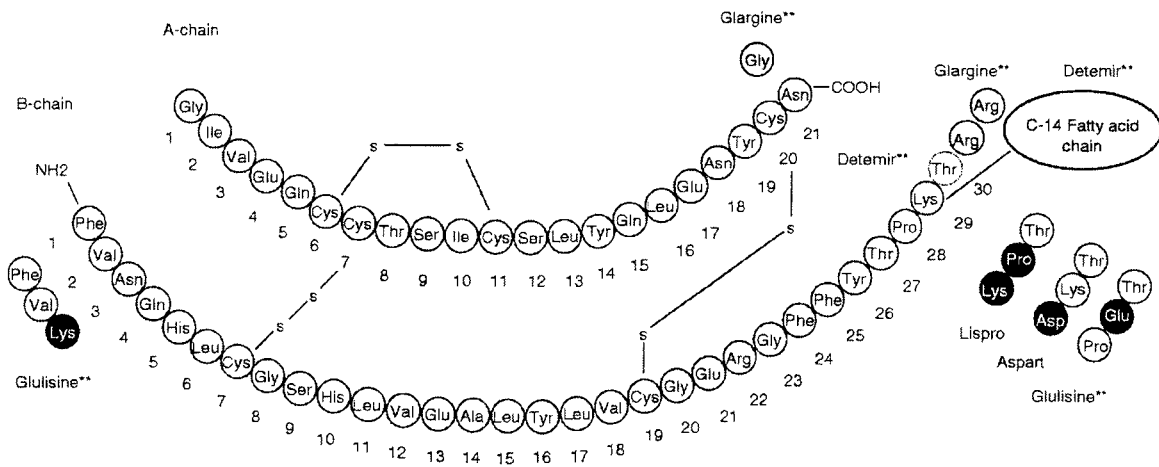
Insulin lispro

Insulin aspart

Long-acting analogues

Insulin glargine

Detemir insulin

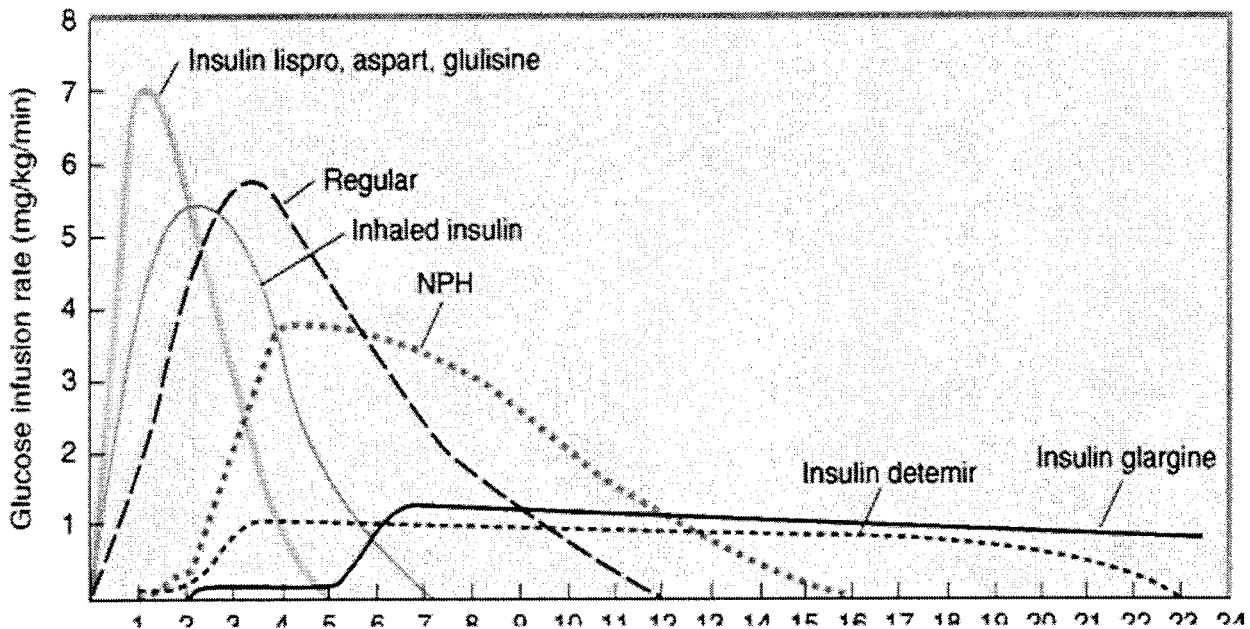


Insulin Pharmacokinetics

Type of Insulin	Onset (Hours)	Peak (Hours)	Duration (Hours)	Maximum Duration (Hours)	Appearance
Rapid-acting					
Aspart	15-30 min	1-2	3-5	5-6	Clear
Lispro	15-30 min	1-2	3-4	4-6	Clear
Glulisine	15-30 min	1-2	3-4	5-6	Clear
Short-acting					
Regular	0.5-1.0	2-3	3-6	6-8	Clear
Intermediate-acting^a					
NPH	2-4	4-6	8-12	14-18	Cloudy
Long-acting					
Detemir	2 hours	6-9	14-24	24	Clear
Glargine	4-5	—	22-24	24	Clear

NPH, neutral protamine Hagedorn.

^aLente and ultralente insulin has been discontinued.



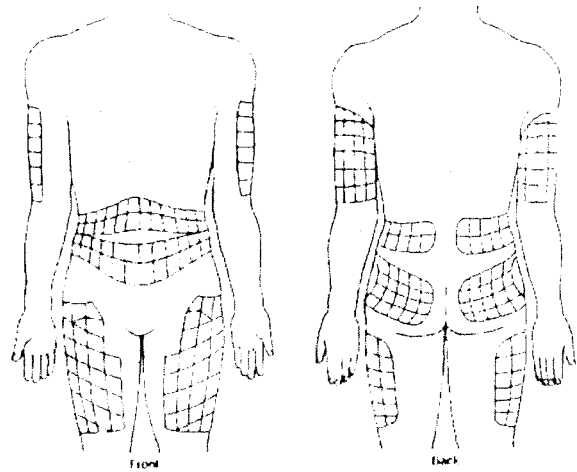
Source: Katzung BG: *Basic & Clinical Pharmacology*, 10th Edition:
<http://www.accessmedicine.com>

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Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2-0.3 U/kg; with the exception of insulin lispro, aspart, and glulisine, duration increases considerably when dosage is increased.

Insulin

- Basal Insulin
 - mimics normal pancreatic insulin secretion with constant levels
 - suppresses glucose production in the fasting & postabsorptive period
- Bolus Insulin
 - mimics spikes of physiologic secretion insulin after eating



Common insulin injection sites

Long-Acting Insulin

- Insulin glargine, insulin detemir
 - mimic basal insulin secretion
 - slow action over 24 hours
 - lower risk of hypoglycemia
 - daily or BID dosing

Long-Acting Insulin

- Mechanism of action
 - insulin glargine
 - low solubility at neutral body pH, microprecipitates form at injection site & are slowly released
 - insulin detemir
 - forms a fatty acid chain that binds interstitial albumin at injection site; causes prolonged absorption
 - dissociated detemir molecules enter circulation & again bind albumin causing further delay in distribution

Intermediate-Acting Insulin

- NPH
 - mimics basal insulin secretion
 - administered twice daily

Short-Acting Insulin

- Regular insulin
 - bolus insulin to control post-prandial spikes
 - inject 30 to 60 min prior to meals due to onset of action
 - may cause postprandial hyperglycemia due to rapid increase in blood glucose after meals & delayed onset of action
 - late hypoglycemia due to prolonged duration of action

Rapid-Acting Insulin

- Insulin lispro, insulin aspart, insulinalgulisine
 - recombinant insulin analogs
 - bolus insulin
 - faster absorption & shorter duration of action than regular insulin
 - administer 5 to 15 min AC (AC = before meal)
 - superior postprandial glucose lowering of glucose compared to regular insulin

Pre-mixed Insulin Products

Trade/Generic Name	Administration Options	Room Temperature ^b Expiration
Premixed insulin analogs		
Humalog Mix 75/25 (75% neutral protamine lispro, 25% lispro)	Vial, prefilled pen	Vial: 28 days; pen: 10 days
NovoLog Mix 70/30 (70% aspart protamine suspension, 30% aspart)	Vial, prefilled pen, 3-mL pen cartridge	Vial: 28 days; others: 14 days
Humalog Mix 50/50 (50% neutral protamine lispro/ 50% lispro)	3-mL pen	10 days
NPH-regular combinations		
Humulin 70/30	Vial, prefilled pen	Vial: 28 days; pen: 10 days
Novolin 70/30	Vial, pen cartridge, InnoLet ^c	Vial: 30 days; others: 10 days
Humulin 50/50	Vial	28 days

^cInnoLet: A prefilled insulin pen with a "kitchen timer" type of dial for determining the number of insulin units. Can be useful in patients with impaired eyesight or dexterity.

Insulin Dose

- Individualized dosing
- Type 1 DM: average daily requirement 0.5-0.6 units/kg
 - basal insulin 50%
 - mealtime insulin 50%
- Type 2 DM: doses vary depending on degree of insulin resistance
 - 0.7 to 2.5 units/kg or more

How should glycemia in T1D be managed?

Insulin Regimens

- Insulin is required for survival in T1D
- Physiologic regimens using insulin analogs should be used for most patients

Multiple daily injections (MDI)

- 1-2 injections basal insulin per day
- Prandial insulin injections before each meal

Continuous subcutaneous insulin infusion (CSII)

- Insulin pump using rapid acting insulin analog

How should glycemia in T1D be managed?

Pharmacokinetics of Insulin

	Agent	Onset (h)	Peak (h)	Duration (h)	Considerations
Basal	NPH	2-4	4-10	10-16	Greater risk of nocturnal hypoglycemia compared to insulin analogs
	Glargine Detemir	~1-4	No pronounced peak*	Up to 24 [†]	Less nocturnal hypoglycemia compared to NPH
Basal-Prandial	Regular U-500	≤0.5	~2-3	12-24	<ul style="list-style-type: none"> • Inject 30 min before a meal • Indicated for highly insulin resistant individuals • Use caution when measuring dosage to avoid inadvertent overdose
Prandial	Regular	~0.5-1	~2-3	Up to 8	<ul style="list-style-type: none"> • Must be injected 30-45 min before a meal • Injection with or after a meal could increase risk for hypoglycemia
	Aspart Gulisine Lispro Inhaled insulin	<0.5	~0.5-2.5	~3-5	<ul style="list-style-type: none"> • Can be administered 0-15 min before a meal • Less risk of postprandial hypoglycemia compared to regular insulin

* Exhibits a peak at higher dosages.

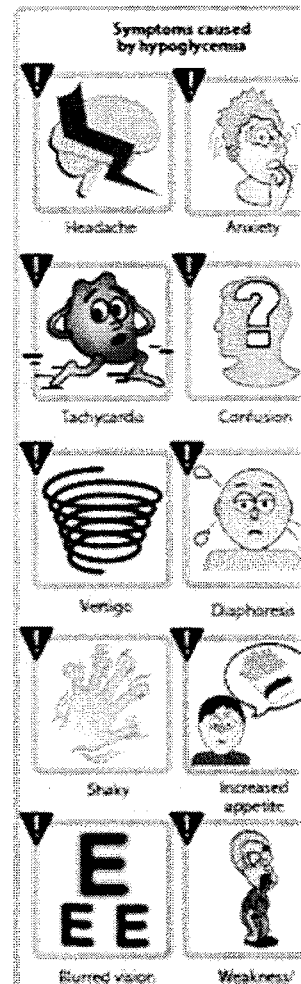
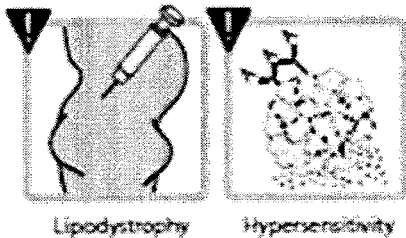
† Dose-dependent.

NPH, Neutral Protamine Hagedorn.

Moghissi E et al. *Endocr Pract.* 2013;19:526-535. Humulin R U-500 (concentrated) insulin prescribing information. Indianapolis: Lilly USA, LLC.

Adverse reactions

- Hypoglycemia
- weight gain
- local injection site reactions
- Lipodystrophy (can be minimized by rotation of injection sites)
- Diabetics with renal insufficiency may require a decrease in *insulin dose*



How should hypoglycemia be managed?

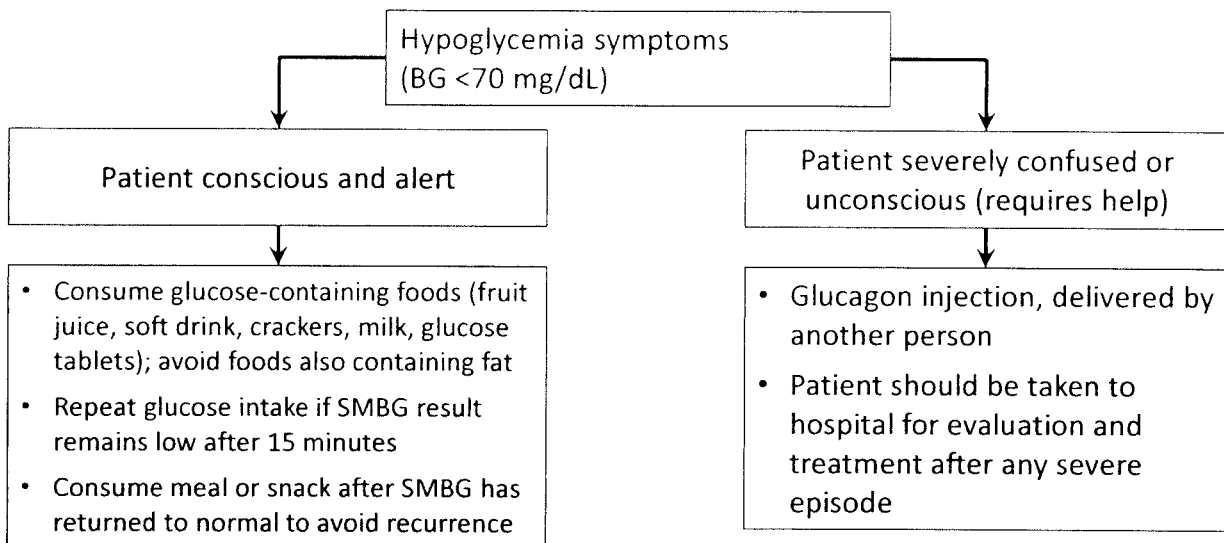
Symptoms of Hypoglycemia

Classification	Blood Glucose Level (mg/dL)	Typical Signs and Symptoms
Mild hypoglycemia	~50-70	<ul style="list-style-type: none"> • Neurogenic: palpitations, tremor, hunger, sweating, anxiety, paresthesia
Moderate hypoglycemia	~50-70	<ul style="list-style-type: none"> • Neuroglycopenic: behavioral changes, emotional lability, difficulty thinking, confusion
Severe hypoglycemia	<50*	<ul style="list-style-type: none"> • Severe confusion, unconsciousness, seizure, coma, death • Requires help from another individual

*Severe hypoglycemia symptoms should be treated regardless of blood glucose level.

How should hypoglycemia be managed?

Treatment of Hypoglycemia



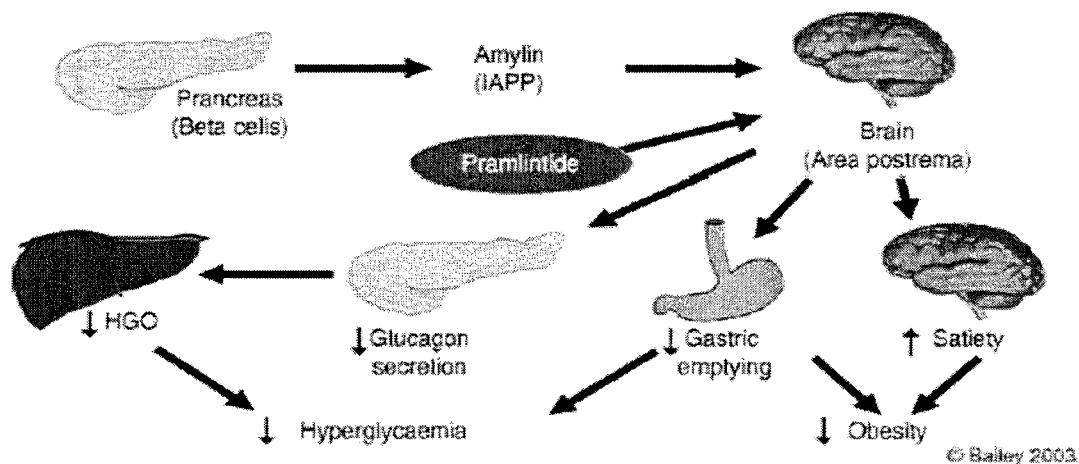
BG = blood glucose; SMBG = self-monitoring of blood glucose.

Insulin Storage

- Refrigerate unopened injectable insulin
 - do not freeze
- Use unopened insulin by manufacturer's expiration date
- Opened insulin expire based on type & delivery device
 - may be kept at room temperature (15-30°C or 59-86°F)
- Inspect before use for clumping, precipitates, discoloration, etc.

Synthetic amylin analog: Pramlintide

- ❑ Used as an adjunct to mealtime insulin therapy in patients with type 1 and type 2 diabetes
- ❑ Acts as amylinomimetic, delaying gastric emptying, decreasing postprandial glucagon secretion, and improving satiety
- ❑ Administered SC and should be injected immediately prior to meals
- ❑ When pramlintide is initiated, the dose of rapid- or short-acting insulin should be decreased by 50% prior to meals to avoid a risk of severe hypoglycemia
- ❑ Pramlintide may not be mixed in the same syringe with any insulin preparation



Antidiabetic Drugs other than Insulin. Figure 7 Mechanisms of action of the amylin analogue pramlintide.

Amylin	KCNTA TCATQ RLANF LVHSS NNFGA ILSST NVGSNT
Pramlintide	KCNTA TCATQ RLANF LVHSS NNFGP ILPPT NVGSNTY

Antidiabetic Drugs other than Insulin. Figure 8 Structure of human amylin and its soluble analogue pramlintide.

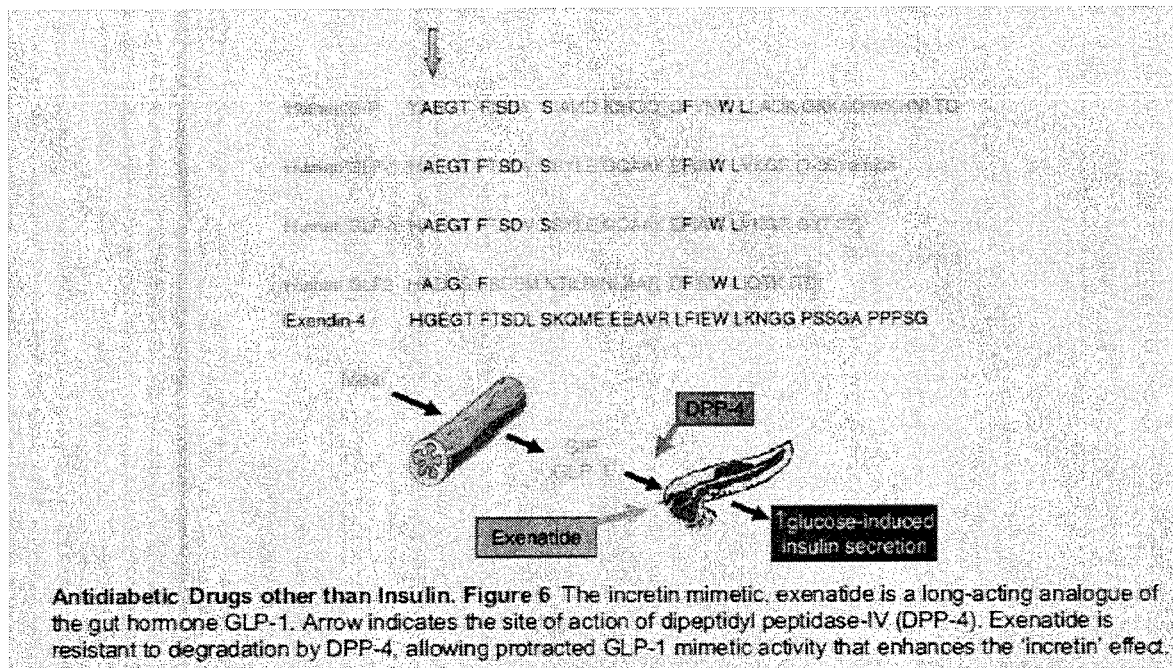
Synthetic amylin analog: Pramlintide

- ❑ Adverse effects
 - Nausea
 - Anorexia
 - Vomiting

- ❑ Pramlintide should not be given to patients with diabetic gastroparesis, cresol hypersensitivity, or hypoglycemic unawareness

Incretin mimetics

- ❑ Oral glucose results in a higher secretion of insulin than occurs when an IV glucose “**incretin effect**”
- ❑ Incretin effect is markedly reduced in type 2 diabetes
- ❑ The incretin effect occurs because the gut releases incretin hormones, notably GLP-1 and glucose dependent insulinotropic polypeptide after a meal
- ❑ Incretin hormones are responsible for 60%-70% of postprandial insulin secretion



Incretin mimetics

- ❑ Exenatide (Bydureon[®], Byetta[®])
- ❑ Liraglutide (Victoza[®])
- ❑ Injectable incretin mimetics are used for the treatment of patients with type 2 diabetes
- ❑ These agents may be used as adjunct therapy in patients who have failed to achieve adequate glycemic control on a sulfonylurea, metformin, a glitazone, or a combination of them

Incretin mimetics

Mechanism of action

- ☐ The incretin mimetics are analogs of GLP-1 that act as GLP-1 receptor agonists
- ☐ Improve glucose- dependent insulin secretion
- ☐ Slow gastric emptying time, decrease food intake
- ☐ Decrease postprandial glucagon secretion
- ☐ Promote β -cell proliferation
- ☐ Weight gain and postprandial hyperglycemia are reduced
- ☐ HbA1c levels decline

Antidiabetic Drugs other than Insulin. Table 3 Actions of the incretin hormones GIP (glucose-dependent insulinotropic polypeptide, gastric inhibitory peptide) and GLP-1 (glucagon-like peptide-1)

	GIP	GLP-1
Pancreatic		
* Glucose-induced insulin secretion	Yes	Yes
* Proinsulin biosynthesis	Yes	Yes
* β -Cell survival (rodents)	Yes	Yes
. Glucagon secretion	-	Yes
Other actions		
. Gastric emptying	No (<i>slight</i>)	Yes
. Appetite/feeding	No	Yes
. Weight gain	No	Yes
* Myocardial glucose metabolism	-	Yes?
Type 2 Diabetes	Incretin effect reduced	
Postprandial response	About normal	Reduced (<i>late phase</i>)
Insulin-releasing effectiveness	Reduced	Retained (<i>mostly</i>)

Incretin mimetics

- ❑ Administered subcutaneously
- ❑ Liraglutide is highly protein bound and has a long half life allowing for once-daily dosing
- ❑ Exenatide should be injected twice daily within 60 minutes prior to morning and evening meals
- ❑ Exenatide should be avoided in patients with severe renal impairment

Incretin mimetics

Adverse effects

- ❑ Nausea, vomiting, diarrhea, constipation
- ❑ Patients may form antibodies to these agents, in most cases the antibodies do not result in adverse effects
- ❑ Exenatide and liraglutide have been associated with pancreatitis