29 Emerging Therapies in DM

Fig. 1: Incretin effect
Fig. 2: The incretin effect in subjects without and with Type 2 diabetes
Fig. 3: Effects of diabetes and impaired glucose tolerance on plasma GLP-1 concentrations

The Enteroinsular Axis

Incretin Physiology (Figs 1 and 2)

1. Stimulates glucose induced insulin secretion.
2. Inhibits glucagon secretion.
3. Increases somatostatin secretion.
4. Induces insulin biosynthesis.
5. Reduces b-cell apoptosis.
6. Increases b-cell neogenesis.
7. Site of GLP-1 synthesis from L-cells of colon in response to nutrient ingestion.
8. Reduces gastric emptying and acid secretion.
9. Indirectly stimulates glycogen synthesis and reduces hepatic glucose production.
10. Reduces appetite, increases satiety.
11. Reduces food and water intake.
12. Involved in "portal signal" that replenishes hepatic glycogen stores postprandially.
13. Vagus nerve plays a role in GLP-1 release.
14. Local GLP-1 release plays a significant role.
15. Increases glucose uptake
16. Increases glycogen synthesis

The last 2 effects are indirect effects through hormonal changes.

GLP-1 Physiology/Pharmacology (Figs 3 and 4)

- GLP-1 (7-36 amide) plasma t½ = 2 min
- Degraded by DPP-IV present on endothelial cells to inactive GLP-1 (9-36).
- Exenatide (Byetta) is an analogue resistant to DPP-IV action with t½ = 2.5 hours.
- DPP-IV inhibitors (Sitagliptin/Vildagliptin) prolong $t^1/_2$ of native GLP-1.

Biological effects of incretin are shown in Table 1 while pharmacological characteristic are shown in Table 2.

Exenatide/Liraglutide

- Exenatide approved by FDA April 2005 for T2DM with SU and/or Metformin.
  - Starting dose 5 μg bid → 10 μg bid sq.
  - 40-50% of treated patients may develop weak titers of antibodies that are not clinically relevant for the most part.
- Liraglutide has t ½ of 10-14 hours.
  - Once daily dose of 0.6 → 1.8 mg sq.
  - Antibody development not reported yet.
  - Awaits FDA approval.

Exenatide LAR

- Microsphere suspension of exenatide.
- Prelim studies in T2DM with once weekly dosing of LAR vs. exenatide shows greater HbA1c lowering with LAR over a 15 weeks period.
- Long-term phase III trials are underway.

Exenatide: Indications/Precautions

1. Diabetes mellitus type 2 in patients taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea or a thiazolidinedione, but have not achieved adequate glycemic control; adjunct.

2. Antibody development; high titers of anti-exenatide antibodies resulting in poor glycemic control may occur in end-stage renal disease, dialysis, or severe renal impairment (creatinine clearance less than 30 ml/min).
3. Increased risk of gastrointestinal adverse effects, severe gastrointestinal disease, including gastroparesis.
4. Increased risk of gastrointestinal adverse effects insulin-requiring patients.
5. Exenatide is not a substitute for insulin type-1 diabetes or diabetic ketoacidosis; should NOT be used for this indication.
6. Cases of pancreatitis have been reported. Cause?

GLP-1 and GIP are Degraded by the DPP-4 Enzyme (Fig. 5)

Sitagliptin

- Sitagliptin approved by FDA Oct 2006, for T2DM with metformin and/or TZD or monotherapy.
  - Dose 100 mg once daily.
  - Minimal if any side effects.
  - Does not cause nausea or weight loss.
  - DPP-IV inhibition could affect other hormone degradation including hGH.
  - Concern regarding anti-apoptotic effects on lymphocytes but long-term safety data pending.
  - Would not use in transplant patients.

Sitagliptin Phosphate: Indications/Precautions

1. Diabetes mellitus type 2: 100 mg *orally* once daily as monotherapy or in combination with metformin or PPARγ agonist.
2. Mild renal insufficiency (CrCl at 50 ml/min or greater): 100 mg *orally* once daily.
3. Moderate renal insufficiency (CrCl at or greater than 30 ml/min and < 50 ml/min): 50 mg *orally* once daily.
4. Severe renal insufficiency (CrCl < 30 ml/min): 25 mg *orally* once daily.
5. End-stage renal disease requiring hemodialysis or peritoneal dialysis: 25 mg *orally* once daily, administered regardless of the timing of hemodialysis.
6. Safety and efficacy untested in pediatric population.

Vildagliptin

- Another DPP-IV inhibitor in phase III trials.
- Dosage studied; 50-100 mg daily.
- Side effect and efficacy profiles similar to sitagliptin.

Amylin/IAPP

- IAPP: 37 AA peptide co-secreted with insulin in response to nutrient ingestion.
- Stimulated also by glucagon and GLP-1.
- Main effect of amylin analog on inhibition of gastric emptying and glucagon secretion.
- Leads to reduced food intake and weight loss.
- T1DM amylin deficient state; T2DM amylin? Excess state.

Pramlintide

- Pramlintide (amylin analog) differs from IAPP by 3 AAs.

- Reduces gastric emptying; reduces food intake and facilitates weight loss.
- Decrease glucagon secretion reduces post-prandial glucose levels.

Pramlintide: Dose and Indications

1. Diabetes mellitus type 1, **adjunctive treatment**: initial, 15 μg *subcutaneously* immediately prior to major meals.
2. Diabetes mellitus type 1, **adjunctive treatment**: maintenance, titrate at 15 μg increments to 30 to 60 μg subcutaneously as tolerated.
3. Diabetes mellitus type 2, **adjunctive treatment**: initial, 60 μg *subcutaneously* immediately prior to major meals.
4. Diabetes mellitus type 2, **adjunctive treatment**: maintenance, 120 μg *subcutaneously* as tolerated.

Pramlintide: Precautions

1. Glycosylated hemoglobin (HbA1c) above 9%; should NOT be considered for pramlintide therapy.
2. Patients showing poor compliance with insulin regimen or prescribed self-blood glucose monitoring; should NOT be considered for pramlintide therapy.
3. Patients requiring drugs that stimulate gastrointestinal motility; should NOT be considered for pramlintide therapy.
4. Recurrent episodes of severe hypoglycemia requiring assistance within past 6 months; should NOT be considered for pramlintide therapy.
5. Pediatric patients; should NOT be considered for pramlintide therapy.
6. Concomitant use of glucose-lowering agents or other drugs that may increase the blood glucose-lowering effect and susceptibility to hypoglycemia.
7. Pramlintide and insulin should NEVER be mixed and always administered as separate injections.

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Multiple Choice Questions

1. **GLP-1 administration in humans:**
   A. Inhibits insulin secretion
   B. Inhibits glucagon secretion
   C. Inhibits cortisol secretion
   D. Inhibits growth hormone secretion
   E. Inhibits thyroxine secretion.
2. **GLP-1 administration in humans reduces glucose levels primarily by:**
   A. Improving peripheral insulin action
   B. Improving glucose effectiveness
   C. Improving hepatic insulin action
   D. Altering insulin/glucagon ratio
   E. Inhibiting cortisol secretion.
3. **GLP-1's effects on the GI tract include all of the following except:**
   A. Inhibits gastric acid secretion
   B. Improves gastric motility
   C. Delays gastric motility
   D. Stimulates satiety
   E. Decreases gastric accommodation.
4. **Apart from the large intestine, GLP-1 is also secreted by:**
   A. The pancreas
   B. The brain
   C. The heart
   D. The kidney
   E. The liver
5. **GLP-1 analogs initiate weight loss by:**
   A. Inhibiting glucagon secretion
   B. Suppressing satiety
   C. Its effects on carbohydrate metabolism
   D. Reducing food intake
   E. Altering insulin/glucagon ratio
6. **DPP-IV inhibitors improve glycemic control by:**
   A. Reducing food intake
   B. Promoting weight loss
   C. Increasing incretin release
   D. Improving insulin action
   E. Prolonging GLP-1 half-life
7. **Pramlintide:**
   A. Increases insulin release
   B. Can be administered orally
   C. Inhibits glucagon release
   D. Promotes modest weight gain
   E. Can be used as monotherapy for type 2 diabetes.

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1. B 2. D 3. B 4. B 5. D 6. E 7. C