Insulin

Lecture 3

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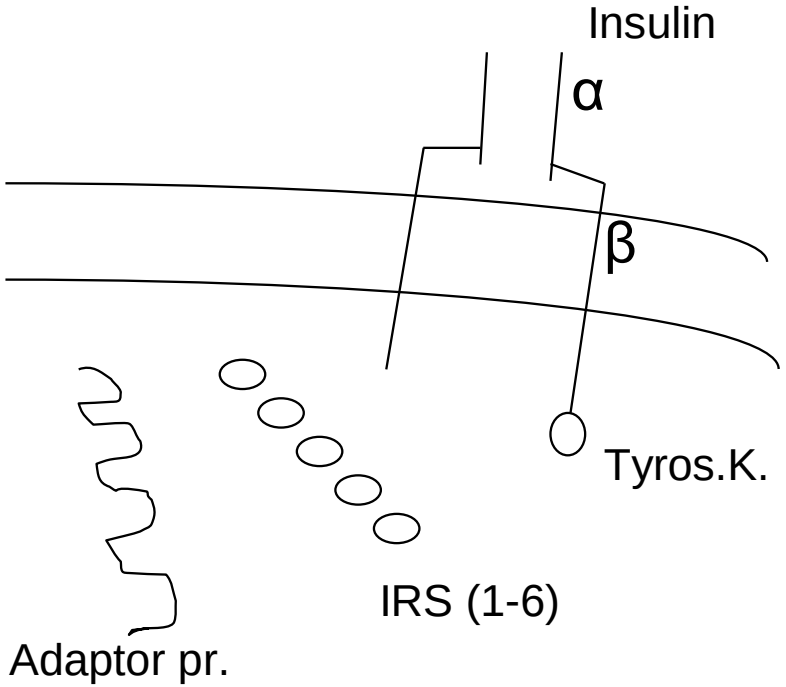
Insulin

Islets of pancreas secrete 5 hormones by 4 cell types:

α (glucagon), β (insulin & amylin), delta (somatostatin) and epsilon (ghrelin). Amylin ↓appetite & food intake, slows gastric emptying and ↓ glucagn secretion. Ghrelin ↑ appetite & food intake.

Mechanism



Insulin receptors (in all tissues) consist of 2 extracellular α subunits (for insulin binding) 2 β subunits (along cell membrane with intracellular end carrying tyrosine kinase).

Insulin binding ↑ phosphorylation of tyrosine kinase causing phosphorylation cascade of proteins with insulin signaling.

The 1st are the docking proteins insulin receptor substrates

(IRS-1 …..IRS-6). Then phosphorylation of adaptor proteins.

This activates enzymes & carrier for transport.

Insulin receptor number is ↑ by ↓ body weight, high fiber diet, exercise & oral hypoglycemics.

Insulin receptor number is ↓ by obesity, simple sugars, sedentary life & other hormones.

Actions

Anabolic, → storage of the 3 macronutrients.

A) On carbohydrates:

↑ uptake, utilization of glucose & storage of glycogen → **hypoglycemia**.

1. ↑cellular uptake of glucose (with K+) by facilitating its diffusion across cell membranes except in brain, RBC, intestine & kidney. By stimulation of 5 glucose transporters, e.g. Glut 4 in skeletal muscles & fat and Glut 2 in β cells of pancreas for insulin release.

2. ↑glycolysis.

3. ↑glycogenesis (↑ glycogen storage) in liver & skeletal muscles

and ↓glycogenolysis.

B) On proteins:

↑cellular uptake of amino acids (↑amino acids transporters), incorporation into proteins (anabolic) & ↓gluconeogenesis.

C) On fats:

1.↓ lipolysis in fat cells by inhibiting hormone - sensitive (intracellular) lipase enzyme →↓FFAs mobilization to blood.

2.↑ lipogenesis:

Converts glucose →→ fats mainly in adipose tissue.

Insulin + lipoprotein lipase are complementary.

Insulin ↑fat synthesis (from glucose) in liver and ↑blood triglycerides & cholesterol levels. Then lipoprotein lipase (in capillaries) → conversion of triglycerides in lipoprotein to free fatty acids → circulation → export of triglycerides (via VLDL) to adipose tissue. More in metabolic syndrome.

3.↓ formation & ↑ uptake of ketone bodies.

In fed state insulin release ↑glycolysis, glycogenesis & lipogenesis.

In fasting: ↑growth h., glucagon & epinephrine →↑fatty acids oxidation (→ fewer free radicals → antioxidant & anti-inflammatory), ↓glucose oxidation & ↑gluconeogenesis → preserve glucose for brain.

D) Vascular insulin actions: ↑NO, VD, ↓vascular smooth m. proliferation, ↑microvascular blood flow & ↓platelet aggregation.

Antagonizes renin angiotensin actions which → opposite…..& ↓glucose uptake.

- A, B & C : metabolic.
- D : vascular.

Control of insulin release

Normally 50% of daily insulin is basal & 50% PP.

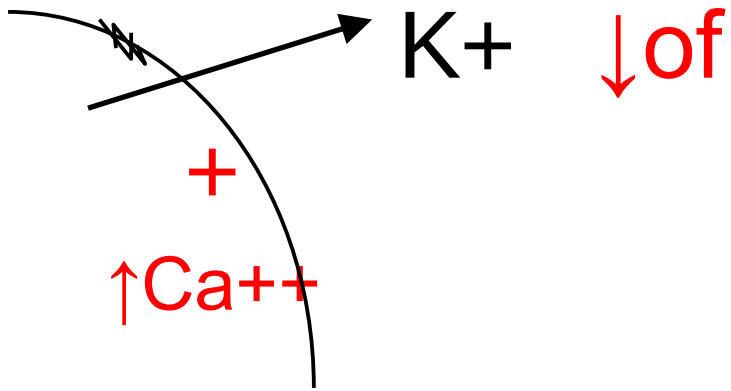
Insulin daily requirements: 0.5- 1 u/Kg. ↑in puberty, pregnancy & medical diseases.

Increase by

1. Glucose → ↑ATP → closure of ATP- sensitive K+ channels → depolarization → opening of voltage dependent Ca++ channels → ↑Ca++ influx → release of stored insulin (rapid) followed by slow release (newly formed insulin).

The 1st phase (& later phase 2) is impaired in T2DM, both in T1DM.

Amino acids & free fatty acids augment glucose – induced insulin release.
Insulinogenic: carbs > proteins > fats.



.2. Sulfonylurea: by closing ATP- sensitive K+ channels

3. - 10…

- **Decrease by:**

1. Hypokalemia by e.g. thiazides, loop diuretics & diazoxide. They are K+ channel openers, increasing K+ efflux → hyperpolarization…..

Types of Diabetes Mellitus

It is a syndrome characterized by disturbance in carbohydrate, protein & fat metabolism beside vascular complications.

Manifested by polyuria, polydepsia, polyphagia, ↑ or ↓body wt. &….

Clinical in 16% of population (diagnosed in 8%).

75% of inpatients are diabetics.

B) Secondary diabetes: by endocrine diseases causing hyperglycemia as Cushing disease, acromegaly, pheochromocytoma and by hyperglycemic drugs **(type 3)**. Gestational (pregnancy) diabetes is **type 4**. In 5-10% of pregnant. 30 - 60 %→ T2DM.

A) Primary:

	Type 1 DM (IDDM)	Type 2DM (NIDDM)
	Insulin dependent	**Insulin receptors dependent**
Age:	Young (<30 years)	Adult (>40 years)
	At 1-2 & 17 years in 75%.	Now…..younger.
%	< 10%	> 90%
Symptoms:	Appear rapidly, with marked hyperglycemia.	Slowly, with mild or mod. hyperglycemia.
Ketosis:	Common	Rare (insulin is enough to prevent ketosis but not hyperglycemia)
Obesity:	Not common (thin)	Common
	due to ↓insulin (anabolic)	(the anabolic insulin is present)
Insulin	↓	Variable (↑ then↓)
ttt.	Insulin	Oral antidiabetics
Family hist.	Not common (10%)	Common

T1DM

Type Ia: >95%. Autoimmune.

Viral infection of β-cells in genetically predisposed pts.

→ mild hyperglycemia → healing & recovery (honey moon period) → autoimmune reactions → destruction of these cells (>90% at diagnosis) → severe hyperglycemia.

Contribution is genetic (1/3) in pts. with HLA-DR3 & 4 (regulate immune response) and environmental (by viruses).

Screening done at time of diagnosis shows high circulating levels of antibodies to insulin and components of insulin receptors .

Type Ib: <5%. Idiopathic.

T2DM

A) Hereditary. Contribution is mainly genetic (strong). Mainly in 1st degree family history relatives (parents & siblings).

B) Environmental:

1. Obesity. Mainly visceral (metabolic) obesity more than SC abdominal fat due to its link with insulin resistance.

2. ↑diet sugars & other drugs with high glycemic or insulin index.

3. Lack of exercise.

4. Emotions.

5. Periodontitis, intestinal dysbiosis and vitamin & mineral deficiency.

Insulin resistance (receptor or post-receptor defect) →

1. ↑insulin release.

2 .↓insulin release by exhaustion of β-cells (2ry failure).

Metabolic syndrome
(insulin resistance syndrome, X syndrome)

Most important factor in development of T2DM.

Very common, with many associations:

1. ↑body wt .
2. ↑BP.
3. ↑plasma lipids .
4. ↑plasma insulin then glucose.
5. ↑prothrombotic & proinflammatory state (↑CRP), thrombophilia & oxidative stress. Astherosclerosis.
6. ↑uric acid.
7. Fatty liver. NAFLD is better predictor of cardiovascular disease & mortality. Also cholecystitis & gall stones. ↑GGT.
8. Polycystic ovary syndrome.
9. Rheumatoid arthritis.

Causes of metabolic syndrome:

1. Life style….
2. Periodontitis:

Bidirectional relationship between periodontitis & DM.

Predictor of mortality.

3. Intestinal dysbiosis:
4. Deficiency of Mg, K, vit. D, omega 3 fatty acids, ….

Insulin resistance ttt.:

1. Life style modification of diabetics…….
2. Metformin.
3. Pioglitazone (insulin sensitizer).
4. ACEIs & ARBs:

Stages of diabetes – induced metabolic syndrome

A. Impaired glucose tolerance (prediabetes): 10 years, with complications.

B. Metabolic diabetes: Hyperglycemia.

Hypoglycemia → many complications as cardiovascular & ↑mortality.

Brittle diabetes is that with unstable blood glucose levels (marked fluctuations). Food →marked hyperglycemia. Normally this is compensated by ↑insulin release → ↑glycogen storage & ↑ glucose uptake & utilization. ↓insulin activity in diabetics reduces glycogen storage & ↓ glucose uptake & utilization. Fasting → hypoglycemia because low glycogen stores cannot supply enough glucose by ↑glycogenolysis induced by other hormones.

C. Vascular diabetes: Microvascular (& macrovascular) complications (we are as old as our arteries, carotid intima media thickness).

Tight glycemic control improves micro & not macroangiopathy.

↓1% HbA1c → ↓microvascular complications by 40% & mortality by15%.

D. Cancer: By ↓immunity, ↑insulin→ ↑growth..., cancer cells need glucose.