Hashemite University
H·U·M
Medical School Committee

Scientific Team
الفريق العلمي

PHARMACOLOGY

Lecture : 3 (PART 1)

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Lecture 3 (part 1)

Diabetes type 1: insulin dependent (often in young age)

insulin deficiency يعني المشكلة هي

Diabetes Type 2: insulin resistant (90% of cases) (in adults)

Insulin receptor deficiency يعني المشكلة هي

Insulin

Lecture 3

رح نبدأ موضوع diabetes mellitus
طبعا هذا الموضوع مرتبط مع الInsulin

Insulin

Anti-insulin

الhormones β هم يلي
بفيدوني بالdiabetic case

Inhibits insulin

Islets of pancreas secrete 5 hormones by 4 cell types:

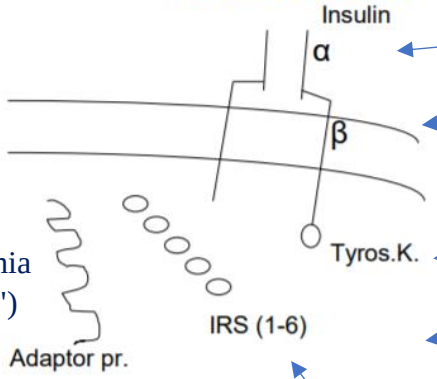
α (glucagon), β (insulin & amylin), delta (somatostatin) and epsilon (ghrelin).

Amylin ↓appetite & food intake, slows gastric emptying and ↓ glucagn secretion. Ghrelin ↑ appetite & food intake.

Mechanism

↓appetite and food intake
= less Hyperglycemia

slows gastric emptying
= ↓ absorption of carbohydrates and protein
= ↓ postprandial hyperglycemia
(**postprandial** = "after eating")



Mechanism:
insulin binds to α (extracellular) = activation = phosphorylation
after phosphorylation of α = activation of β units (transmembrane to intracellular)
this will lead to the activation or phosphorylation of tyrosine kinase causing post-receptors that is responsible for insulin signaling

مشكلة الناس يلي عندهم diabetes
هو β cell decline
يعني في نسبة معينه بين α و β
في مرضى السكري النسبة بتكون لصالح α ال
وبتقل الactivity ل β cell

مرضى السكري مش بس ممكن يكون عندهم مشكلة بال(insulin receptor (α/ β/Tyros.k.

ممكن يكون عندهم كمان post receptor defect
وهو عبارة عن مشكلة تبدا من
insulin receptor substrate (IRS)

وهو عبارة عن docking proteins

(docking = isolated)not attached to any structure

هاي دورها انها بتعمل Amplification لل Tyros.k.
بالتالي بدل Tyros.k واحد رح تعمللنا عشرات من Tyros.k

لكن هدول الIRS متفرقين ولازم يتحدوا
عن طريق الadaptor proteins
ليش لازم يتحدوا؟ عشان يعملونا اكشن قويSynchronization

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. ← نتيجة العملية كلها

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.

Sedentary life: is a type of **lifestyle** involving little or no physical activity.

هدف الinsulin الاساسي

Actions

Anabolic, → storage of the 3 macronutrients.(Carbohydrates – proteins -fats)

So, insulin = ↑anything anabolic =↓ anything catabolic
And anabolic = needs Energy = insulin want energy also

A) On carbohydrates:

↑ uptake, utilization of glucose & storage of glycogen → **hypoglycemia**. ← هدف ثاني فرعي

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.(utilization of glucose = to make energy)
3. ↑glycogenesis (↑ glycogen storage) in liver & skeletal muscles(to save excess energy) and ↓glycogenolysis. (prohibit breakdown of glycogen into glucose)

B) On proteins:

↑cellular uptake of amino acids (↑amino acids transporters), incorporation into proteins (anabolic) & ↓gluconeogenesis. (prohibit formation of glucose to non-carbohydrate s)

Insulin is eating hormone

بعد الاكل (**postprandial**)
رح يزيد الglucose بالتالي رح يطلع
الInsulin و يمنع الhyperglycemia

لذلك مرضى السكري بصير عندهم
postprandial hyperglycemia

C) On fats:

(adipose tissue)

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

=make the fat stay in adipose tissue

2.↑ lipogenesis: محطوط سهمين لانه بياخذ اكثر من مرحلة

Converts glucose →→ fats mainly in adipose tissue.

لذلك يلي باكلوا حلويات (دهون) بينصحوا لان الانسولين بيخزنها وبتضل

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.

الinsulin رح يعمل تنشيط للlipase واللي من غيره رح يكون الوضع سيء

(شرح الخط المائل (مهم جدًا)) :-

المفروض fats بالشكل الطبيعي ما يكون بال Liver كثير بل يكون mainly in adipose tissue

اذا زاد الfat formation (triglycerides and cholesterol↑) بشكل كبير بالliver

رح يعمل مصيبة fatty liver

واذا زاد بالblood يعمللنا hyperlipidemia مصيبة ثانيه !

طيب شو يلي بيصلح هاي العملية بالشكل الطبيعي وبمنع هالمصايب؟ هو الLipoprotein lipase

وهو بيحول الtriglycerides الى Free Fatty Acids

بعدها بتنتقل ال FFA عن طريق الcirculation من الliver الى ال adipose tissue (via VLDL)

المشكلة بتظهر اكثر عند metabolic syndrome يعني بالذات Diabetes Type 2

ليش ؟

1. لان الجلوكوز لم يتم استخدامه لان الانسولين ناقص بالتالي زاد الجلوكوز وتحول الىfat كثير

2.بما انه الانسولين ناقص (نتيجية receptor deficiency) فهذا يعني نقص الLipoprotein lipase

↓formation of ketone bodies = ↓ catabolic

↑uptake of ketone bodies

المشكلة بتكون اكثر ب type 1 اللي عندهم نقص في الانسولين لانه هو الاصل لذلك بيكون عندهم تكوين اكثر للketone bodies وبصير معهم diabetic ketoacidosis

اما type 2 (نتيجية receptor deficiency) المشكلة عنده اقل لانه بضل عنده الهرومن ولو بكميات قليله يعني مش لدرجة انه يعملي ketoacidosis

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

In fasting = no insulin, as we said it is eating hormone

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

رح يزداد gluconeogenesis لان الbrain بيتحتاج glucose
وفي نفس الوقت رح يزداد استخدام الFFA بدل الglucose وهاي فكرة رجيم الكيتو و الصيام المتقطع

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

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

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

↑NO = Nitric Oxide
VD = ↑ diffusion and blood supply for organs

Diabetes has two types: metabolic + Vascular
Metabolic Diabetes = عكس كلشي قلنا

مثلا بدل hypoglycemia بيكون hyperglycemia

نحن قلنا من قبل ان لو insulin ناقصه = diabetes

طيب لو زاد الinsulin هاد كمان مش كويس
وهذا بيحدث في ال metabolic diabetes بسبب ان
الreceptors قليلة والاكشن بسيط فيزداد كمية الinsulin

↑insulin = ↑anabolic = ↑fat in liver + circulation =obesity

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).

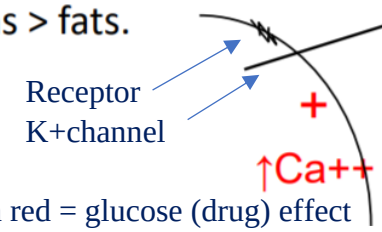
= K+ inside = depolarization

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

Both = not rapid and not slow

Because it doesn't even have insulin

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



control of post-prandial سريع فيعملي hyperglycemia

in red = glucose (drug) effect
= inhibit K+ channel
+ increase Ca++ influx

لذلك بنصحوا ان لا تأكل الحلويات مع البروتين عشان ما يحصل

Augmentation glucose - induced insulin release

THANK YOU AND GOOD LUCK

there is also part 2