Farmakologi & Terapi

OBAT ANTIDIABETIK

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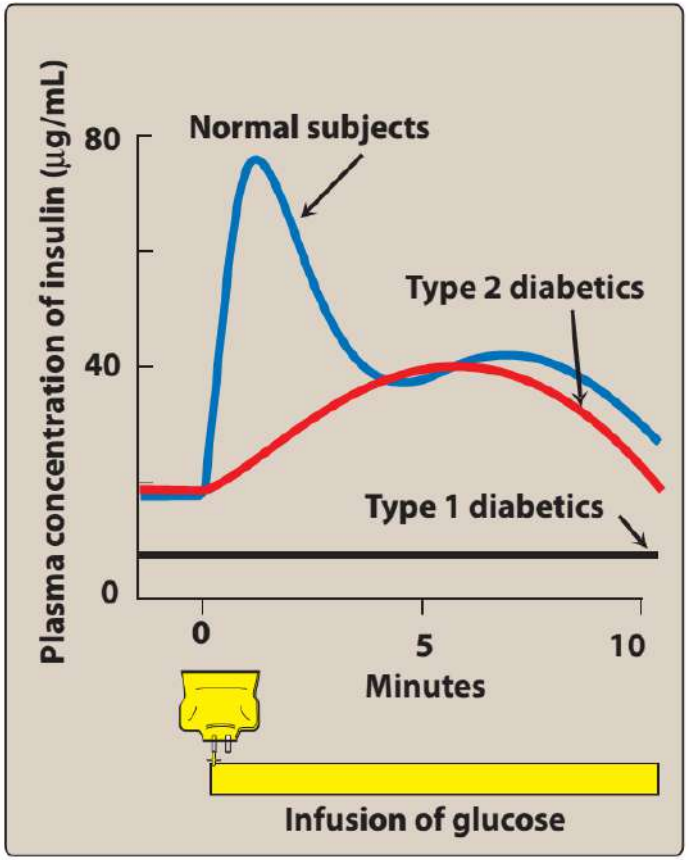
LABORATORIUM FARMAKOLOGI FK-UMM

2020

Diabetes Mellitus :

kelompok penyakit yg mempunyai karakteristik adanya peningkatan kadar gula darah yang disebabkan karena adanya gangguan sintesa / sekresi insulin, gangguan kerja insulin atau kombinasi keduanya



	Type 1	Type 2
Age of onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence	5 to 10 percent of diagnosed diabetics	90 to 95 percent of diagnosed diabetics
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

Diabetes Mellitus

2 Types of diabetes:

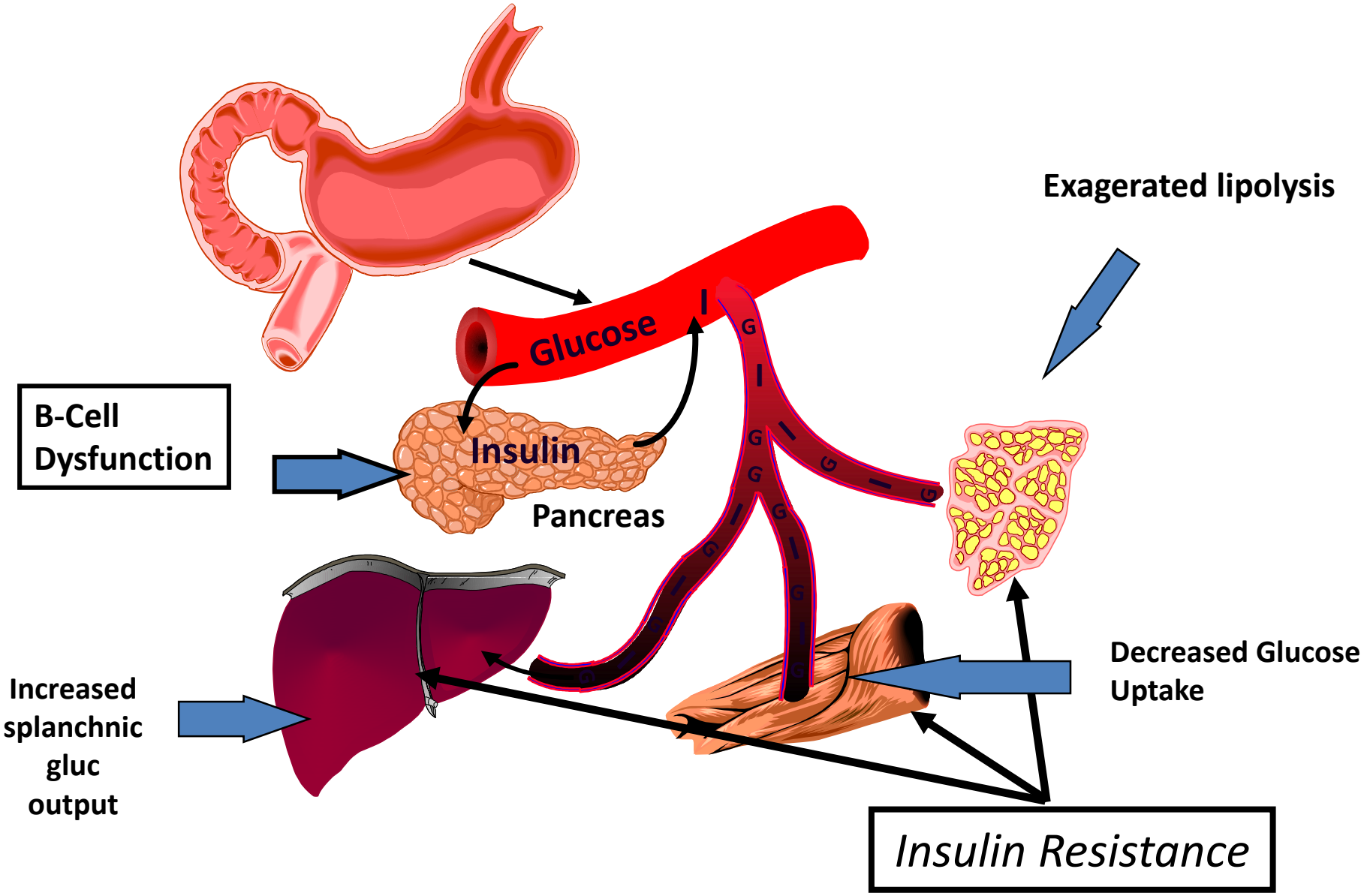
Type I diabetes (10% of cases)

- Develops suddenly, usually before age 15.
- Caused by inadequate production of insulin because T cell-mediated autoimmune response destroys beta cells.
- Controlled by insulin injections.

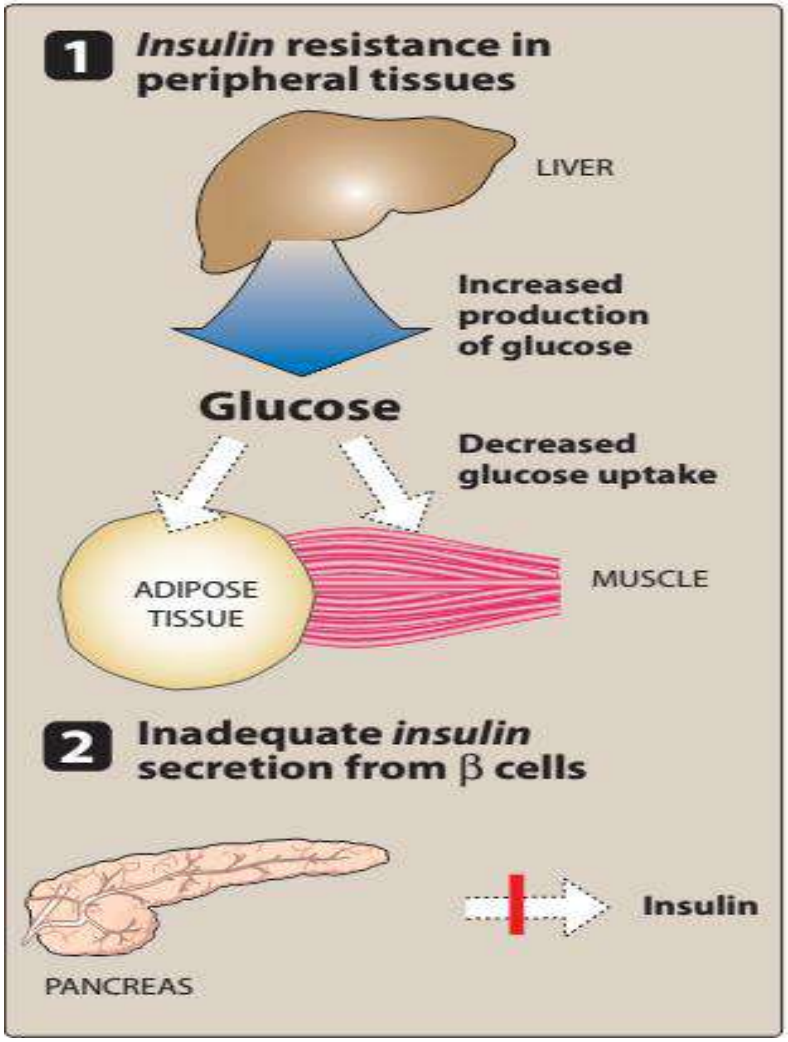
Type II diabetes (90% of cases)

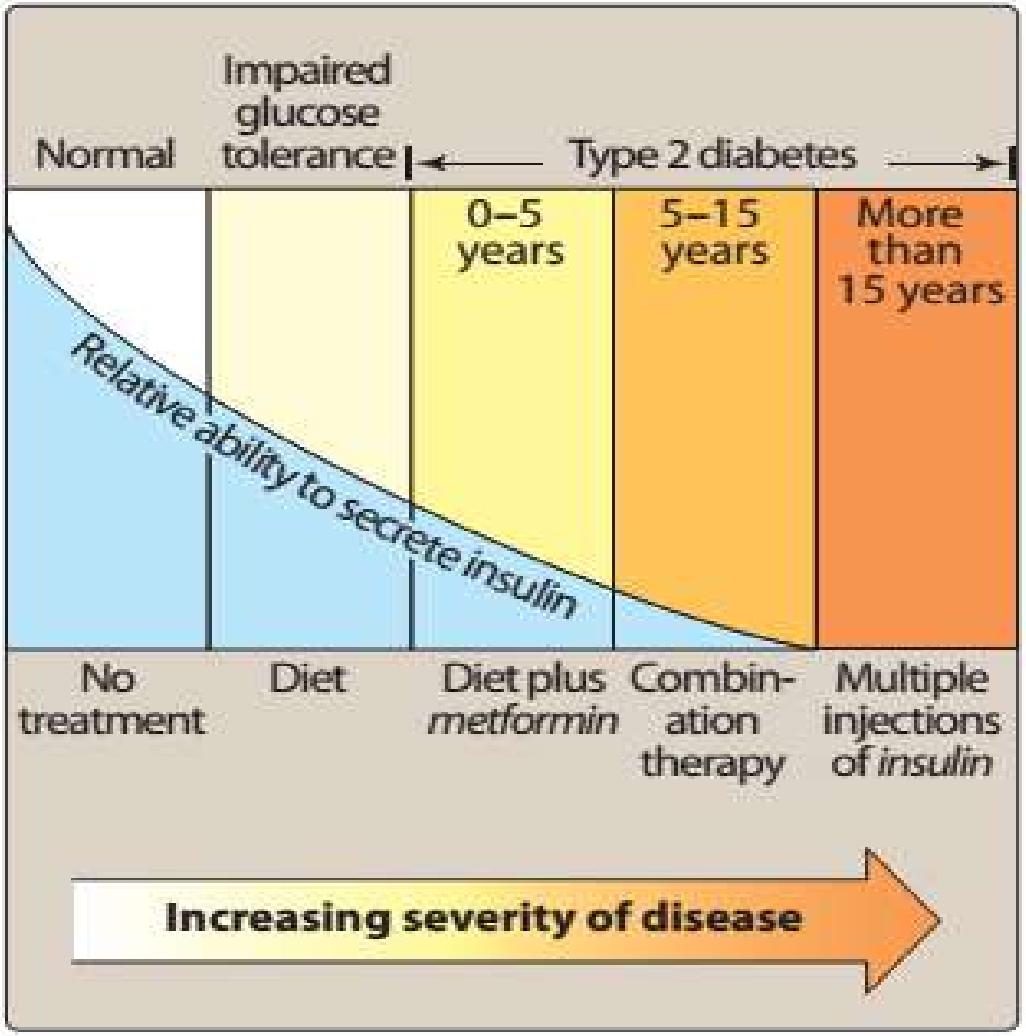
- Usually occurs after age 40 and in obese individuals, but genetics, aging, and peripheral insulin resistance also.
- Insulin levels are normal or elevated but there is either a decrease in number of insulin receptors or the cells cannot take it up.
- Controlled by dietary changes and regular exercise.

Pathophysiology Diabetes



TYPE 2 DIABETES





- **Glucose homeostasis**

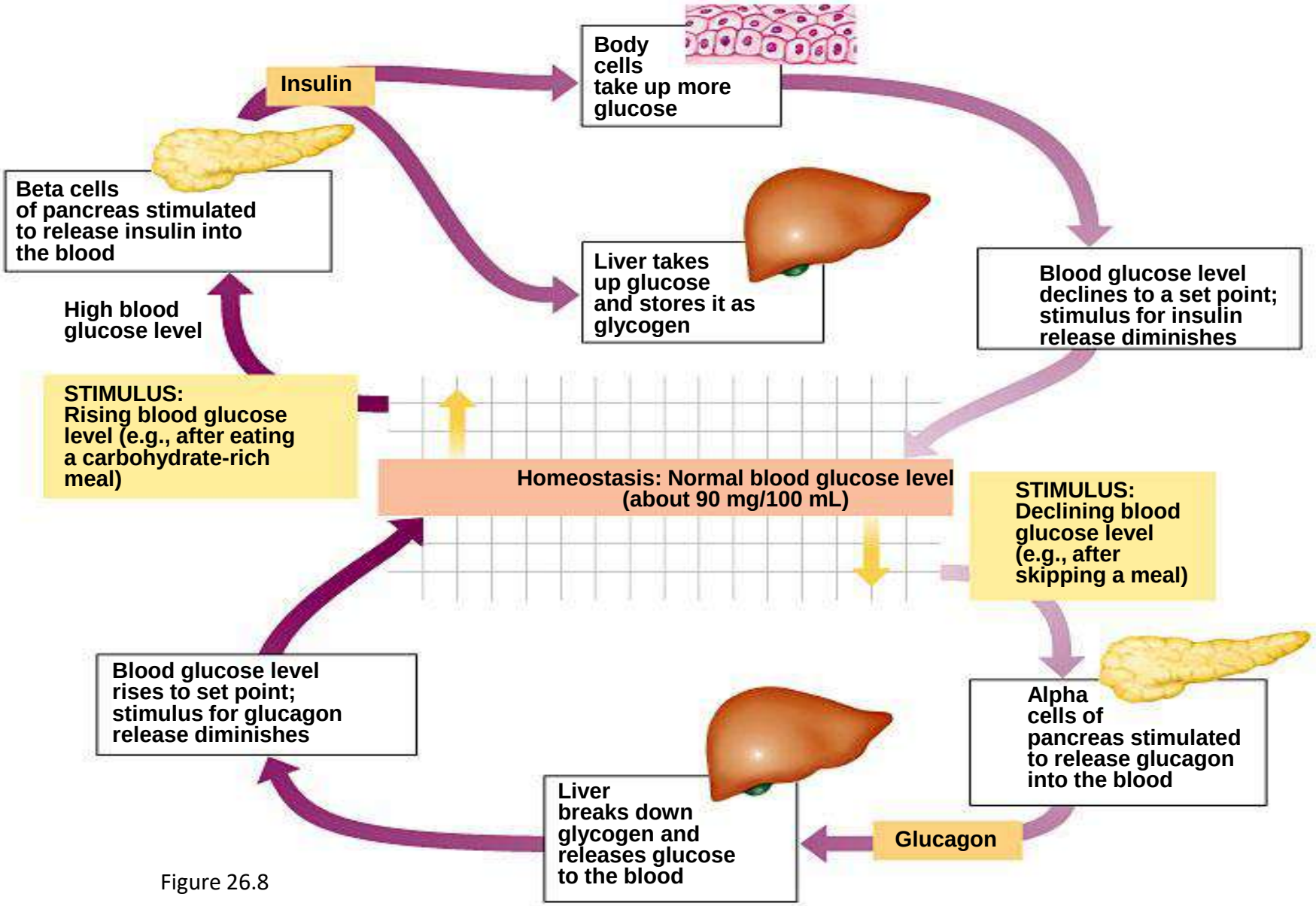


Figure 26.8

Normal Glucose Control

- Pd individu normal, kadar basal insulin dipertahankan melalui sekresi sel β secara konstan. Hal ini menekan lipolisis, proteolisis dan glikogenolisis. Setelah makan, sekresi insulin ↑ sbg respons pe↑ glukosa dan asam amino. Ketika kadar glukosa kembali ke level basal, sekresi insulin kembali ke tingkat basal juga.
- DM tipe I: Kurangnya β-sel fungsional, insulin terbatas sehingga tjd pe↑glukosa. Onset & perkembangan mjd neuropati, nefropati dan retinopati berkaitan langsung dengan hiperglikemia episodik.
- DM tipe II: β-sel fungsional masih ckp tp respon insulin tidak memadai. Kadar insulin sebenarnya mungkin normal atau supra-normal tetapi tidak efektif (resistensi insulin).

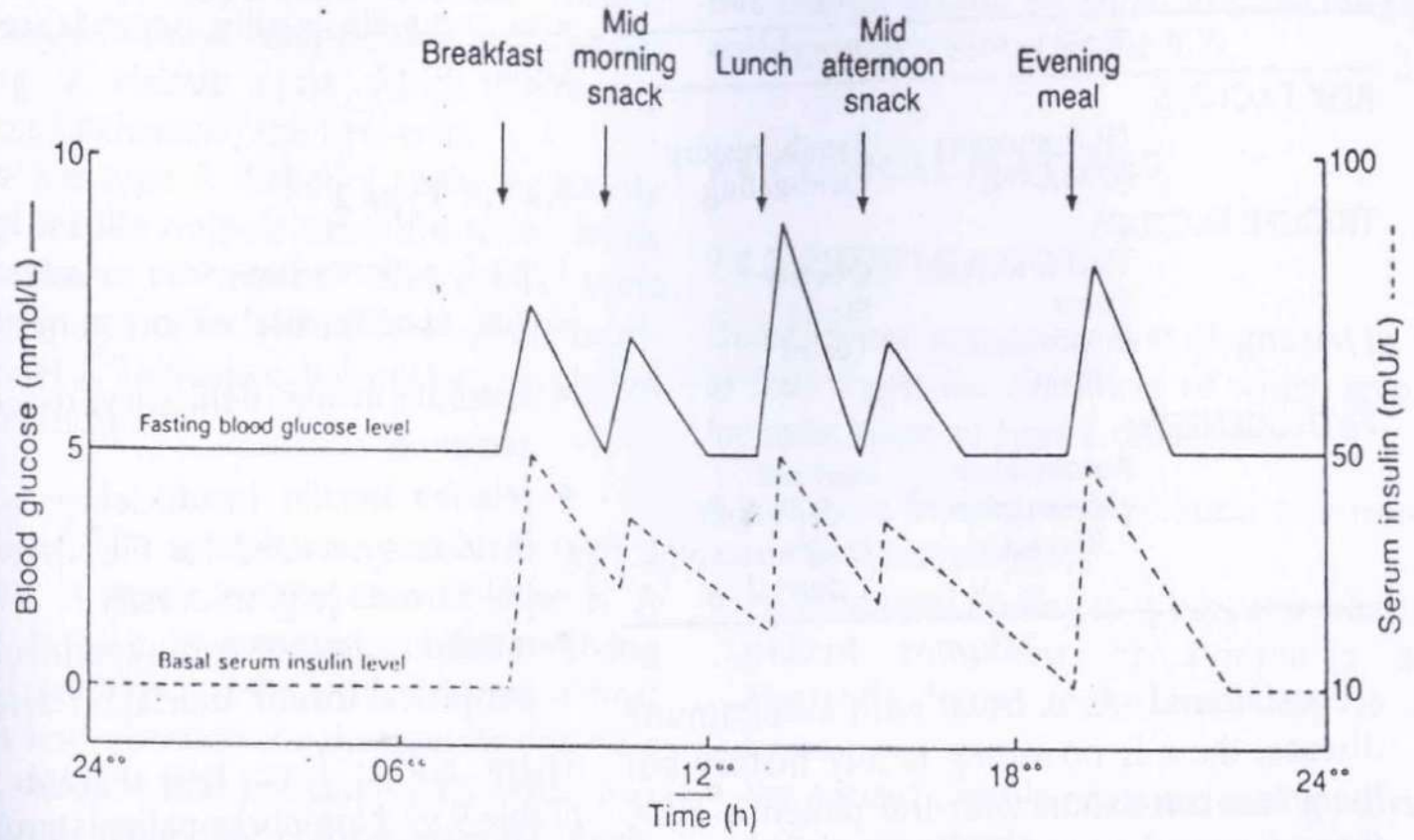


Figure 9.4 Schematic representation of normal diurnal variations in blood glucose and insulin levels. As the blood glucose level rapidly rises after a meal, it is closely followed by an increase in insulin level to prevent too great a rise. The insulin returns towards the basal level as blood glucose reaches the normal fasting level once more. Note how the two substances follow almost parallel curves. The small but positive basal insulin level serves to emphasize that insulin has functions other than just dealing with dietary glucose. -------, insulin level; ——, glucose level.

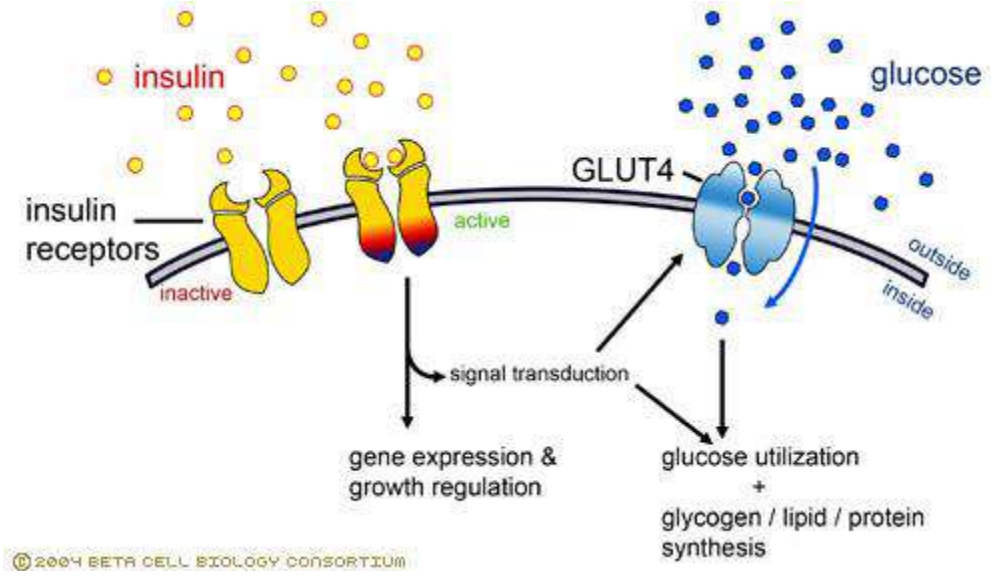
Faktor yg mempengaruhi sekresi Insulin

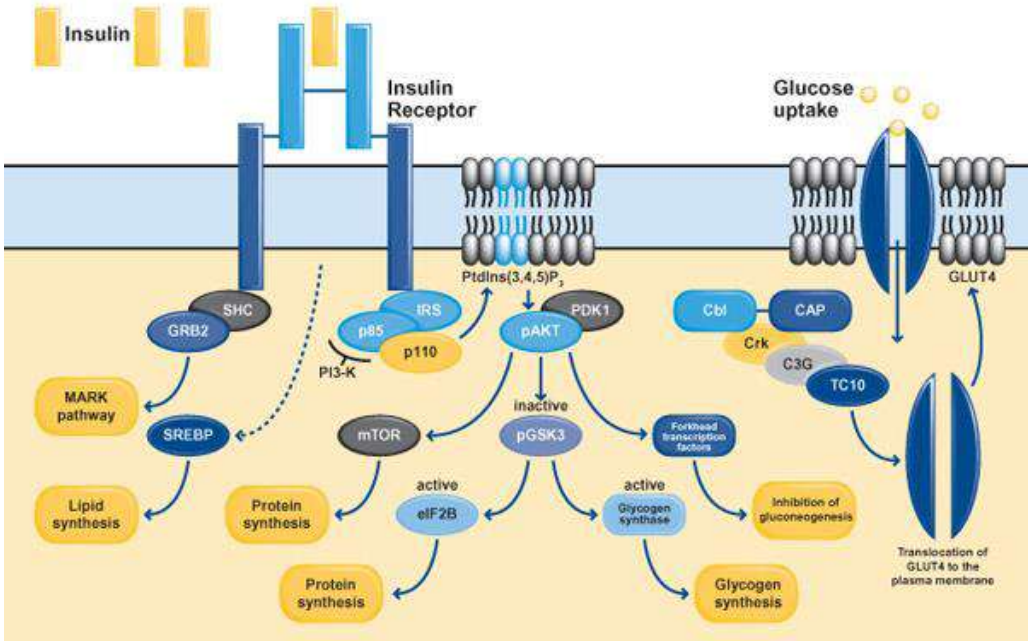
	Stimuli release	Inhibisi release
Hormon	sekretin, GIP, GLP-1, gastrin, kolesistokinin, enteroglucagon	Somatostatin
Autonomic	β2-agonist Parasimpatis (M2 agonis)	α2-adrenergik agonis
Nutrient	Glukosa, Amino Acid, Fatty Acid, keton bodies	
Drug	theophylline, sulfonylurea, meglitinid	diazoxide,thiazides, ethacrynic acid, furosemid, phenytoin, Klonidin, Kalsium antagonis Beta bloker, Fenitoin

Obat yg kerjanya berlawanan dg kerja insulin : Epinefrin, Glukokortikoid, Kontrasepsi oral

Mekanisme kerja Insulin

- Insulin mengikat reseptor spesifik di membran & mengaktivasi tirosin kinase
- Fosforilasi sec kaskade menyebabkan translokasi protein transpor Glut-4 (& bbrp Glut-1) ke dalam membran plasma.
- Hal ini menginduksi transkripsi bbrp gen yg terlibat dlm katabolisme glukosa & menghambat transkripsi gen yang terlibat dlm glukoneogenesis.
- Insulin meningkatkan uptake K + ke dalam sel.





Treatment:

DM Type I:

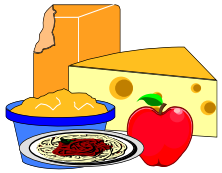
- ✓ Tx =exogenous insulin → memperbaiki insulin basal & postpandrial
- ✓ Tujuan Tx= - mengatasi hyperglycemia & cegah ketoacidosis
  - mencegah terjadinya hipoglikemi akibat Tx .

DM Type II:

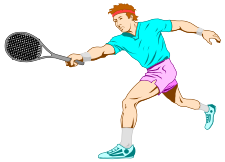
- ✓ Tx= - non-drug (BB ↓, OR, modifikasi diet utk me↓resistensi insulin)
  - drug (OAD, insulin (jika perlu))
- ✓ Tujuan Tx = - memelihara kdr glukosa dlm batas normal
  - mencegah komplikasi jangka panjang

PRINSIP PENATALAKSANAAN T2DM

- **Pengaturan diet**
  - Minum air banyak, susu skim dan minuman berkalori rendah lainnya pada waktu makan
  - Hindari makanan manis, gorengan, biskuit, cake
  - Makanlah dengan waktu yang teratur
  - Tingkatkan asupan sayuran dua kali tiap makan
  - Jadikan nasi, roti, kentang, atau sereal sebagai menu utama
  - Minum air atau minuman bebas gula setiap anda haus

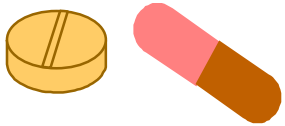


- **Latihan jasmani**

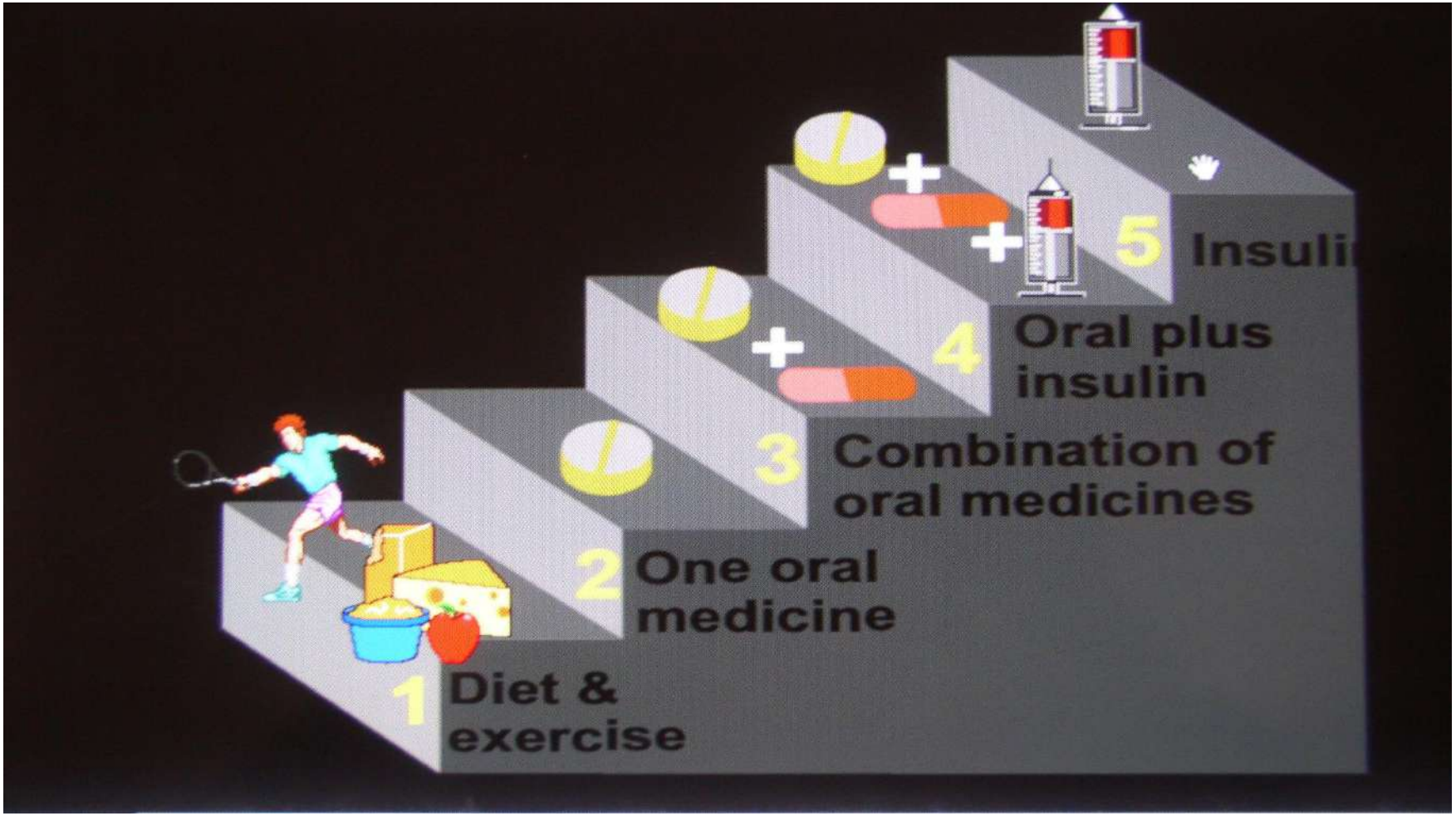


Kegiatan jasmani sehari – hari dan latihan jasmani teratur, 3 – 4 x/mgg, selama ± 30 menit : jalan, bersepeda santai, jogging, berenang. Latihan jasmani ⇨ me↓ BB dan memperbaiki sensitifitas thd insulin, serta me ↑ uptake glukosa oleh otot (tanpa perlu bantuan insulin)

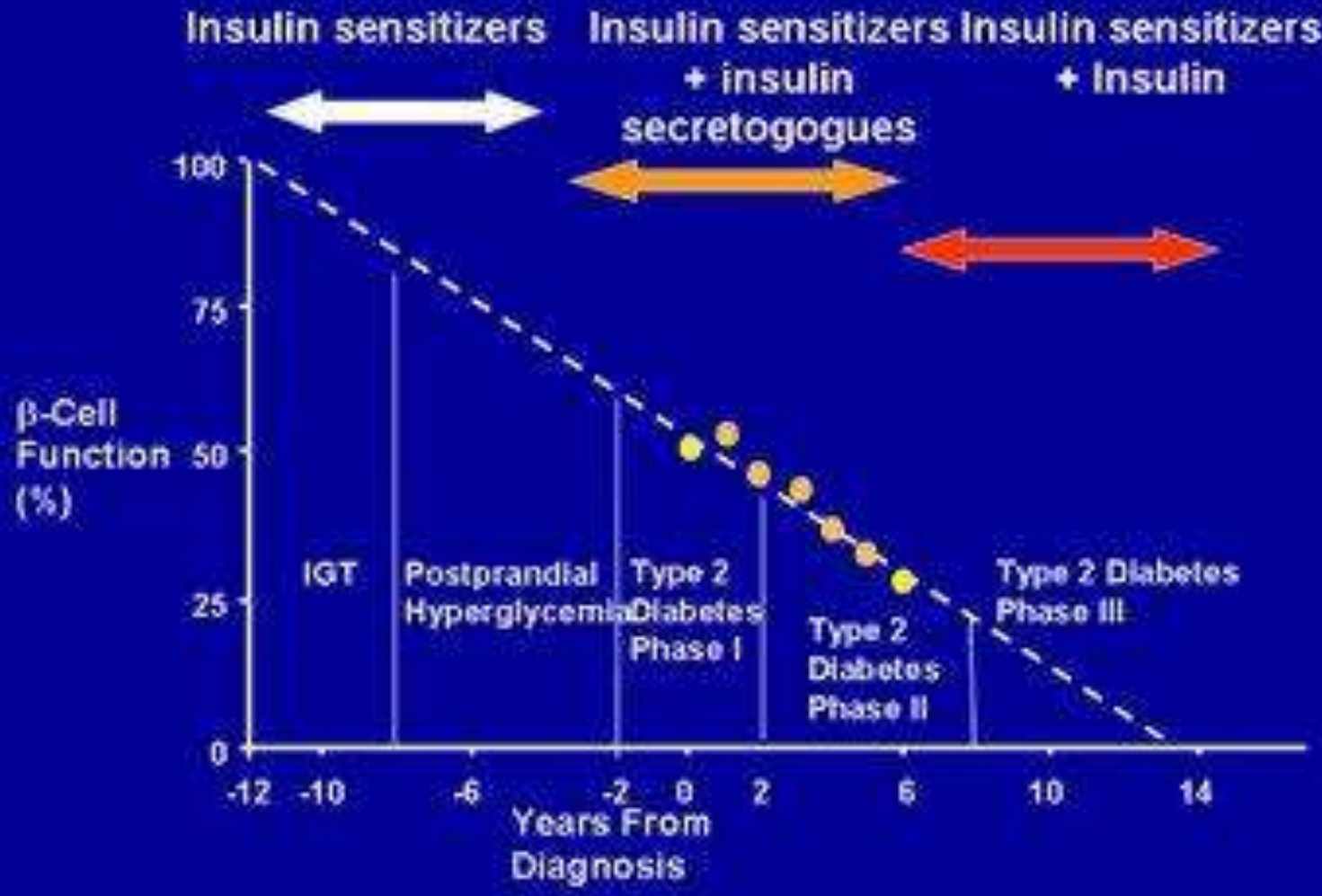
- **Farmakoterapi**



Stepwise Management of Type-2 Diabetes Mellitus



Stages of Type 2 Diabetes



Lebovitz H. *Diabetes Review* 1999.

TERAPI INSULIN

TERAPI INSULIN

- Tujuan : utk mengontrol gula darah sepanjang hari dan menormalkan metabolisme
- Pemberian biasanya dilakukan sendiri oleh pasien
- Regimen diberikan

  - sekitar wkt makan, exercise, tidur
- Faktor yg mempengaruhi kebutuhan insulin : exercise, diet, stress/infeksi, obat ttt

Indikasi Terapi Insulin

- Semua penderita DM tipe I
- Penderita DM tipe II, bila terapi jenis lain tidak dapat mengendalikan kadar glukosa darah.
- Kebutuhan insulin me↑ pd penderita DM dg : infeksi, panas tinggi, trauma, IMA, stroke, stress psikologis berat, hamil, hipertiroid, ketoasidosis diabetik, menggunakan obat yg menyebabkan hiperglikemi, tindakan pembedahan, DM gestasional, Hiperglikemik hiperosmolar non ketotik
- Gangguan fungsi ginjal atau hati yang berat.
- Kontra indikasi atau alergi terhadap obat hipoglikemi oral

Farmakokinetik Insulin

- Pemberian per-oral tidak effektif ⇨ diberikan secara parenteral :

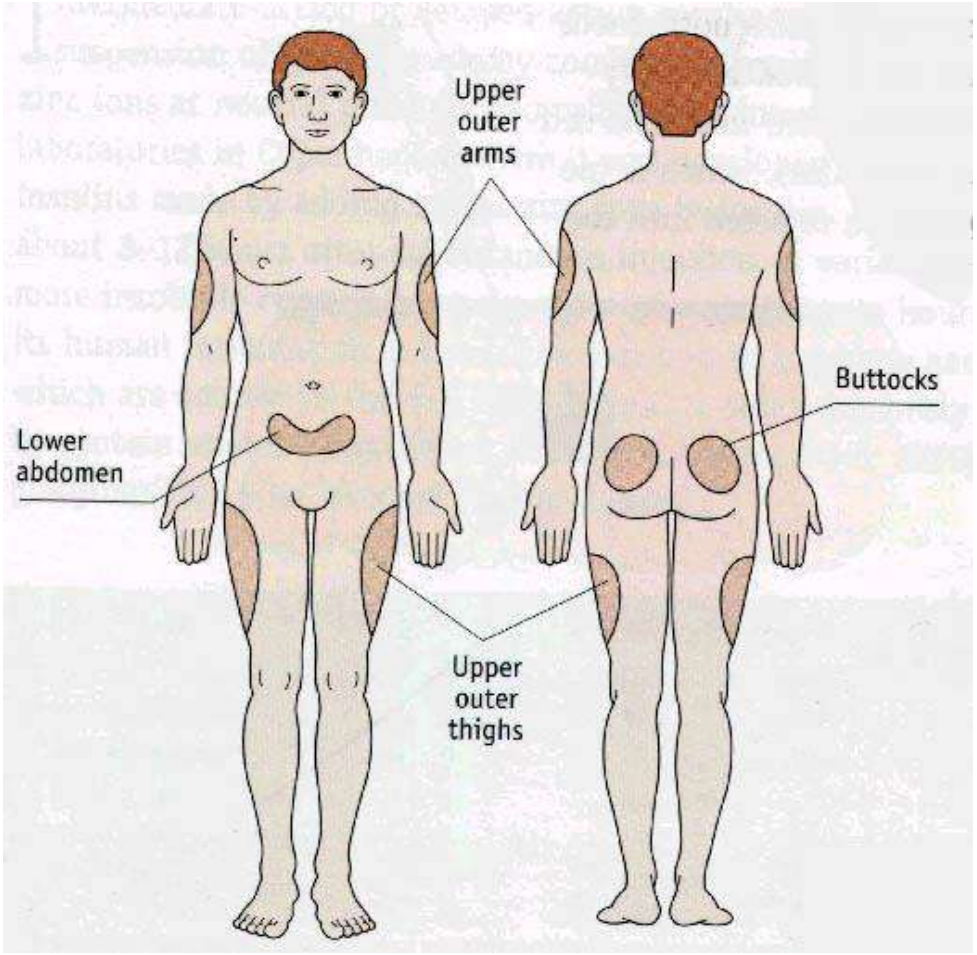
  - sc atau im

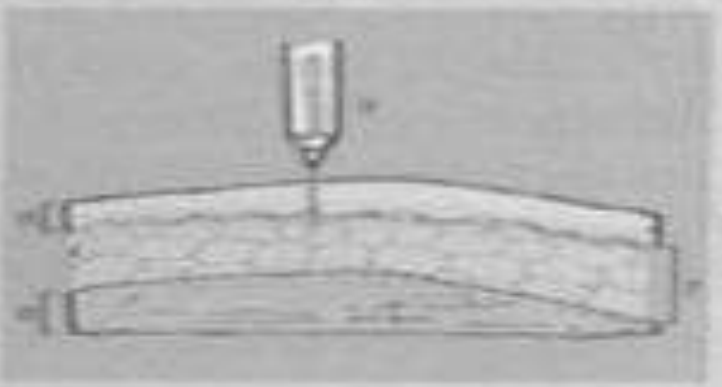
  - iv pd keadaan emmergency atau selama operasi

- T½ plasma <9 menit

- Inaktivasi oleh hepar dan ginjal

Predileksi tempat penyuntikan insulin





Tempat injeksi untuk insulin:

1. Abdomen - absorpsi cepat
2. Lengan - absorpsi sedang
3. Paha atas - absorpsi lambat
4. Bokong - absorpsi lambat
5. Bahu, siku, pinggul & lutut
6. Kulit
7. Subkutaneus
8. Otot
9. Injeksi insulin ke dalam jaringan subkutaneus (di antara kulit & lapisan otot)

TIPE INSULIN

1. Aksi cepat (rapid acting)
2. Aksi pendek (short acting)
3. Aksi menengah (intermediate acting)
4. Aksi lama (long-acting)
5. Campuran (Pre-mixed)

Pharmacokinetics of Insulin Preparations

Insulin Preparations		Onset (hr)	Peak (hr)	Duration (hr)
Rapid-acting	Regular	0.5 to 1	2.5 to 5	8 to 12
	Insulin lispro (Humalog)	0.25 to 0.5	0.5 to 1.5	2 to 5
	Insulin aspart (NovoLog)	0.17 to 0.33	1 to 3	3 to 5
	Insulin glulisine (Apidra)	0.25	0.5 to 1.5	1 to 2.5
Intermediate-acting	NPH	1 to 1.5	6 to 14	16 to 24
Long-acting	Insulin glargine (Lantus)	1.1		24
	Insulin detemir (Levemir)	0.8 to 2		up to 24
Premixed human	NPH/R 70/30	0.5 to 1	2 to 12	24
	NPH/R 50/50	0.5 to 1	2 to 12	24
Premixed analog	Insulin protamine aspart/aspart 70/30 (NovoLog mix)	0.25	1 to 3	24
	Insulin protamine lispro/lispro 75/25 (Humalog mix)	0.25	0.5 to 1.5	24

Adapted from reference 13.

ONSET & DURASI INSULIN

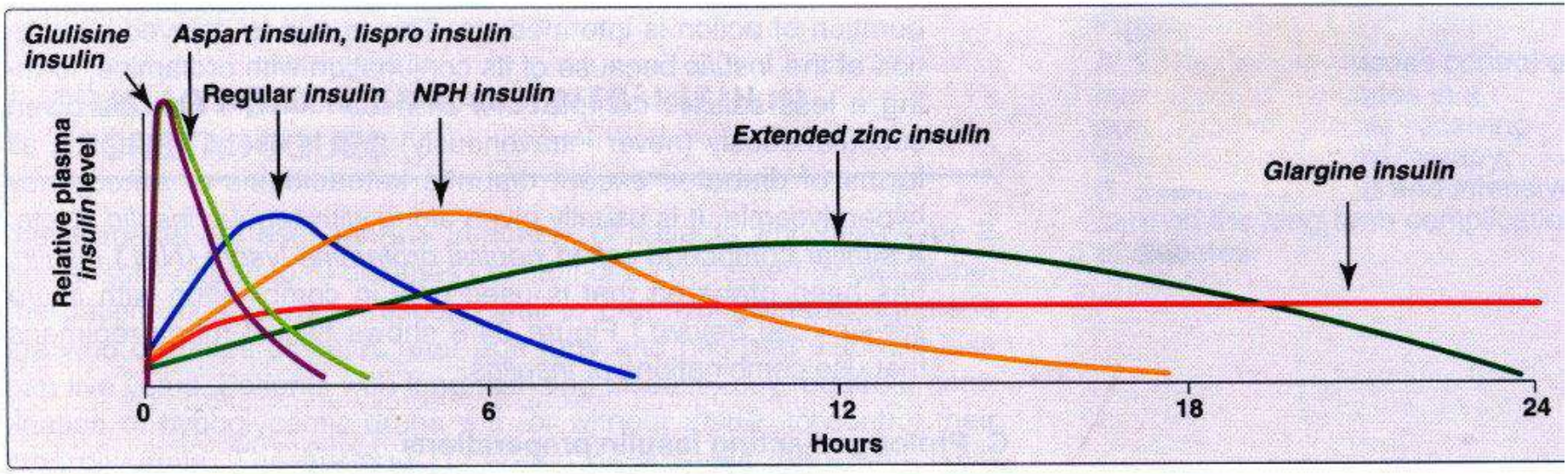
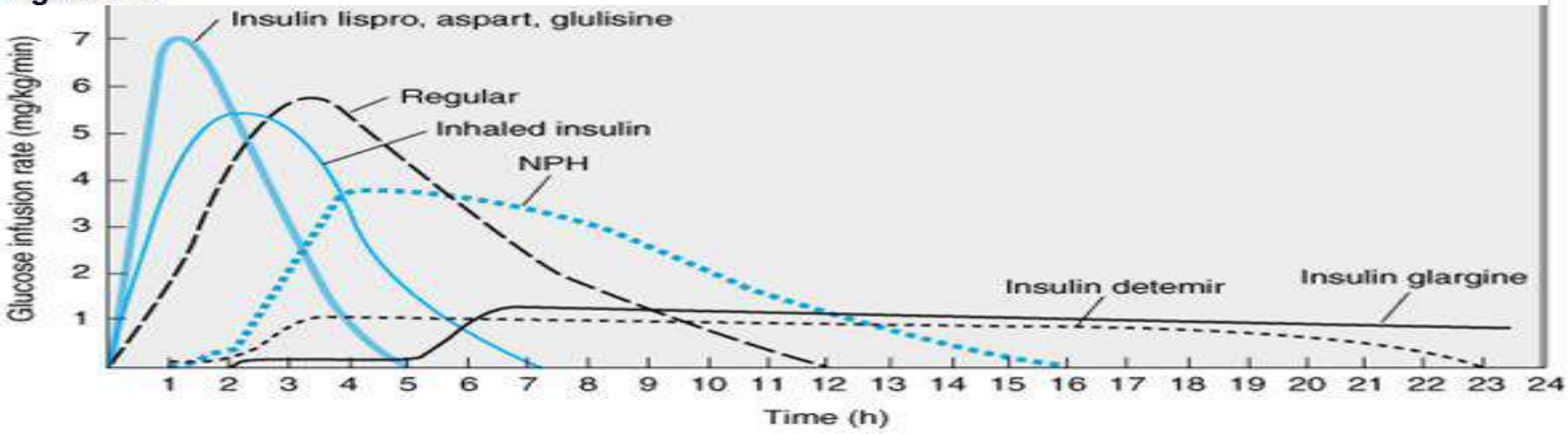
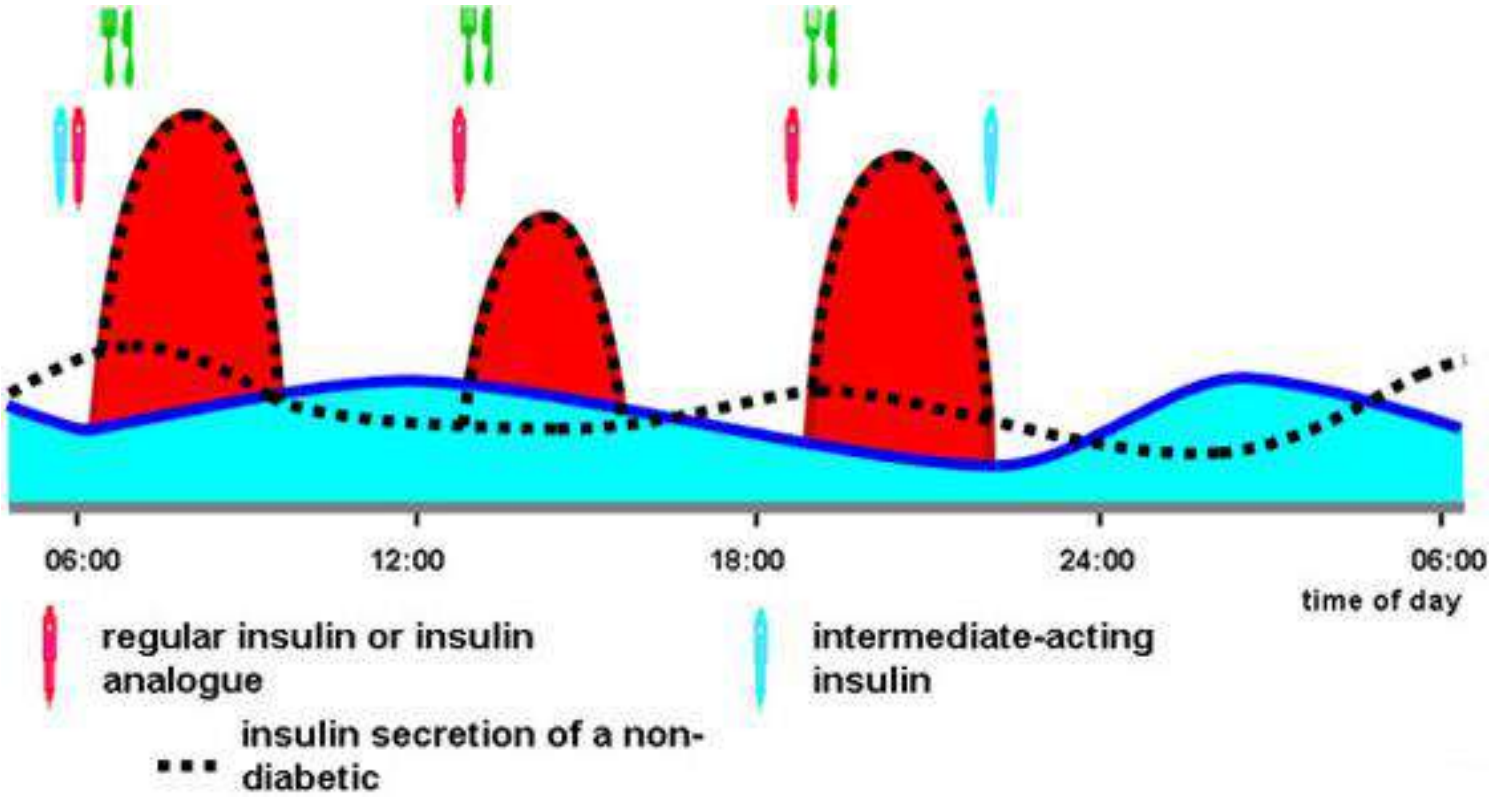


Figure 24.7



The Goal of Insulin Therapy

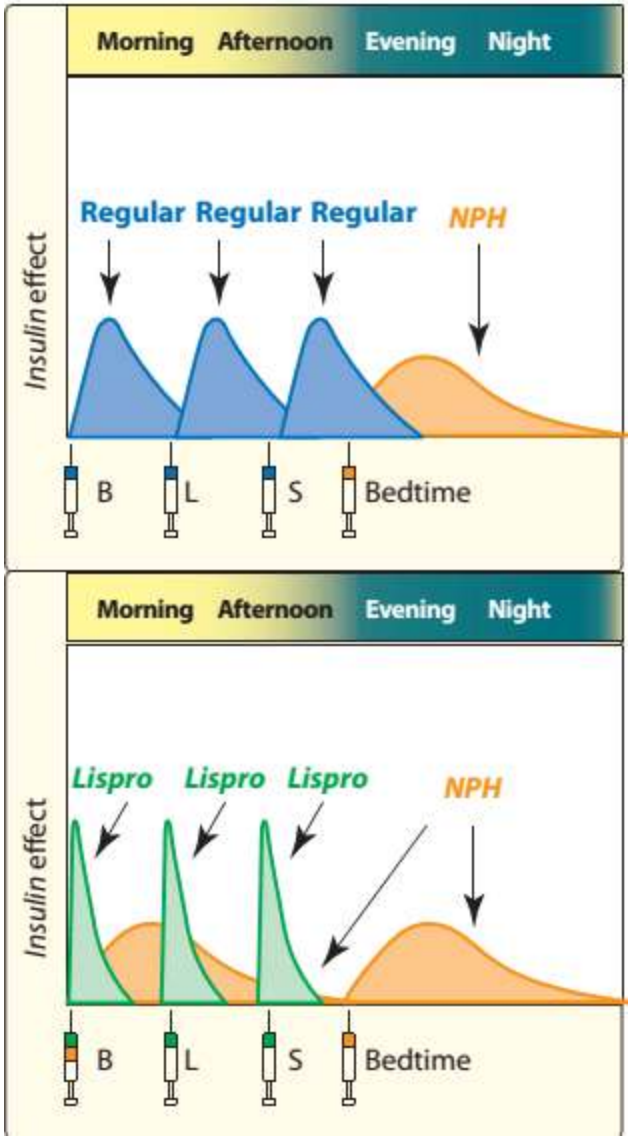
Jadwal Pemberian insulin ditata sedemikian rupa shg mirip dg kondisi basal maupun post-pandrial. Shg utk mencapai hal tsb, pemberian Insulin short-acting biasanya dikombinasi dg insulin long acting.



Rapid Onset & Ultrashort-acting Preparations

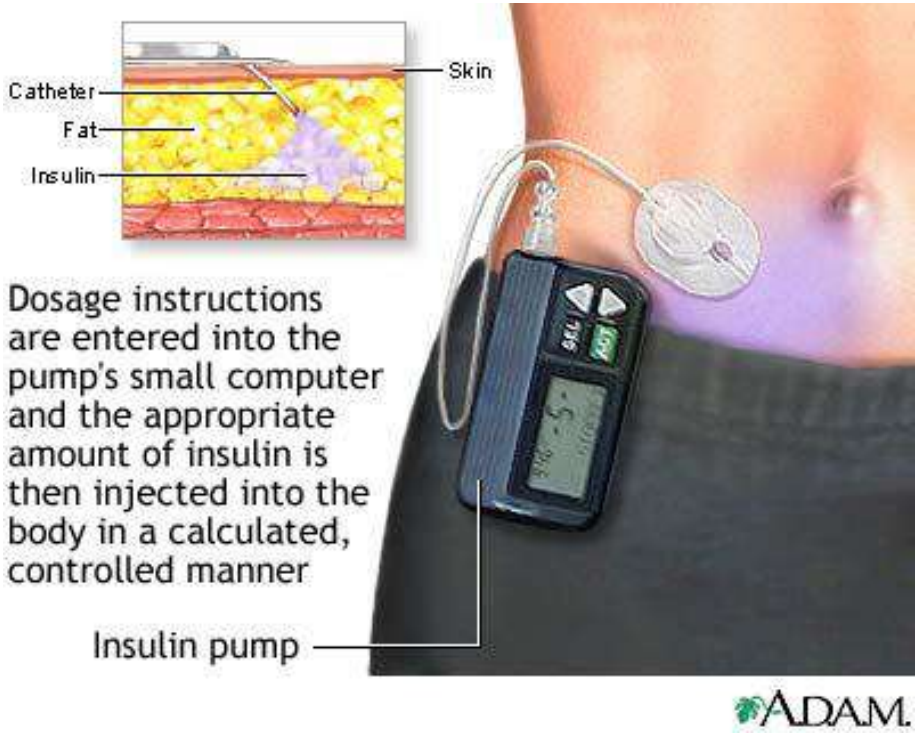
- Insulin reguler: kerja singkat, larut, insulin seng kristal biasanya diberikan subkutan, dengan cepat menurunkan kadar glukosa. Semua insulin reguler sekarang dibuat dengan menggunakan bakteri rekayasa genetika, bukan lagi dar sapi dan babi.

- Lispro, Aspart & Glulisine : ultrashort-acting, onset lebih cepat dp insulin reguler & durasi lebih pendek. Jarang menyebabkan hipoglikemia. Lispro insulin diberikan 15 menit sebelum makan & memiliki efek puncak 30-90 menit setelah injeksi (vs 50-120 menit untuk insulin reguler). Glulisine dapat diberikan 15-20 menit setelah mulai makan.



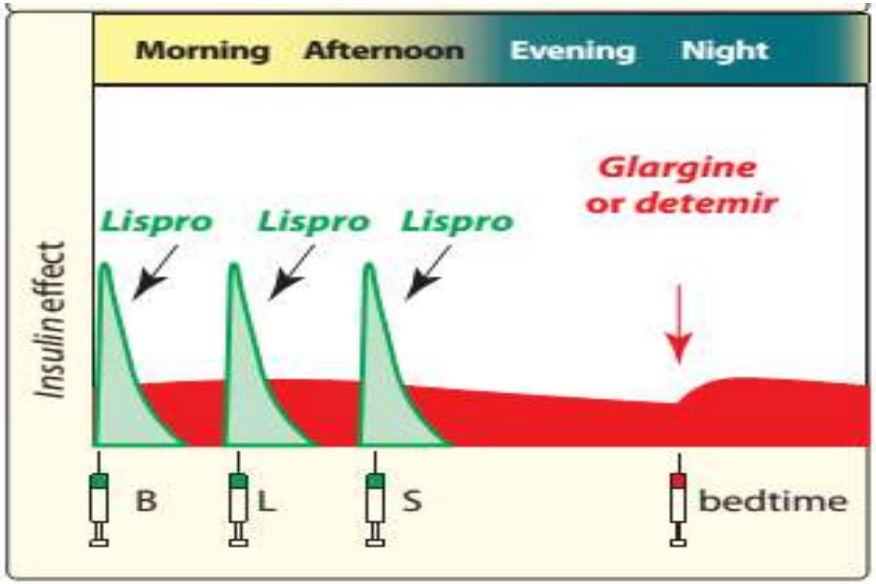
Intermediate –acting Insulin

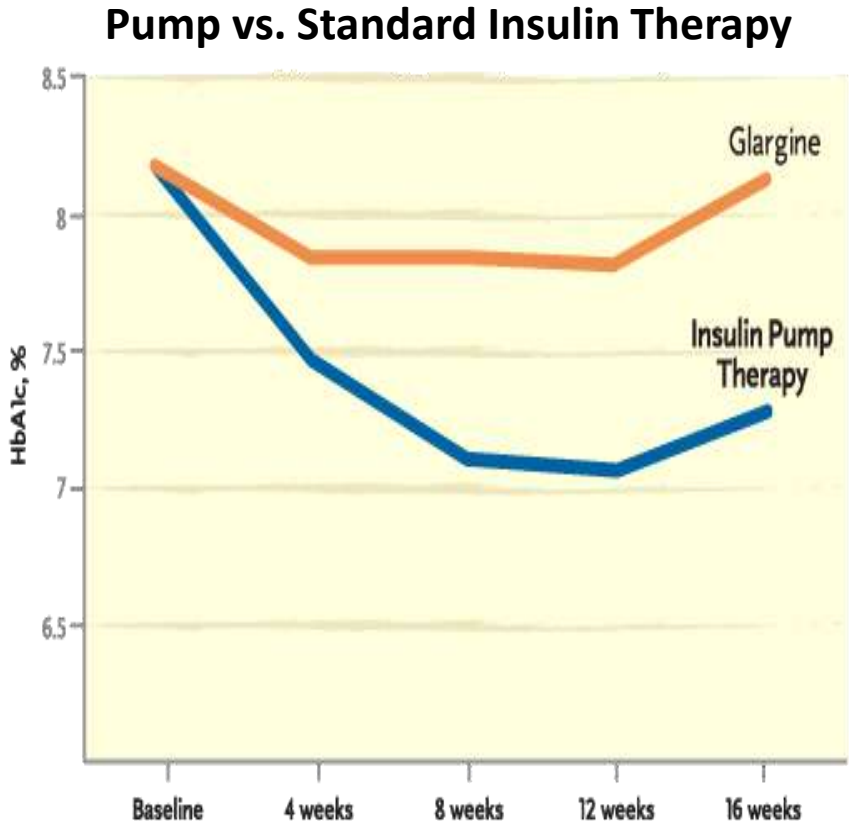
- Lente insulin: endapan amorf insulin mengandung ion seng yg dikombinasikan dg insulin ultralente 70%. Onset lebih lambat tetapi lebih kontinu dp insulin reguler. Tidak dapat diberikan IV (tdk diproduksi lg sejak th 2005).
- Isophane insulin NPH (Neutral Protamine Hagedorn) : suspensi insulin seng kristal yg dikombinasi dg protamine (polipeptida). Konjugasi dg protamine ini memperlambat onset kerjanya & memperpanjang efektifitasnya. Insulin ini biasanya diberikan kombinasi bersama insulin reguler.



Prolonged-acting Insulin

- Ultralente: suspensi insulin seng membentuk partikel besar yang larut lambat, onset lambat dan durasinya panjang.
- Insulin glargine: endapan di tempat suntikan memperpanjang durasi.
- Detemir insulin: membent kompleks dg FA mengakibatkan kelarutan lambat.

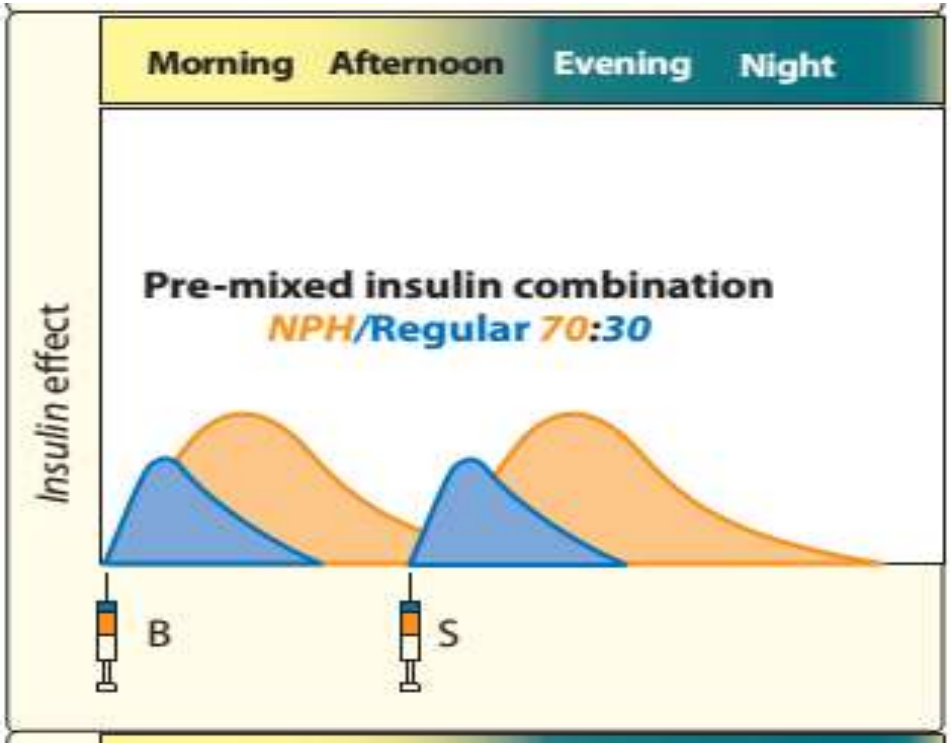




Insulin Premixed (Insulin Kombinasi)

Sediaan Insulin Kombinasi bertujuan memudahkan pemberian.

Penggunaan kombinasi ini sesuai dg yg bisa diterima individu.



Pemilihan tipe insulin

tergantung pada beberapa factor, yaitu :

- ✓ Respon tubuh individu terhadap insulin (berapa lama menyerap insulin ke dalam tubuh dan tetap aktif di dalam tubuh sangat bervariasi dari setiap individu)
- ✓ Pilihan gaya hidup seperti : jenis makanan, berapa banyak konsumsi alcohol, berapa sering berolah raga, yang semuanya mempengaruhi tubuh untuk merespon insulin.
- ✓ Berapa banyak suntikan per hari yang ingin dilakukan.
- ✓ Berapa sering melakukan pengecekan kadar gula darah.
- ✓ Usia
- ✓ Target pengaturan gula darah.

Jenis insulin	waktu	Aturan pengaturan gula darah
Rapid –Acting		
Onset	15-30 menit	Digunakan bersamaan makan. Jenis ini digunakan bersamaan dengan jenis insulin longer-acting.
Peak	30-90 menit	
Duration	1-5 jam	
Short Acting		
Onset	½-1 jam	Digunakan untuk mencukupi insulin setelah makan 30-60 menit.
Peak	2-5 jam	
Duration	2-8 jam	
Intermediate-Acting		
Onset	1-2 ½ jam	Digunakan untuk mencukupi insulin selama setengah hari atau sepanjang malam. Jenis ini biasa dikombinasi dengan jenis rapid-acting atau short-acting.
Peak	3-12 jam	
Duration	18-24 jam	
Long-Acting		
Onset	½-3 jam	Digunakan untuk mencukupi insulin seharian. Jenis ini biasa dikombinasi dengan jenis rapid-acting atau short-acting.
Peak	6-20 jam	
Duration	20-36 jam	
Pre-Mixed*		Produk ini biasanya digunakan dua kali sehari sebelum makan. Premixed insulin adalah kombinasi dengan proporsi yang spesifik insulin intermediate-acting dan insulin short-acting insulin di satu botol atau insulin pen.
Onset	10-30 menit	
Peak	½ -12 jam	
Duration	14-24 jam lebih	

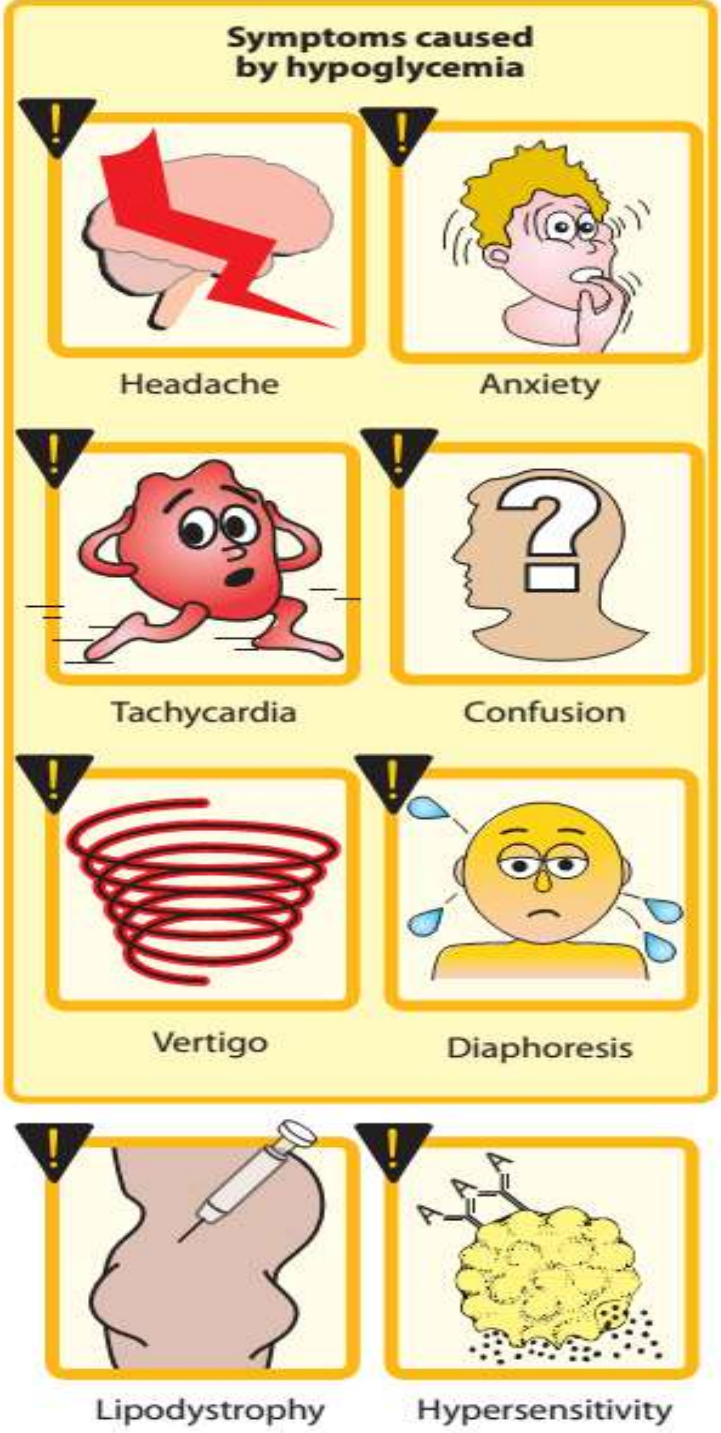
Options of insulin therapy in type 2 diabetes

- ***fasting hyperglycemia:***
  long acting insulin (or analogue) at bedtime
- ***postprandial hyperglycemia:***
  prandial insulin therapy with rapid acting insulin analogues or regular insulin
- ***constant hyperglycemia:***
  pre-mixed insulin (50/50 to 25/75) before breakfast and supper, respectively

NB! All options may by combined with oral agents

ES Terapi Insulin

- ✓ Hipoglikemia terjadi jk : overdose, intake kalori kurang (lupa/malas makan, makan terlambat, komposisi makanan tdk tepat, dll). Konsumsi Etanol meningkatkan respon hipoglikemik.
- ✓ Hipokalemia: insulin menarik + K ke dalam sel.
- ✓ Anafilaksis: ketika sensitif terhadap non-human insulin (jarang)- urtikaria, angioedema, anafilaktik
- ✓ Lipodistrofi di tempat suntikan (perubahan pd subcutaneous fat akibat injeksi berulang di tempat yg sama)
- ✓ Berat badan ↑
- ✓ komplikasi injeksi



TANDA HIPOGLIKEMI

- Tergantung cepat / tidaknya penurunan kadar glukosa dlm plasma
- Cepat :

  keringat dingin, takikardi, tremor, mual, lapar
- Lambat :

  sakit kepala, blurred vision, bingung, inkoheren speech, kejang, koma

TERAPI HIPOGLIKEMI

- Glukosa

  - pasien sadar : p.o

  - pasien tdk sadar : i.v bolus D40%, selanjutnya bisa di maintenance dg Dextrose 10%
- Glukagon injeksi

GLUCAGON

- Mek kerja : Binds cell surface glucagon receptor
  - activates adenylyl cyclase (increases cAMP) via stimulatory G-protein
  - cAMP induces PEPCK gene expression
  - PK-A activates phosphorylase and inactivates glycogen synthetase in liver

- Efek utama :
  - stimulates liver carbohydrate metabolism
    increases glycogenolysis and gluconeogenesis, decreases glycogen synthesis
  - stimulates insulin release
  - cardiac stimulation
    increase contractility, little effect on rate

- FK : Must be given parenterally, plasma half-life about 9 min, degraded by liver, kidney, plasma

ORAL ANTIDIABETICS

ORAL ANTI DIABETIK (OAD)

- INDIKASI :
  - ✓T2DM yg tidak respon dg intervensi non-drug.
  - ✓T2DM yg baru terDx (< 5^{th}), yg berespon baik dg OAD.

- T2DM lama kdg perlu Tx kombinasi OAD +/- insulin yaitu jk tjd penurunan progresif pd sel β fungsional, shg perlu tambahan insulin utk beberapa waktu.
- OAD tidak pernah diindikasikan untuk Type I.

Mekanisme kerja Oral Antidiabetics (OAD)

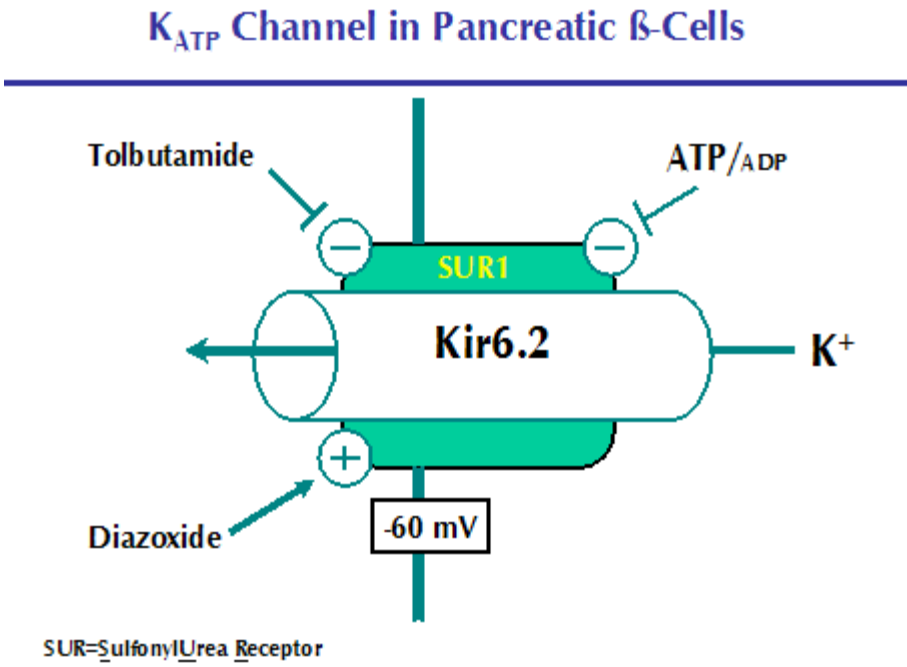
Me ↓ absorbsi glukosa	Me ↑ sekresi insulin	Me ↓ produksi glukosa hepar	Me ↑ uptake glukosa di perifer
Acarbose Biguanid	SU 1st, 2nd ,3rd Meglitinide	Biguanid	SU 2nd & 3rd Biguanid Thiazolidindion

SULFONILUREA (SU)

Mekanisme Kerja :

- Menstimuli release insulin endogen dari sel beta

  SU memblok kanak K yg sensitif ATP → depolarisasi → Ca influk → sekresi insulin
- Pada dosis besar, menghambat metabolisme insulin di hepar
- Menurunkan kdr glukagon. Hambatan sekresi glukagon tjd secara tdk langsung akibat me↑nya sekresi insulin dan somatostatin shg menghambat sekresi sel α pankreas.
- Potensiasi kerja insulin di jaringan target, Me↑ ΣR/insulin



Farmakokinetik :

- 70-90% terikat prot plasma t.u albumin
- metab di hepar

Penggolongan Sulfonylurea

Rel. Potency

- 1st generation
  - **tolbutamide** (Rastinon, Orinase)
  - **tolazamide** (Tolinase)
  - **chlorpropamide** (Diabinese)
- 2nd generation
  - **Gliclazid**
  - **Glipizide** (Minidiab, Glucotrol)
  - **Glyburide / Glibenclamid** (Daonil, Glulo, Prodiabet)
  - **Gliklasid** (Diamicron, Glidiabet, Zumadiac)
- 3rd generation
  - **Glimepiride** (Amaryl)

*Hydroxylation of the aromatic ring appears to be the most favored metabolic pathway
*Hydroxylated derivatives have much lower hypoglycemic activity

Sulfonylureas

ES : BB ↑, hiperinsulinemia , syok hipoglikemia (overdosis), mual, sakit kepala

Resiko toksik ↑: pada insufisiensi hepar & ginjal, interaksi Ox ttt, lanjut usia.

- Tolbutamide is asociated with a 2.5X ↑ in cardiovascular mortality.

Indikasi : Hanya utk T2DM

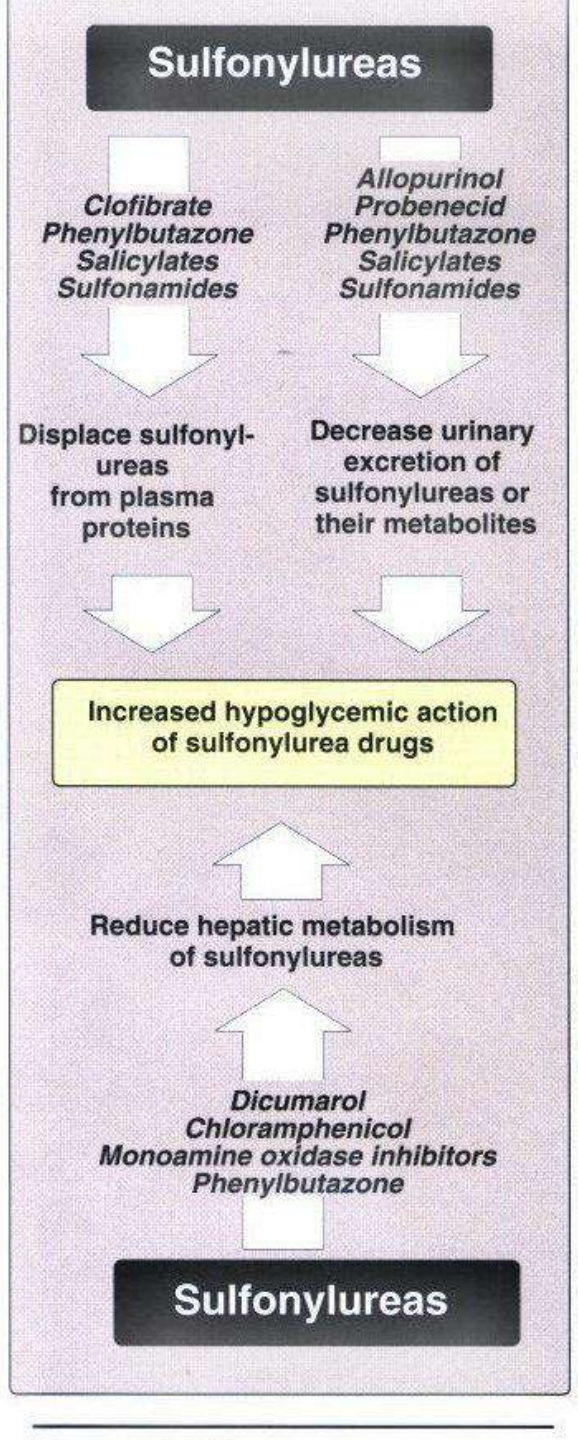
plg baik utk usia > 40 th, menderita DM < 10th, jk memakai insulin < 40 unit

Kontraindikasi :

DM Type-1, diabetes sekunder, kebutuhan insulin tdk stabil, ketosis-prone diabetics, diabetes krn kehamilan

Onset & Duration

- **Short acting**: Tolbutamide (Orinase)
- **Intermediate acting**: Tolazamide (Tolinase), Glipizide (Glucotrol), Glyburide (Diabeta)
- **Long acting**: Chlorpropamide, Glimepiride



Perbandingan SU & Meglitinid

	Repa-glinide	Tolbu-tamide	Gliclazide	Glipizide	Gliben-clamide	Glime-piride
Relative potency	± 400	1	30	50 - 100	150 - 400	400-1000
mg/tablet	0.5-2	500	80	5-10	1.25-5	1- 4
Plasma peak (h)	< 1	3	4	1	3	2.4
Duration (h)	< 6	6 - 10	24	16 - 24	24	24

Gerich N Engl J Med 321 (18) 1231-45,1989
HMR Amaryl Monograph

Sulfonylurea : Hypoglycemic risk

	Relative Risk
Repaglinide	1 - 2
Tolbutamide	1
Gliclazide	1 - 2 (2)
Glipizide	2 (1)
Glimepiride	3 - 4 (3)
Glibenclamide	5 (1)

1) Ferner 1988
(2) Teisse, Diab Med,1994
(3) Dills, Horm Metab Res,1996

Prinsip Pemakaian Sulfonylurea

- Dosis kecil terbagi sebelum makan lebih baik daripada dosis besar yg diminum pagi saja (resiko hypoglycemic >)
- Kontrol sekali seminggu.
- Mulailah terapi dg satu OAD dan monitor gula darahnya
- Jk msh jauh dr target (>8.0%), tambahkan OAD lain (mis:metformin, acarbose, atau pioglitazone jk tdk KI).

Interaksi Obat

- Obat yg dpt me↑ resiko hipoglikemi :

  insulin, alkohol (me↓ glukoneogenesis), fenformin, sulfonamid, salisilat dosis besar (me↑ sekresi insulin), fenilbutazon, oksifenbutazon, probenezid, dikumarol, kloramfenikol, MAO inhibitor, guanetidin, anabolik steroid, fenfluramin, dan klofibrat

- obat yg menutupi tanda hipoglikemi : propanolol

MEGLITINIDE ANALOGS

Contoh : Repaglinide (Prandin) , Nateglinide (Starlix).

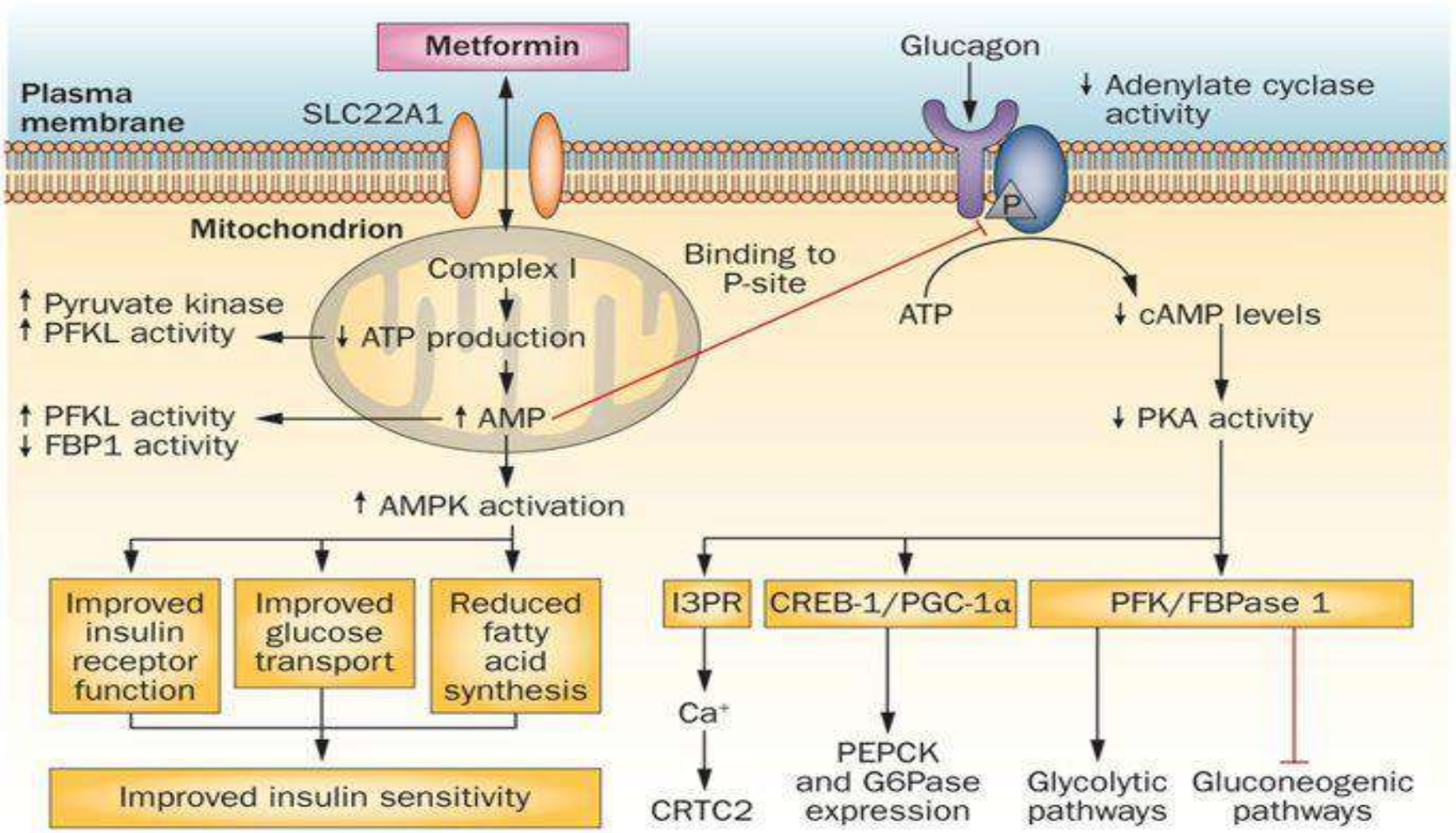
- Mekanisme: menghambat kanal K+ yg sensitif ATP (spt sulfonilurea)→ me↑sekresi insulin (insulin secretogogues). Onset & durasi lebih singkat dp SU. Kurang efektif sbg monoterapi.
- onset cepat, durasi pendek (T1/2 = 1 dan 1.5 jam). Agen ini dimetabolisme oleh CYP3A4 dan diekskresikan dalam empedu.
- Diminum 30 menit (repaglinide) atau 1-10 menit (nateglinide) sebelum makan; skip a meal, skip a dose
- Efek samping: hipoglikemia (lbh jarang dibanding sulfonilurea). Obat yang menghambat CYP3A4 (ketoconozole, flukonazol, eritromisin, dll) dpt memperpanjang durasi. Obat yang menginduksi CYP3A4 (barbiturat, karbamazepin dan rifampisin)dpt menurunkan efektivitasnya. Kombinasi gemfibrozil dan repaglinide telah dilaporkan dpt menyebabkan hipoglikemia berat.

BIGUANID

- Contoh : Metformin
- = sbg insulin sensitizer →me↑uptake & pemanfaatan glukosa oleh jar target. Tidak me ↑sekresi insulin → Risiko hipoglikemia <<<<<<
- Mekanisme:

  - me↓ glukoneogenesis hepatik (UTAMA)
  - memperlambat penyerapan gula di usus
  - me↓ hiperlipidemia (4-6 minggu pengobatan)
  - me↓ nafsu makan.
- Dpt dikombinasi dg OAD lain atau insulin.
- ES: Asidosis laktat (jarang, t.u pd penderita DM dg CHF /gangg ginjal), Gangguan sal. Cerna :Mual, rasa tdk enak di perut, diare, metallic taste, anoreksia. Pd penggunaan kronis dapat me↓ absorbsi vitamin B12 dan folate
- Juga digunakan dlm terapi polycystic ovary syndrome

Mekanisme Kerja Metformin



THIAZOLIDINEDIONES (GLITAZONES)

. Contoh : Troglitazone , Pioglitazone dan Rosiglitazone

- = merupakan insulin sensitizer. Bekerja dg cara me ↓ resistensi insulin mell regulasi gen yg terlibat dlm metab glukosa & lemak serta diferensiasi sel lemak
- Mekanisme kerja : obat ini bekerja melalui aktivasi Peroksisome proliferator-activated reseptor-γ (PPAR-γ). Aktivasi PPAR-γ menyebabkan sensitivitas insulin ↑ di adipocytes, hepatosit dan otot rangka.
- Dpt memperbaiki keadaan Hiperglikemia, hiperTG & pe↑HbA1c. Kadar HDL jg di ↑.
- Troglitazone merupakan 'glitazone' pertama utk NIDDM. Saat ini sdh dilarang penggunaannya krn menyebabkan kegagalan fungsi hepar

- Thd insulin endogen ataupun eksogen, glitazones akan :
  - me↓ gluconeogenesis, glucose output, dan produksi TG di hepar
  - me↑ glucose uptake dan penggunaannya di otot skeletal
  - me↑ glucose uptake dan me↓ fatty acid output di jaringan lemak.
- Effect pd sekresi insulin belum jelas
  - mungkin me↑ sensitifitas sel Beta terhadap glukosa
- Dpt dipakai sebagai monotherapy atau kombinasi dg metformin, sulfonylureas

Efek Samping dan Interaksi Obat

- FK: Keduanya secara ekstensif terikat albumin, mengalami metabolisme P450 yang ekstensif, metabolit yang diekskresikan dalam urin dlm bentuk utuh.
- ES:

  - hepatotoksisitas fatal dpt tjd, perlu monitoring fungsi hati.

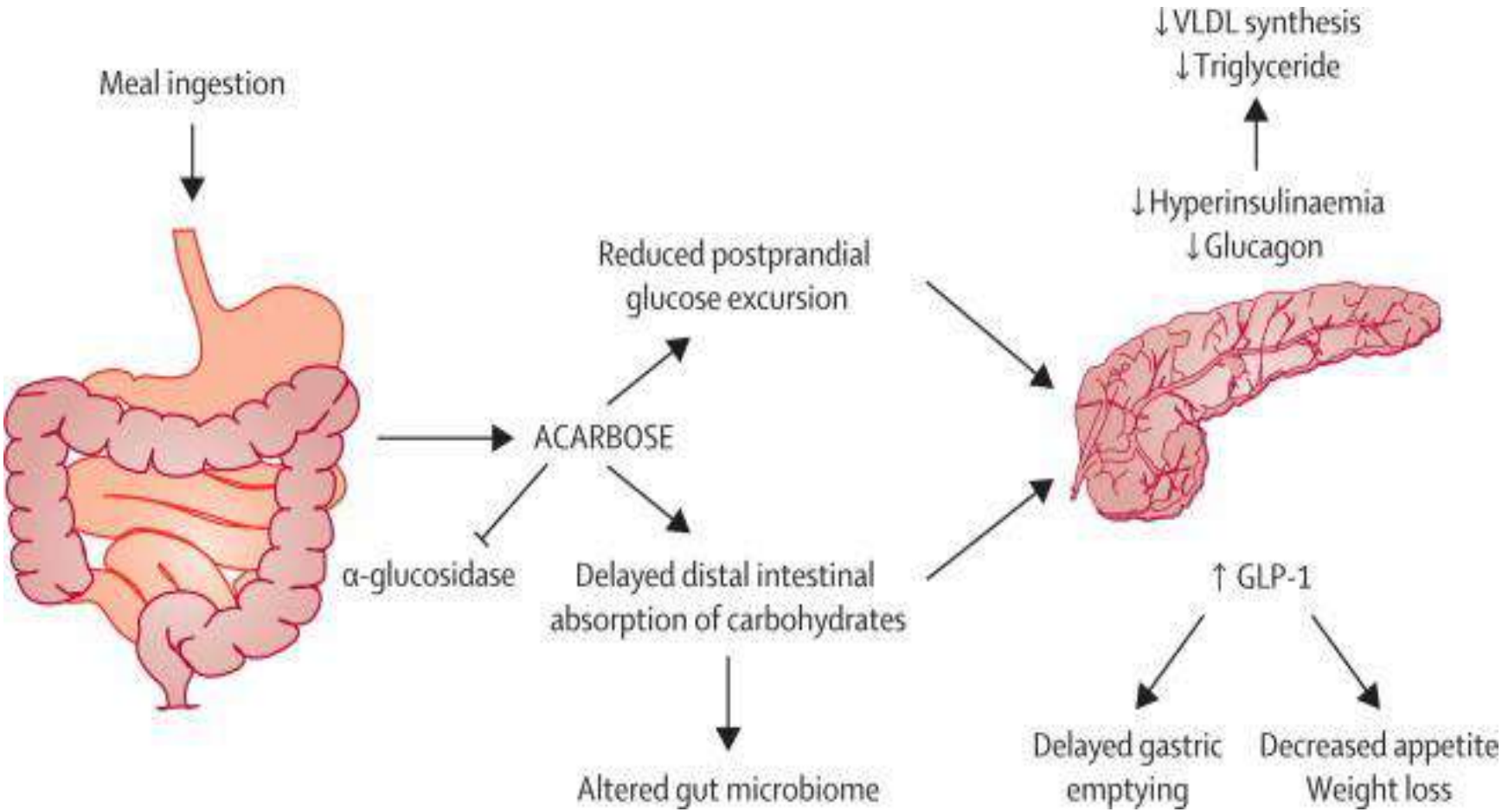
  - Retensi cairan ⇨ edema, mild anemia

  - tdk menyebabkan asidosis laktat , bahkan pd pasien dg gangguan fungsi ginjal
- Pioglitazone berinteraksi dg obat yg dimetabolisme oleh CYP3A4 .
  - Mis. Pioglitazon ⇨ me↑ metabolisme kontrasepsi yg mengandung ethinyl estradiol dan norethindrone ⇨ kdr kontrasepsi tsb di plasma ↓
- Hanya pioglitazone yg dpt dikombinasi dg insulin, dosis insulin harus dimodifikasi. Rosiglitazone dpt digunakan dg OAD lain, namun menyebabkan edema berat jk dikombinasi dg insulin.

α-Glucosidase Inhibitors

- Contoh : Acarbose, Miglitol
- Mek kerja ; menghamb sec kompetitif enzim (maltase,isomaltase, sucrase & glucoamylase) di brush border ➔ menghamb hidrolisis oligosakarida menj monosakarida, memperlambat pemecahan sukrose & memperpanjang masa absorbsi glukosa di GI
- Hasil akhir : me↓ peningktan kdr gula setelah makan. Tidak mempengaruhi kadar gula puasa
- Pd monoterapi, tdk menyebabkan hipoglikemi
- competitive inhibitors ⇨ diberikan sebelum makan
- ES= kembung, diare, kram. Bioavailabilitas Metformin sangat menurun bila digunakan bersamaan.
- KI =DM dg patologi usus.

Mekanisme kerja Acarbose

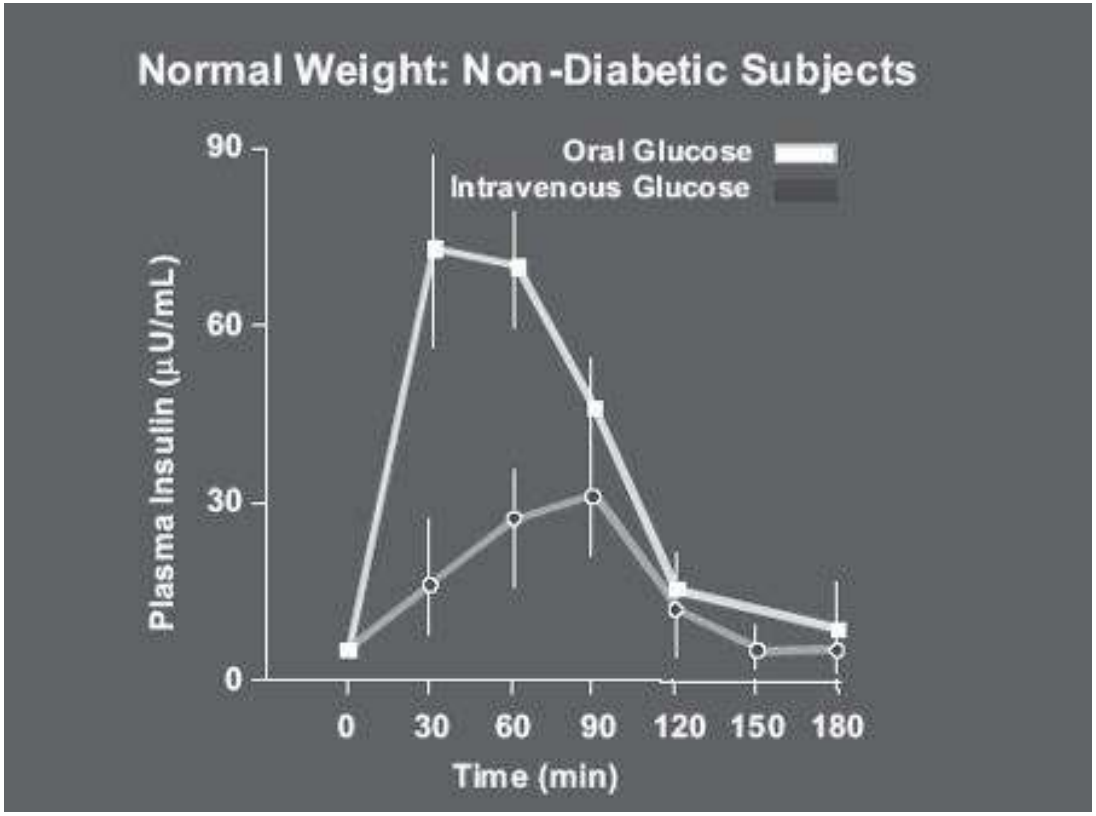


TERAPI BARU T2DM

- **Terapi berbasis Incretin:**
  - GLP-1 analog
  - DPP IV inhibitor
- **SGLT2 inhibitor**
- **Dopamin-2 agonis**

Peran Incretin

- Glukosa oral menyebabkan sekresi insulin >> dp glukosa i.v, krn pemberian sec oral menyebabkan aktivasi hormon GIT Incretin yg selanjutnya akan memperkuat stimulasi pd sel beta pankreas utk sekresi insulin



INCRETIN THERAPY

- Incretin =merup hormon yg disekresi usus. Kdrnya ↑ketika ada makanan yg tertelan.
- GIP dan GLP-1 adalah 2 hormon incretin utama pada manusia GLP-1 (Glucagon-Like Peptide 1) dan GIP (Glukosa-dependen Insulotropic Peptide) bekerja pd sel α&β pankreas dlm menghadapi fluktuasi glukosa.
- GIP = peptida 42-aa berasal dari protein yang lebih besar (ProGIP) & disekresikan oleh sel-sel endokrin K terutama ada di proksimal GIT (duodenum & jejunum proksimal).
- GLP-1 = 30 - peptida atau 31-aa berasal dari protein yang lebih besar (proglucagon) & disekresikan oleh sel-sel L terletak t.u di GIT distal (ileum dan kolon). Protein ini pertama kali diisolasi dari kelenjar ludah racun dari kadal rakasa Gila

Effects of GLP-1 and GIP on Glucose Metabolism

GLP-1

- ↑ insulin (incretin)
- ? insulinomimetic
- ↑ islet/β cell mass
- ↓ glucagon secretion and hepatic gluconeo-genesis
- ↓ gastric emptying

GIP

- ↑ insulin (incretin)
- insulinomimetic
- ↑ islet/β cell mass
- ↑ glucagon secretion but ↓ gluconeogenetic response to glucagon
- ↓ gastric emptying

The Incretin Effect Is Diminished in Type 2 Diabetes

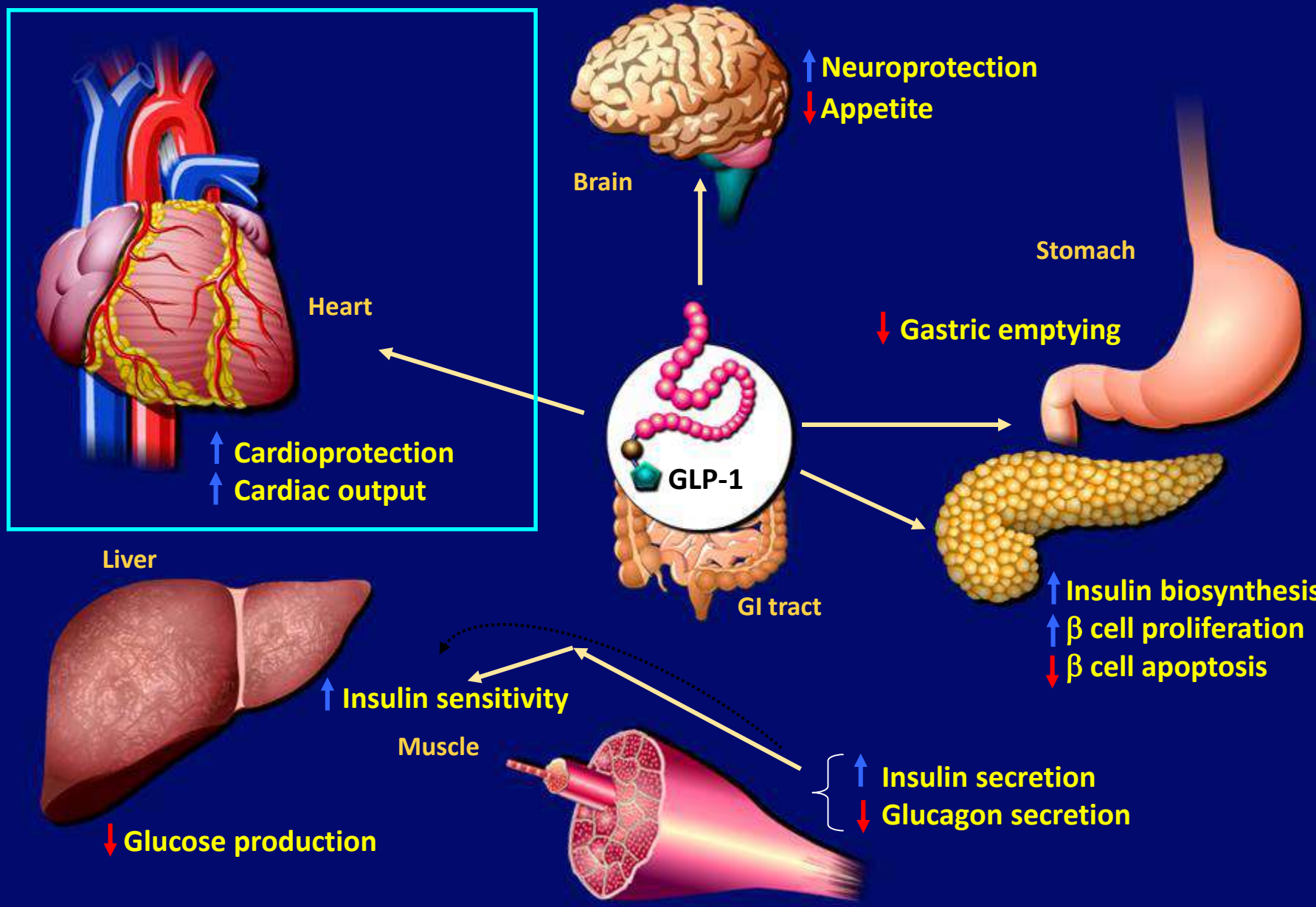
Levels of GLP-1 are decreased.

The insulinotropic response to GIP is diminished but not absent.

Defective GLP-1 release and diminished response to GIP may be important factors in glycemic dysregulation in T2DM.

The physiologic activity of incretins is limited by the enzyme dipeptidyl peptidase-4 (DPP-4), which rapidly degrades active incretins after their release.

Summary of Incretin Actions on Different Target Tissues

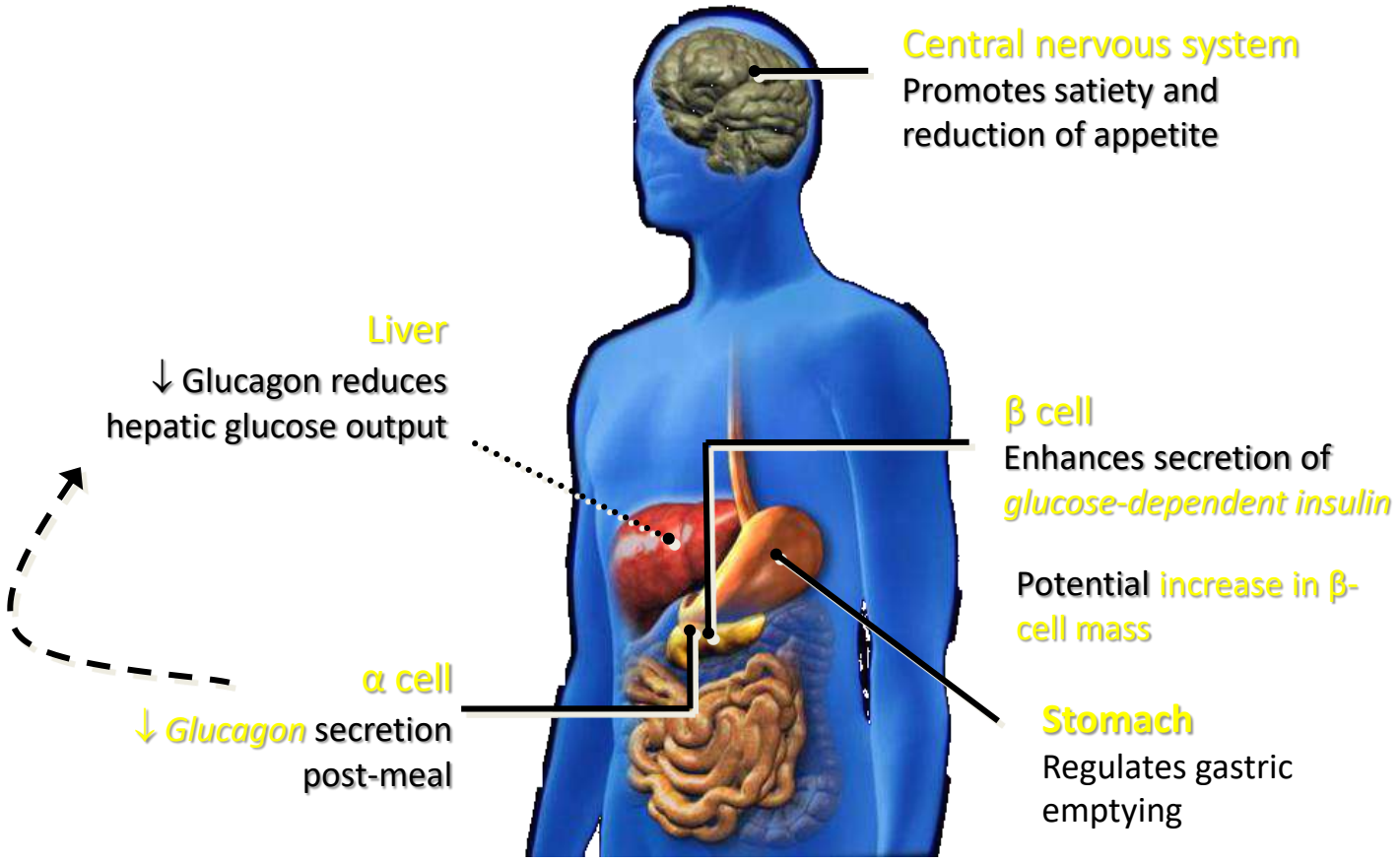


Drucker D. J. *Cell Metabolism* 2006

GLP-1 analog

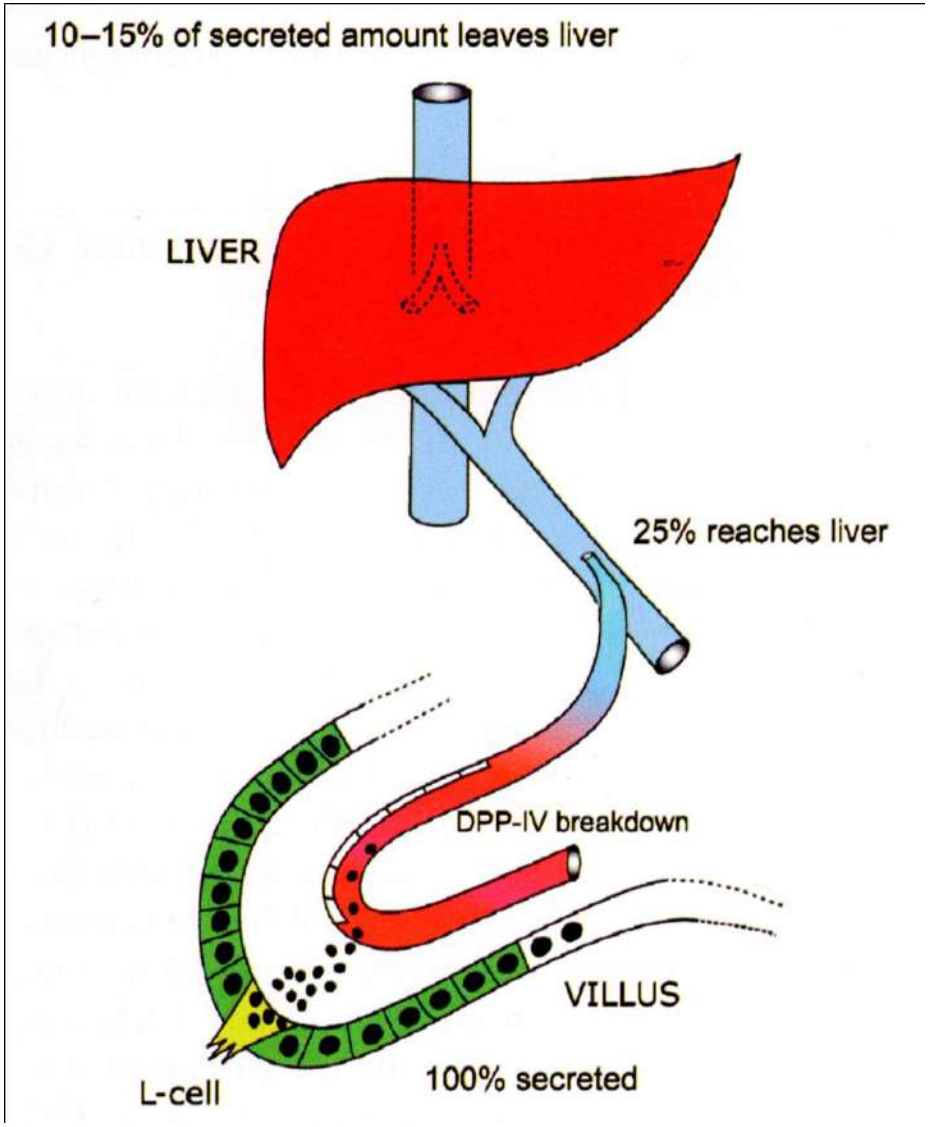
- Contoh : Exenatide and Liraglutide,
- Mek kerja : sbg analog GLP-1 yg resisten terhadap enzim **dipeptidyl peptidase-4 (DPP-4)** $\rightarrow$ waktu paruh GLP-1 memanjang.

Summary of GLP-1— Effects in Humans



Flint A et al. *J Clin Invest*. 1998;101:515-520. Larsson H et al. *Acta Physiol Scand*. 1997;160:413-422. Nauck MA et al. *Diabetologia*. 1996;39:1546-1553. Drucker DJ. *Diabetes*. 1998;47:159-169.

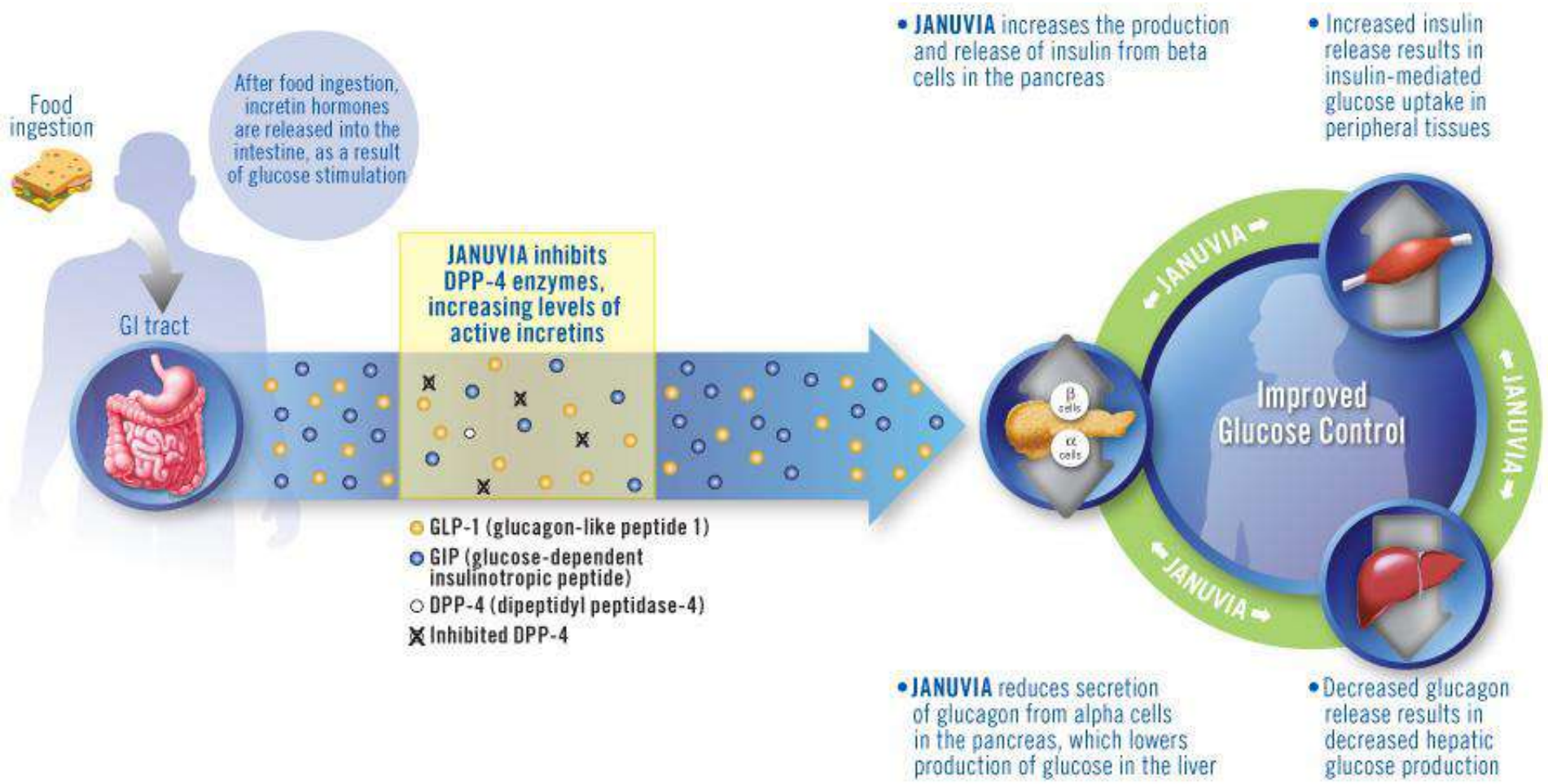
GLP-1 breakdown by DPP IV



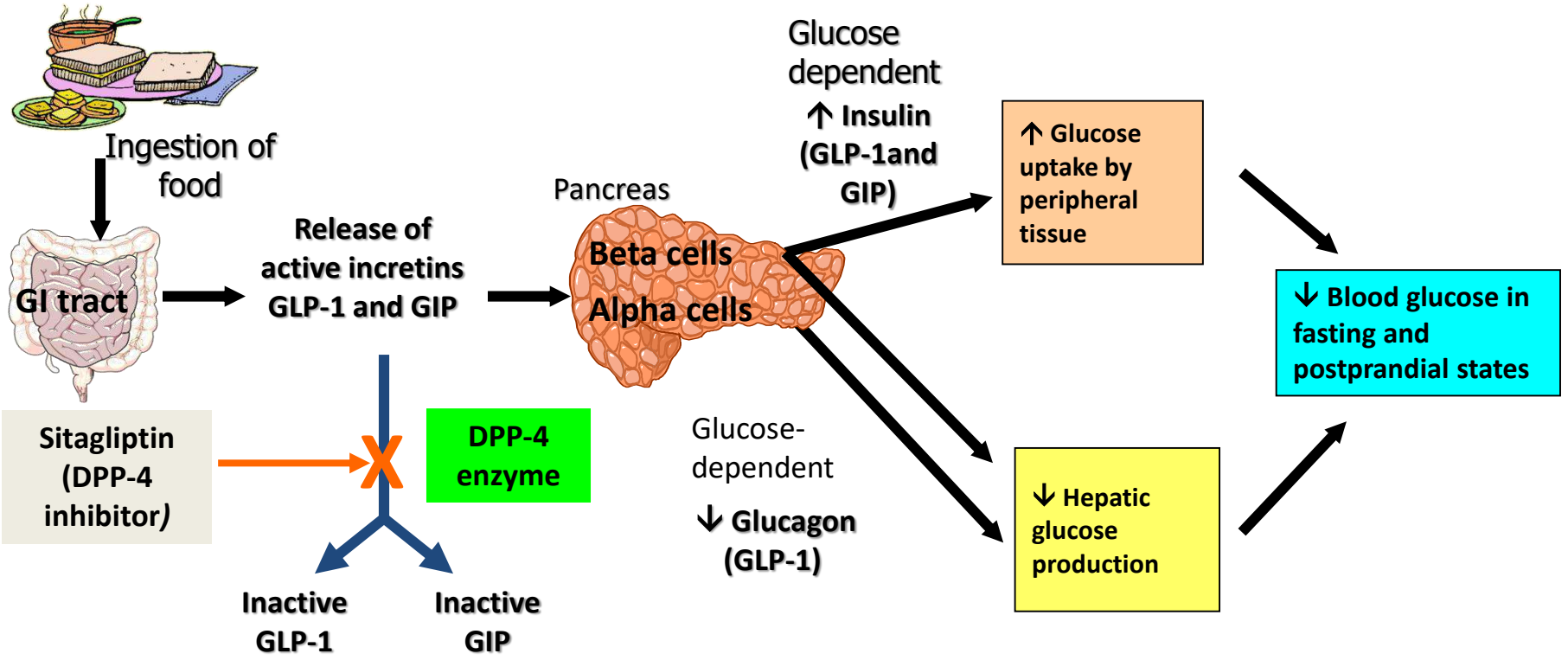
Holst, Diabetologia 48(2005) 612-15

DPP IV inhibitor

Sitagliptin , vildagliptin



Sitagliptin: Mechanism of Action (cont)



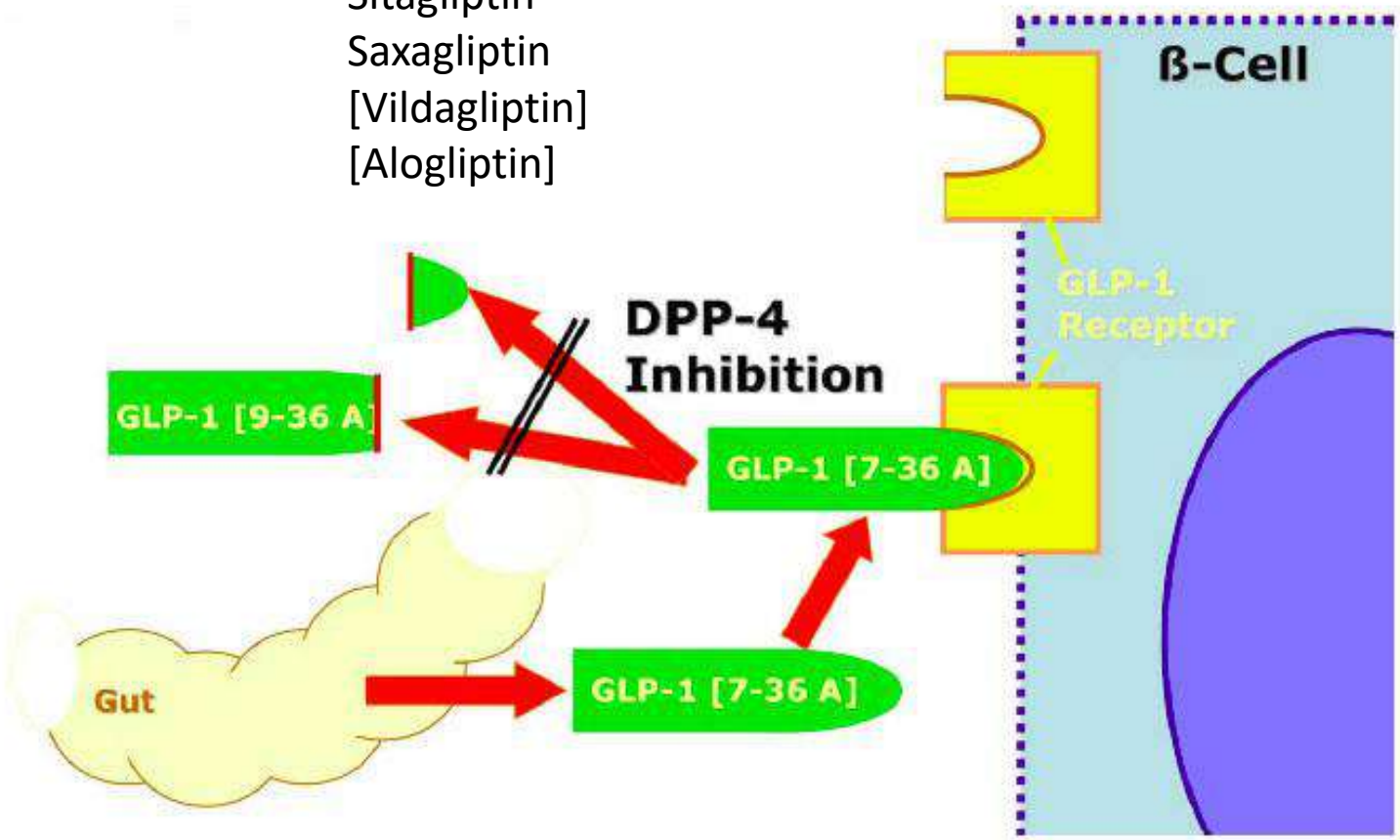
Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels ↑ in response to a meal

Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the actions of these hormones

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide.

DPP-IV INHIBITORS

Sitagliptin
Saxagliptin
[Vildagliptin]
[Alogliptin]

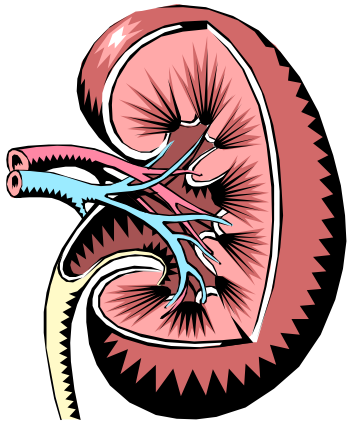


- Glucose-dependent stimulation of insulin secretion
- Reduction of gastric emptying
- Reduction of inappropriate glucagon secretion
- Beta-cell proliferation / regeneration

Adapted from: Nauck MA et al. (2009). Diabetes Care 32(S2):S223

Kidney and Glucose Homeostasis

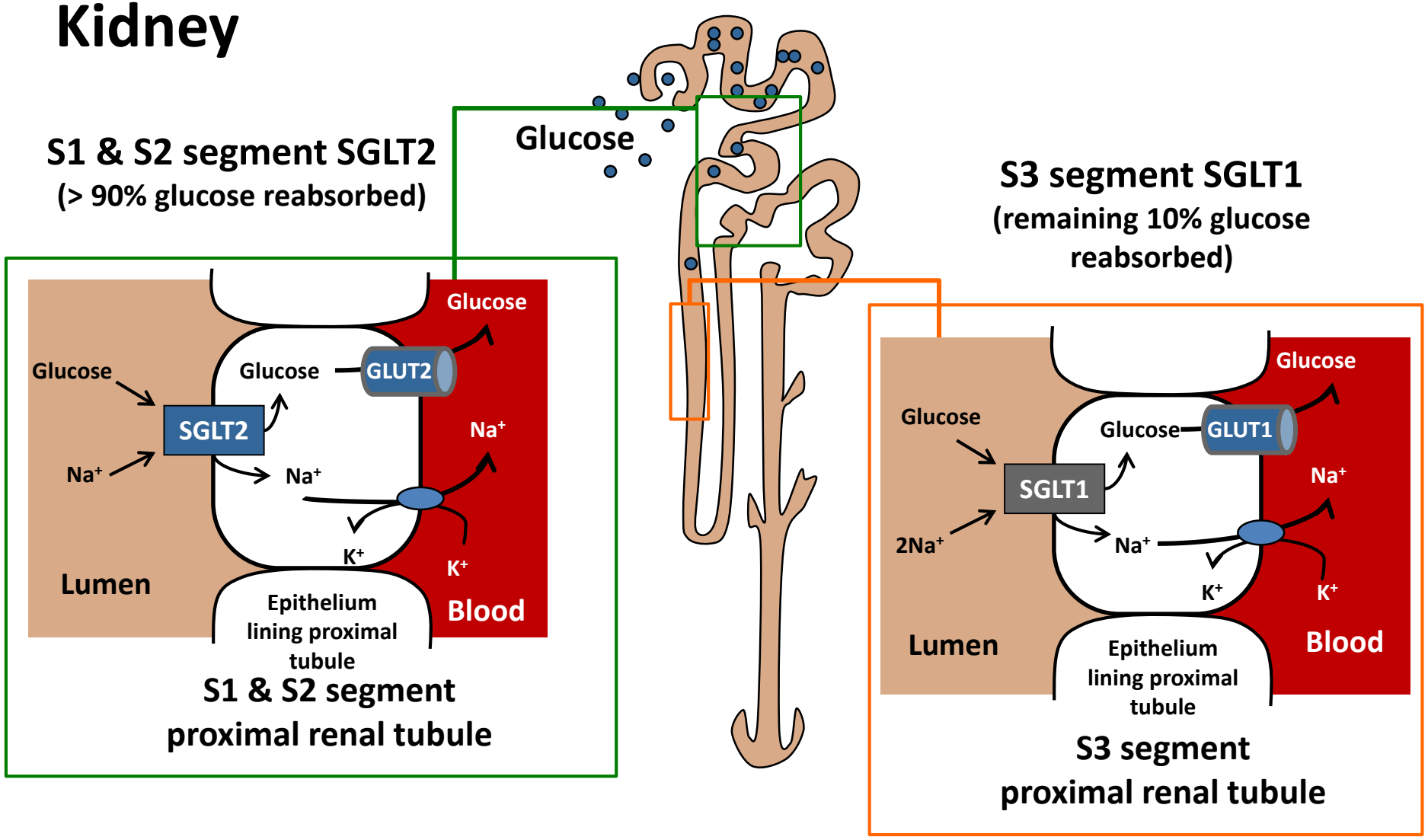
The Kidney



- Produces glucose
- Uses glucose
- Filters glucose
- Reabsorbs glucose

Courtesy of Clifford Bailey, PhD

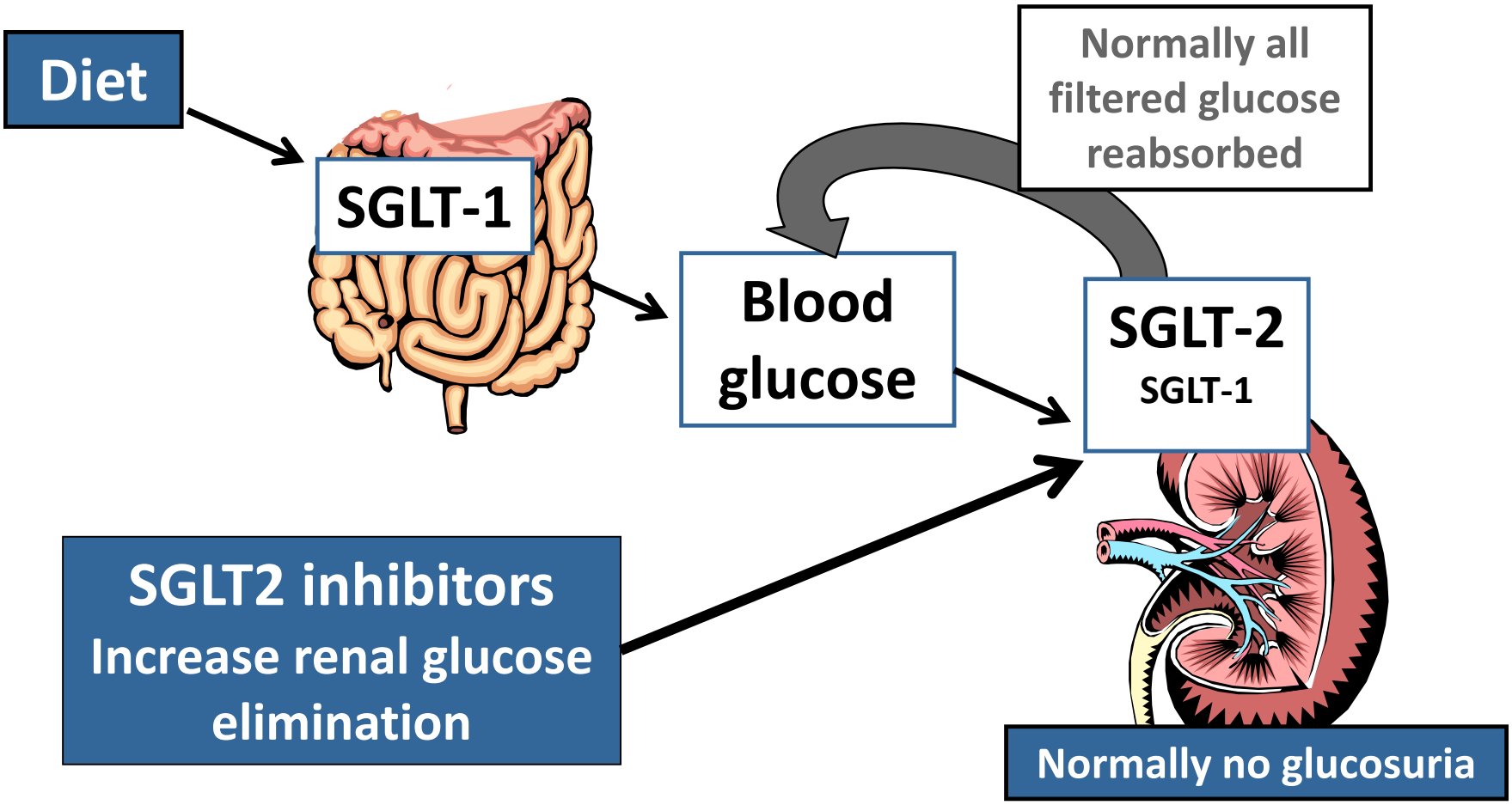
Location of Sodium Glucose Transporters in the Kidney



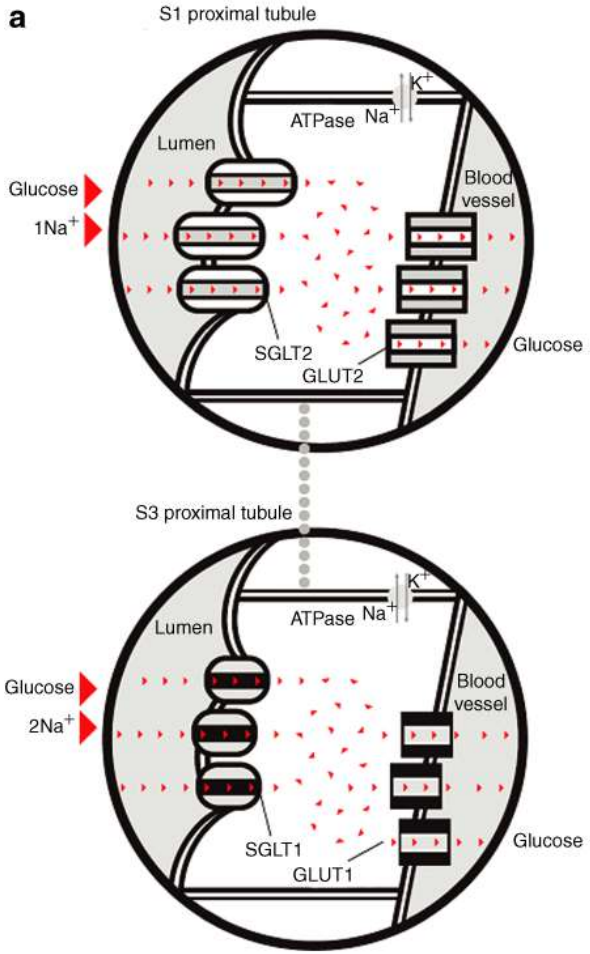
Adapted from Bailey CJ, Day C. *Br J Diabetes Vasc Dis.* 2010;10:193-199.

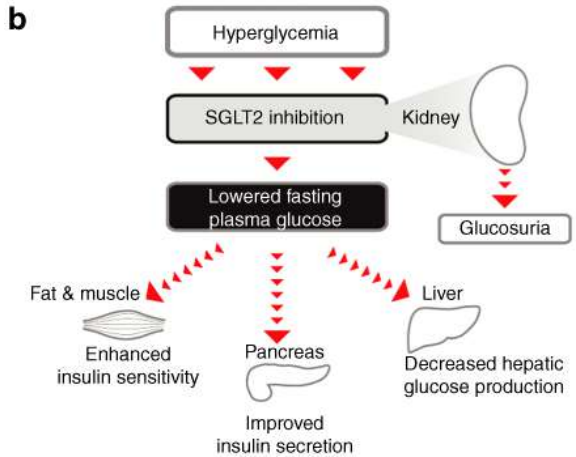
Sodium-Glucose Co-transporter-2 Inhibitors

SGLT-2 - in proximal tubules *reabsorbs most of filtered glucose*
SGLT-1 - also in proximal tubules, normally *reabsorbs remaining filtered glucose*

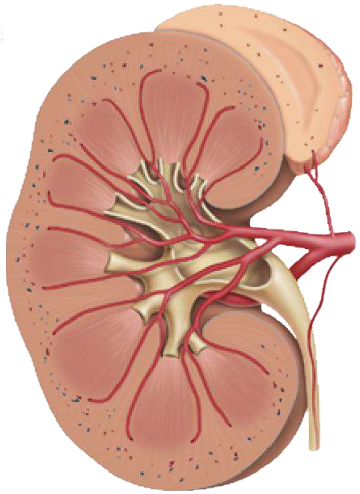


Courtesy of Clifford Bailey, PhD





SGLT2 Inhibitor



- Sodium–glucose cotransporter-2 (SGLT2) reabsorbs glucose in the proximal tubule
- Dapagliflozin induces glucosuria by inhibiting sodium–glucose cotransporter-2
- Insulin-independent glucose lowering
- Lowers A1C by 0.6-0.8%
- 2-3% body weight loss

Komoroski B et al. Clinical Pharm & Therapeutics 2009;85:513–519

DOPAMIN-2 AGONIS

- Contoh ; Bromokriptin
- Mek kerja ; mengatur aktivits neuronal di hypothalamus $\rightarrow$ mengatur kdr glukosa drah, TG, FFA pd keadaan puasa dan post pandrial
- Sbg monoterapi dpt me$\downarrow$ HbA1c, TG dan FFA
- ES : hipotensi ortostatk,mual, muntah, sakit kepala.

Perbandingan OAD

Drug	Half-Life (hr)	Duration of Action (hr)
Sulfonylureas		
First generation		
Acetohexamide	0.8–2.4	12–18
Chlorpropamide	24–48	60
Tolazamide	4–7	12–24
Tolbutamide	3–28	6–12
Second generation		
Glyburide	2–4	16–24
Glipizide	1–5	12–24 (XL > 24)
Glimeperide	5–9	>24
Meglitinides		
Repaglinide	1	4–6
Nateglinide	1–2	4
Biguanides		
Metformin	4–8	18–24
α-Glucosidase inhibitors		
Acarbose	2	4–6
Miglitol	2	4–6
Thiazolidinediones		
Pioglitazone	26–30	days
Rosiglitazone	4	days

Obat Antidiabetik (OAD) Ideal ??

- Dapat mengendalikan gula darah dlm 24 jam
- Praktis (diminum sekali sehari) $\rightarrow$ me $\uparrow$ kepatuhan
- Dpt memperbaiki GDP, GD2PP, HbA1c, insulin plasma puasa, dan C-peptida (perbaiki sensitivitas insulin)
- Resiko hipoglikemi minimal
- Aman utk penderita resiko tinggi : usia lanjut, gangg hepar, ginjal, dll

Kombinasi OAD

1. OAD mempunyai mekanisme kerja yg berbeda-beda.
2. Kombinsi OAD akan meningkatkan efek hipoglikemi (sama halnya dg terapi Hipertensi).
3. Penggunaan kombinasi OADs dg mekanisme kerja yg berbeda, masing2 OAD harus dimulai dg dosis kecil dulu, utk meminimalisir resiko hipoglikemi .

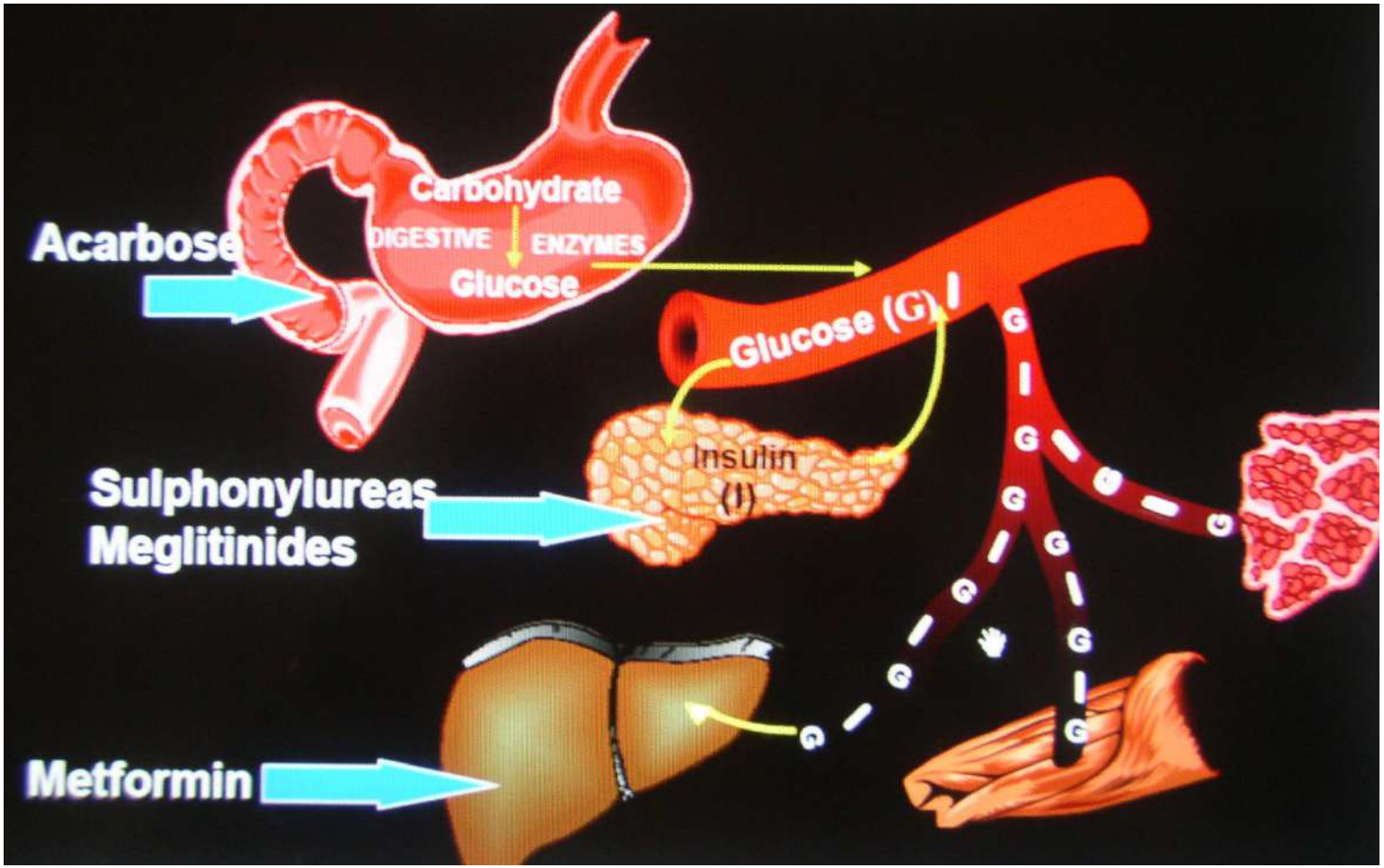
Pharmacological Therapy of Type 2 Diabetes: Comparison of Available Agents

AGENT	Efficacy (ΔHbA1c)	Mechanism of action	Benefits	Risks/Concerns
Sulfonylureas	~1 to 2%	Binds to sulfonylurea receptor on ß-cells, stimulating insulin release	Extensive experience; improved microvascular outcomes in UKPDS; low cost; QD dosing	Hypoglycemia; weight gain; may impede ischemic preconditioning
Meglitinides	~1 to 1.5% (Nateglinide less potent)	Binds to sulfonylurea receptor on ß-cells, stimulating insulin release	Targets post-prandial glucose; mimics physiological insulin secretion	Hypoglycemia; weight gain; no long-term experience; expensive; frequent dosing (compliance)
Biguanides	~1 to 2%	Decreases hepatic glucose production	Weight loss or weight neutrality; no hypoglycemia; extensive experience; improved microvascular outcomes in UKPDS; QD dosing available	Diarrhea; lactic acidosis; many contraindications to consider prior to prescribing; lowers vitamin B-12 levels (but no apparent effects on hematological indices)
α-Glucosidase Inhibitors	~0.5%	Retards gut carbohydrate absorption	Targets post-prandial glucose; weight-neutral; no hypoglycemia; non-systemic	Intestinal gas; expensive; frequent dosing (compliance)
Thiazolidinediones	~1 to 1.5%	Activates PPAR-γ, increasing peripheral insulin sensitivity	Addresses primary defect of T2DM; no hypoglycemia; lipid & other "non-glycemic" vascular benefits; potential anti-atherosclerotic properties (pioglitazone); potential for ß-cell preservation; QD dosing	Edema; heart failure in predisposed individuals; weight gain; increase in bone fractures in women; slow onset of action; expensive; liver monitoring still advised; rosiglitazone may increase risk of myocardial infarction

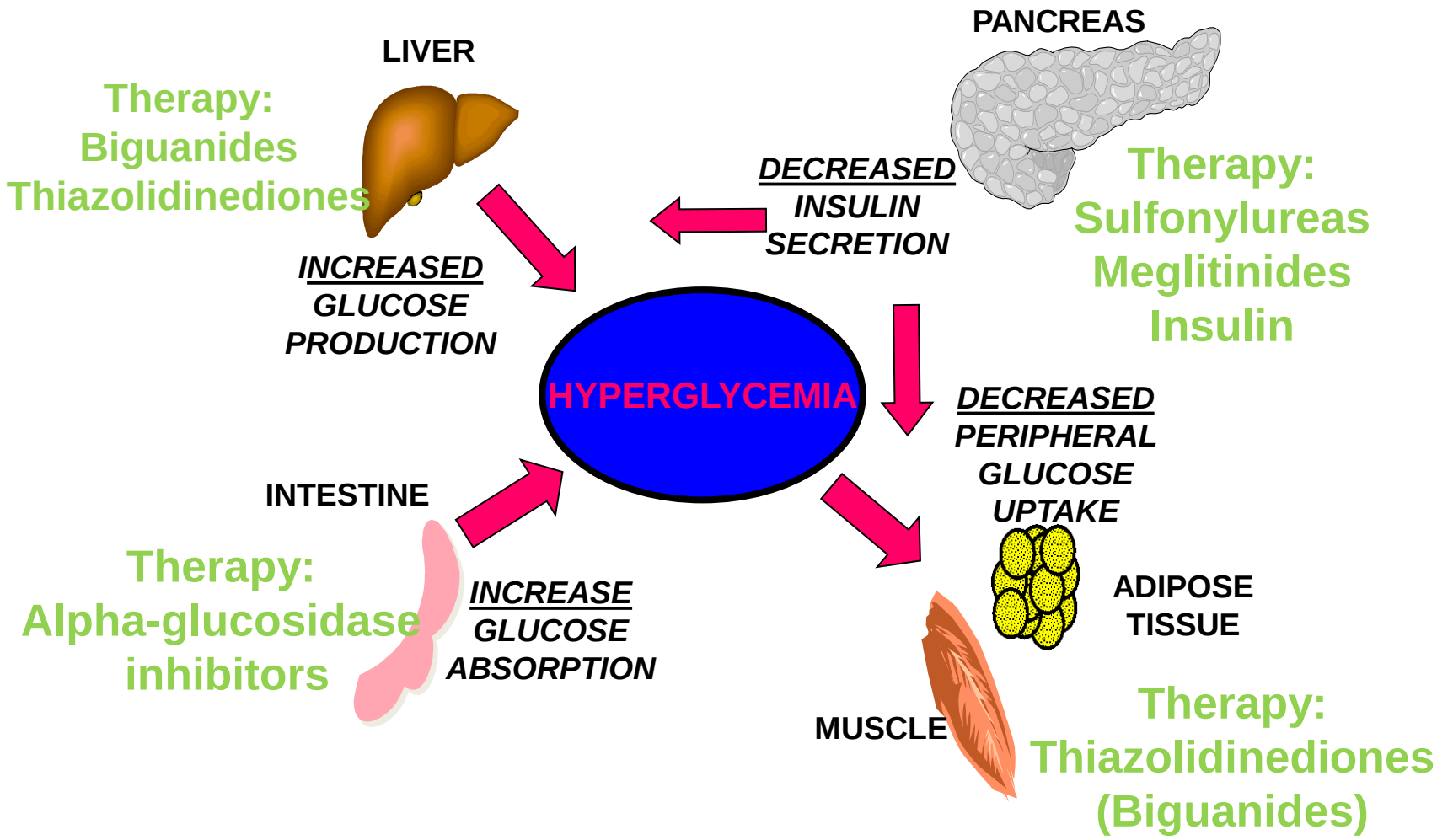
Pharmacological Therapy of Type 2 Diabetes: Comparison of Available Agents cont.

AGENT	Efficacy (ΔHbA1c)	Mechanism of action	Benefits	Risks/Concerns
DPP-4 Inhibitors	0.6 to 0.8%	Inhibits enzyme that deactivates endogenous incretins, GLP-1 and GIP, thereby increasing glucose-dependent insulin release and suppressing glucagon secretion	Low incidence of side effects; no hypoglycemia; QD dosing; potential ß-cell preservation	Expensive; limited clinical experience; urticaria and angioedema reported; pancreatitis reported
Bile Acid Sequestrants	0.4 to 0.5%	Unknown	LDL reduction; non-systemic	Constipation; increases TG's; multiple pills per day; expensive
Dopamine-2 Agonists	0.4 to 0.7%	Alters hypothalamic neurotransmitter tone and may reduce hepatic glucose production	No hypoglycemia; QD dosing	Orthostatic hypotension, dizziness, syncope; exacerbation of psychotic illness; nausea, vomiting; fatigue
GLP-1 Mimetics	-1%	Glucose-dependent stimulation of insulin release; suppresses glucagon; retards gastric emptying; enhances satiety	Weight loss; no hypoglycemia; potential ß-cell preservation	Injectable; nausea; expensive; pancreatitis reported
Amylinomimetics	0.4 to 0.6%	Suppresses glucagon release; retards gastric emptying; enhances satiety	Targets post-prandial glucose; weight loss	Injectable; nausea; expensive
Insulin	No "ceiling"	Increases insulin supply	Extensive experience; rapidly effective in all circumstances; no contraindications; improved microvascular outcomes in UKPDS; mortality benefits in acute settings; low cost	Hypoglycemia; weight gain; injections and more frequent glucose monitoring required; increases complexity of management; "stigma"

Summary : Site of action OAD



Summary : Mekanisme kerja OAD



Adapted from Sonnenberg and Kotchen *Curr Opin Nephrol Hypertens* 1998;7(5):551-555.

Policy of selecting the appropriate antidiabetic therapy according to the metabolic situation

Postprandial hyperglycaemia	alpha-glucosidase inhibitor, short acting sulphonylurea, Glinide, short acting regular insulin or insulin analog, respectively
Fasting hyperglycaemia	biguanide, long acting sulphonylurea, glitazone, long acting insulin or insulin analog, respectively
Insulin resistance	biguanide, glitazone, alpha-glucosidase inhibitor
Insulin deficiency	sulphonylurea, glinide, Insulin

Standl et al, Diabetologia (2003) 46 Suppl 1:30-36

Sekian….
Terima kasih atas perhatiannya…

Selamat belajar….