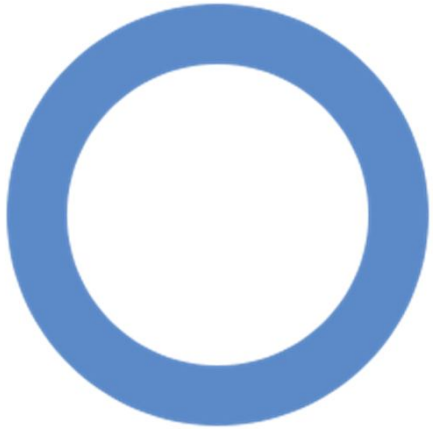
Diabetes,
SAR in delovanje antidiabetikov

Izr. prof. dr. Marko Anderluh

6. junij 2013



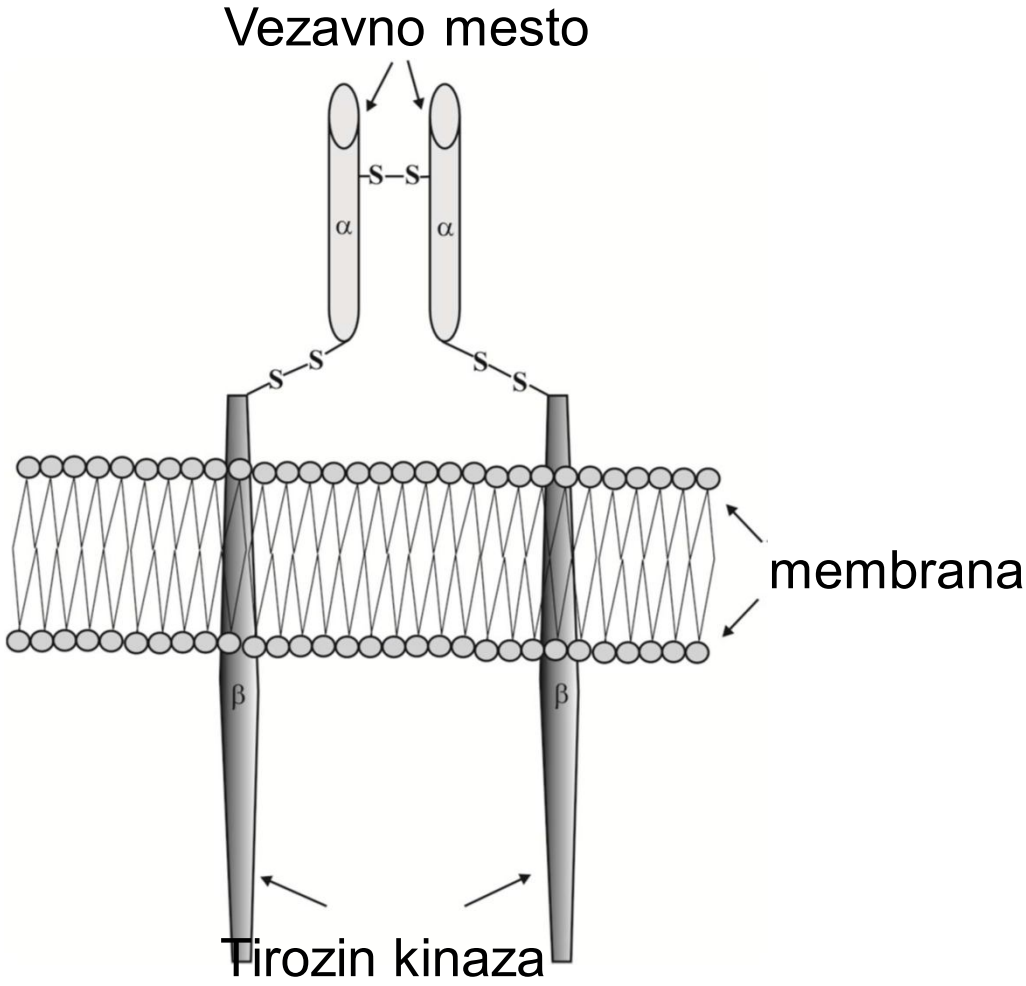
http://www.idf.org/

Uravnavanje krvnega sladkorja

- Glukoza edini vir energije za CŽS
- Možgani – stalna oskrba z glukozo!
- normalno: 3,6-6,1 mmol/L
- Uravnava s hormoni: insulin, glukagon

Insulin

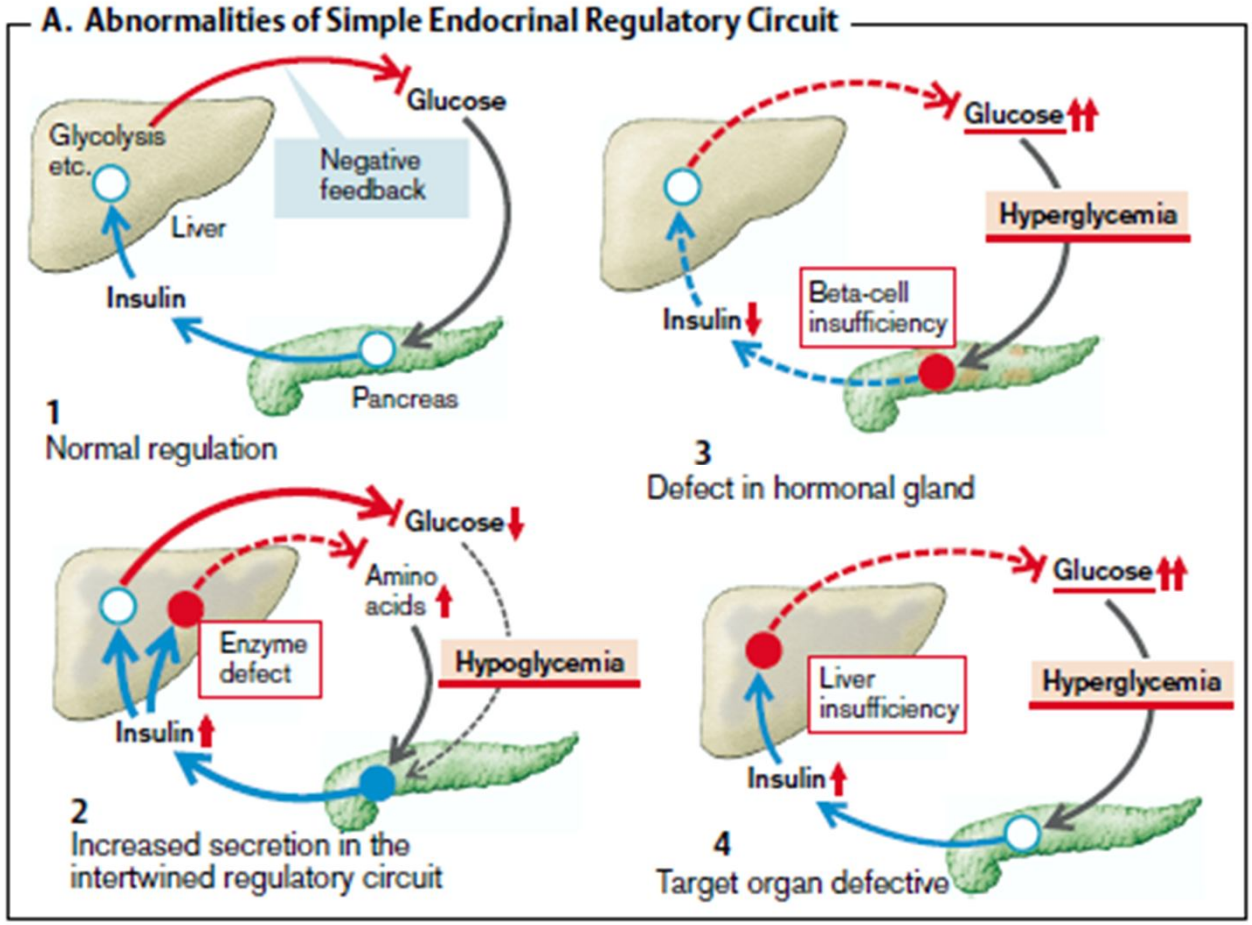
- Delovanje – insulinski receptor



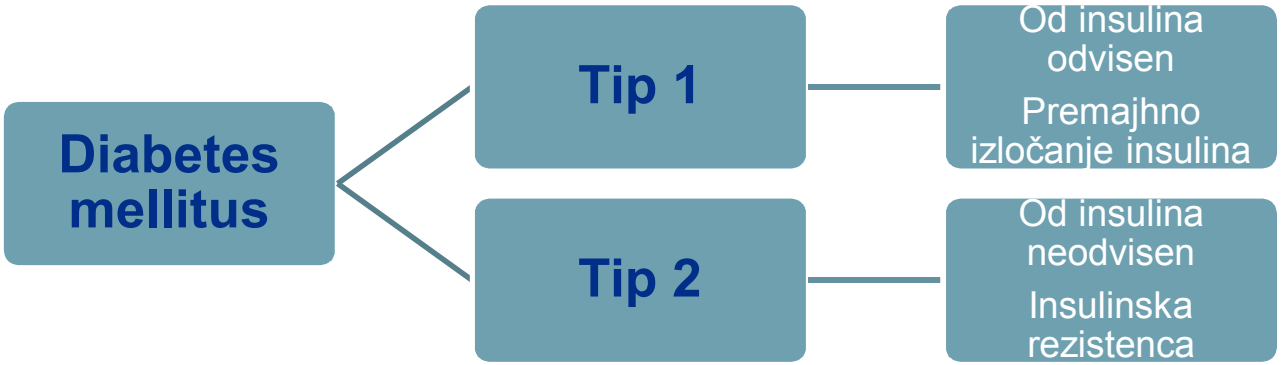
- Agonisti?

http://www.youtube.com/watch?v=FkkK5lTmBYQ

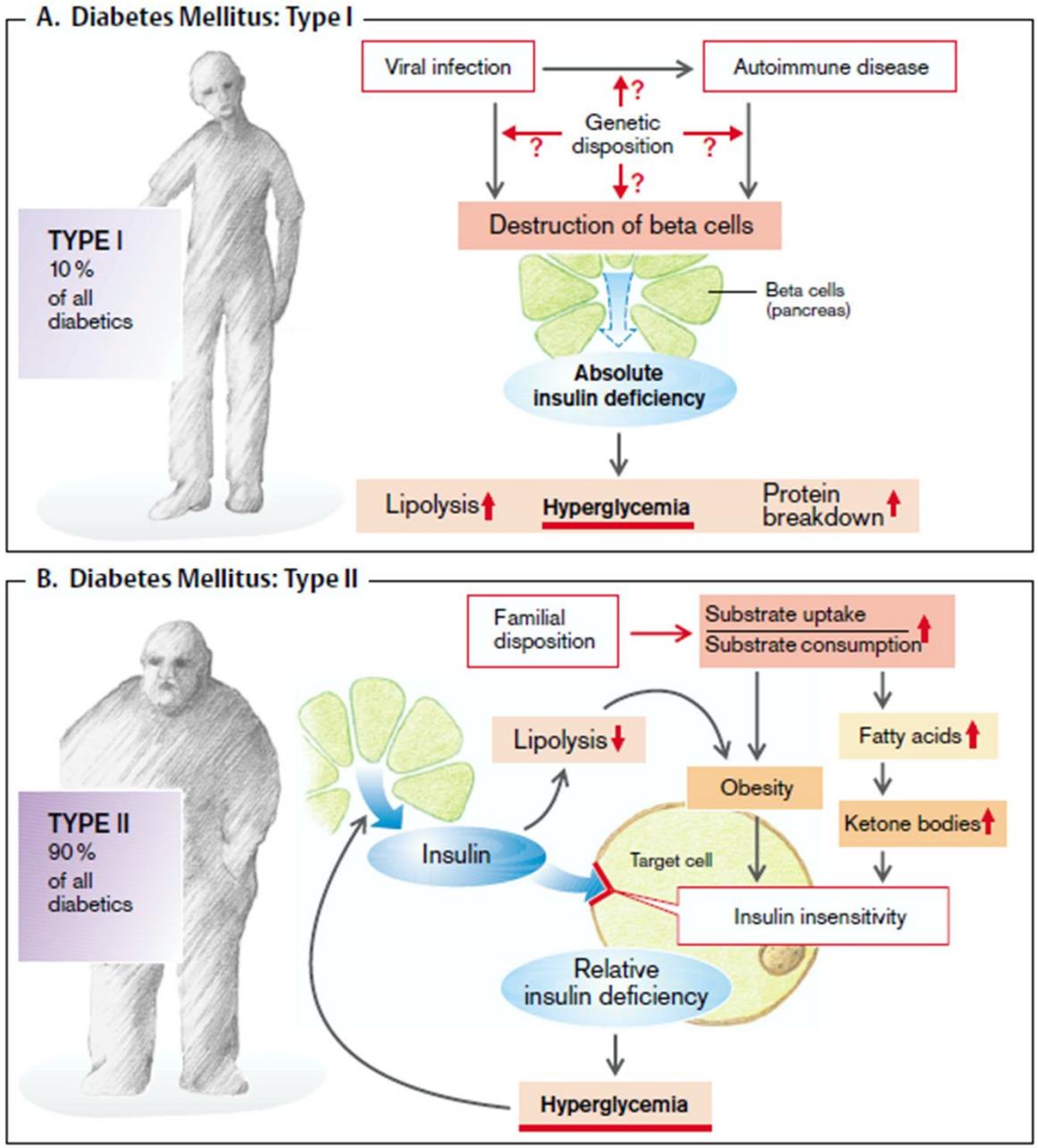
Uravnavanje krvnega sladkorja



Sladkorna bolezen



- Diabetes mellitus



Diagnostika

diagnoza po WHO:

- klinični znaki+↑glukoza v plazmi (>7 mmol/L na tešče, >11,1 mmol/L kadarkoli)
- 2x zaporedoma ↑glukoza v plazmi (...)
- 2x zaporedoma +OGTT (2h po obremenitvi s 75g glukoze: glukoza v plazmi>11,1 mmol/L)

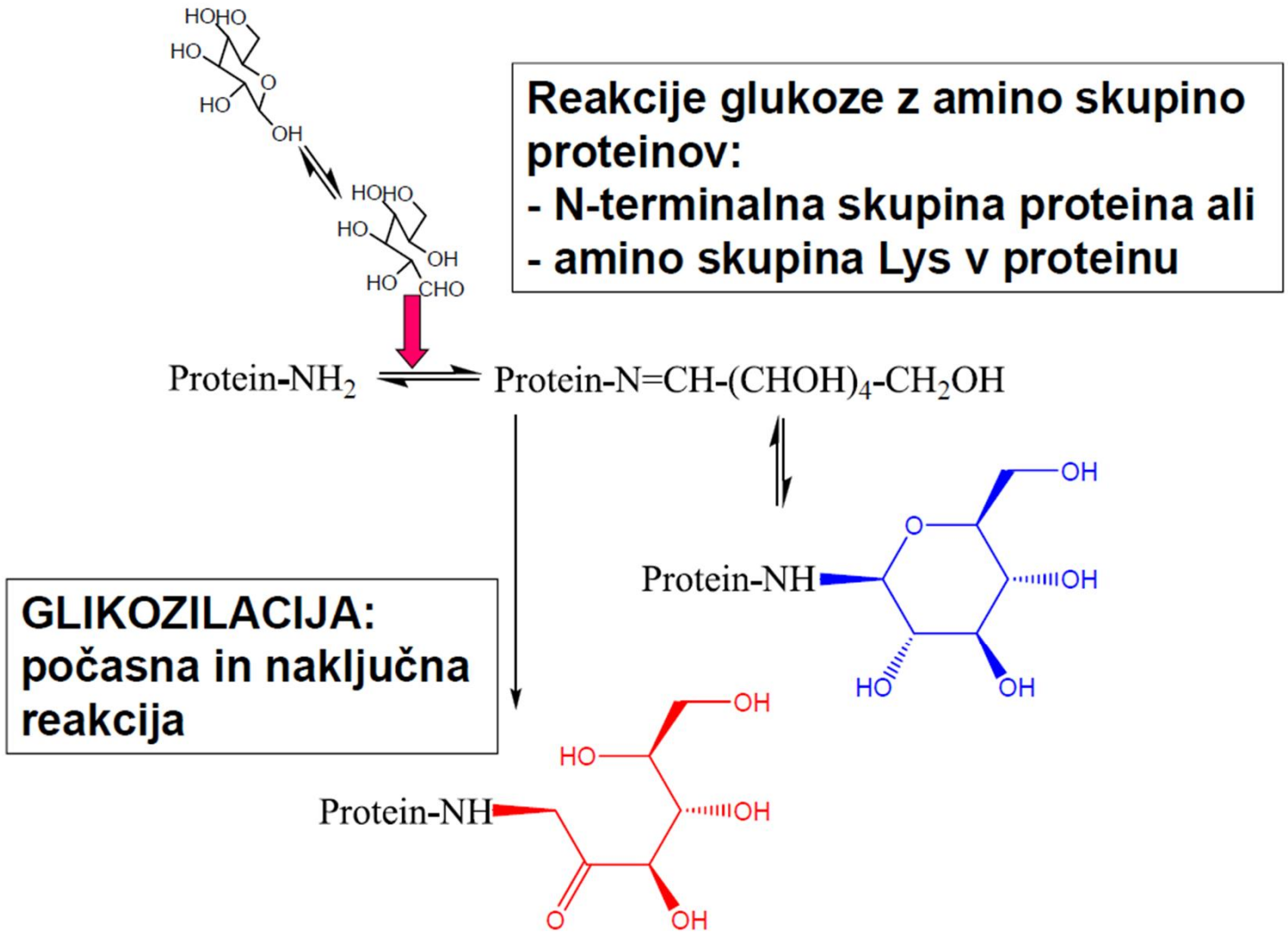
motena toleranca za glukozo: OGTT: c=7,8-11 mmol/L

glikiran hemoglobin: HbA_{1c} > 6,5%

Problematika

- Povišane vrednosti glukoze v krvi (norm. 3,6-6,1 mmol/L)
- Zakaj nevarno?

Problematika



Komplikacije zaradi povišanega krvnega sladkorja

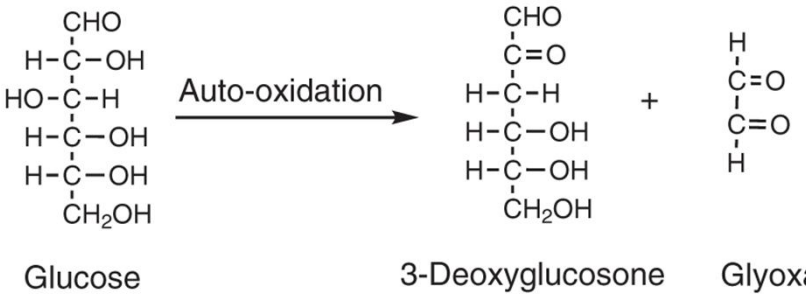
Akutne (ponavadi tip I):

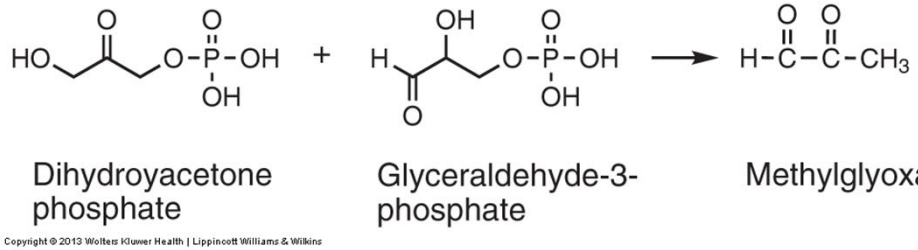
- Poliurija, polidipsija, polifagija, infekcije UT, utrujenost, hujšanje
- Ketoacidoza, hiperosmolarno hiperglikemično stanje

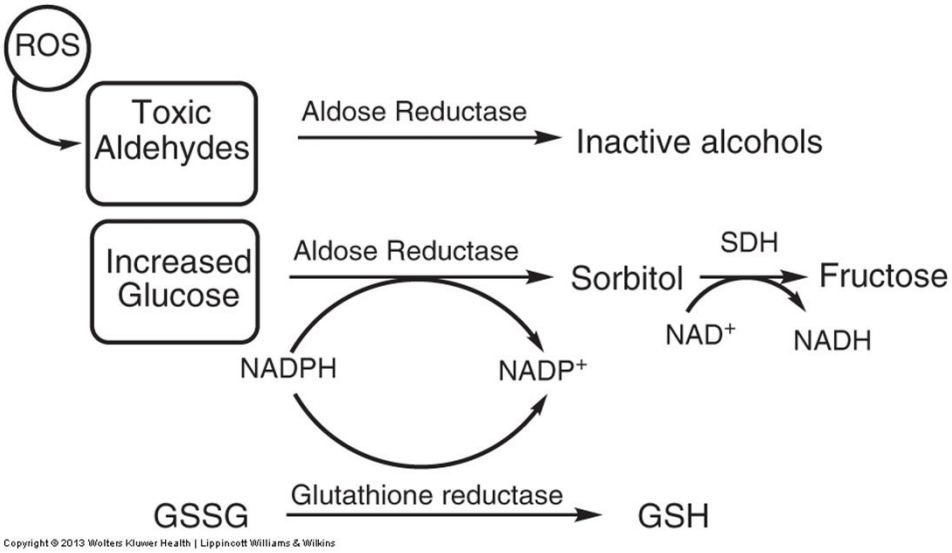
Kronične

- Mikrovaskularne (mikroangiopatije), makrovaskularne (akroangiopatije);
- nevropatije
- oksidativni stres

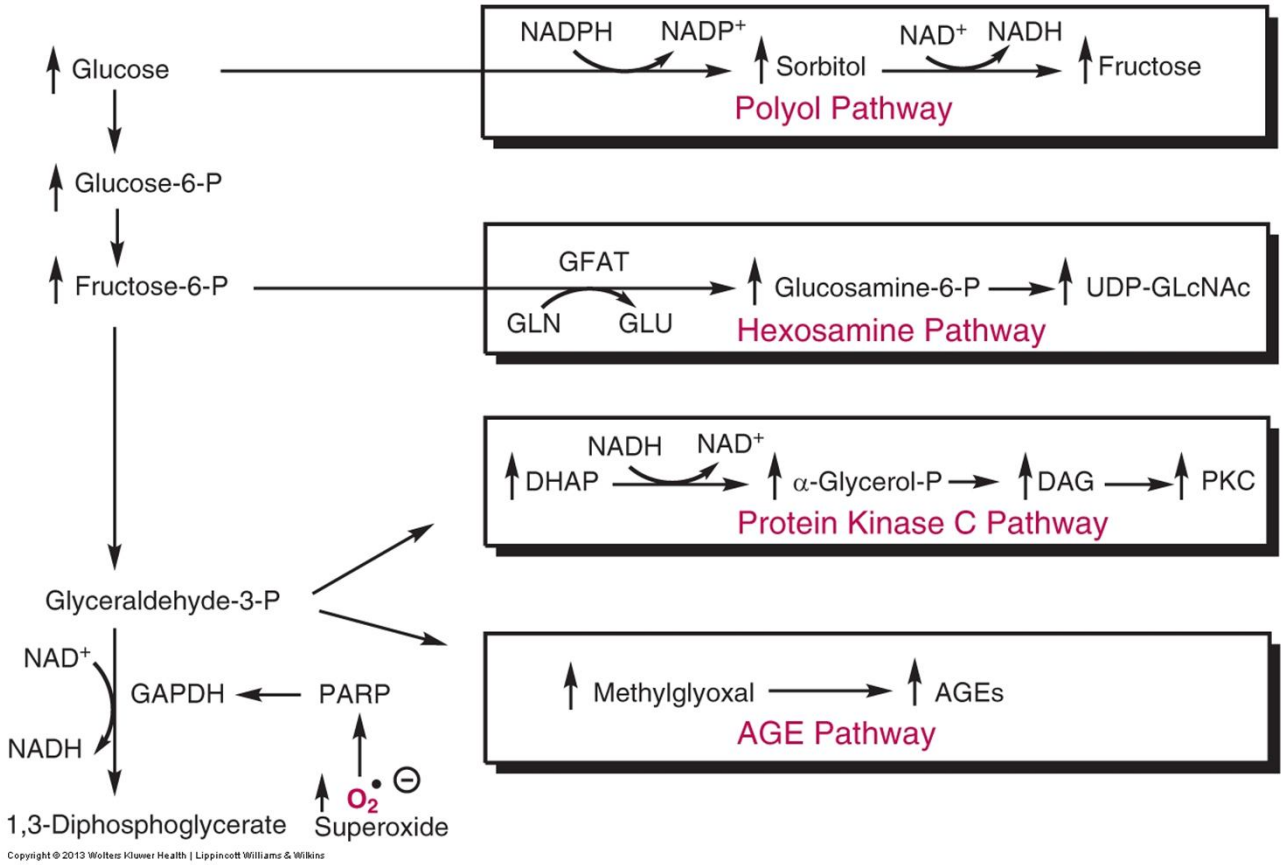
Komplikacije zaradi povišanega krvnega sladkorja

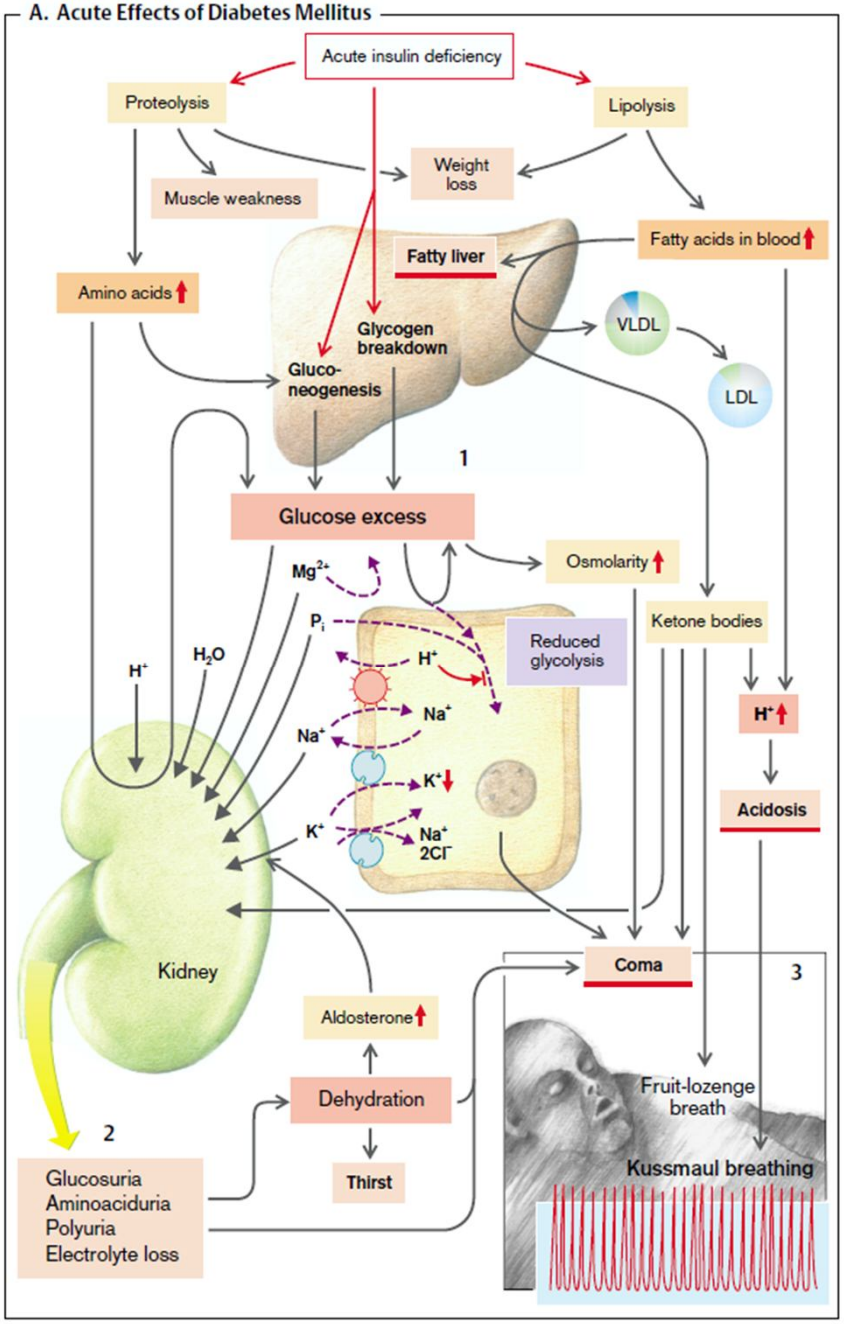






Komplikacije zaradi povišanega krvnega sladkorja





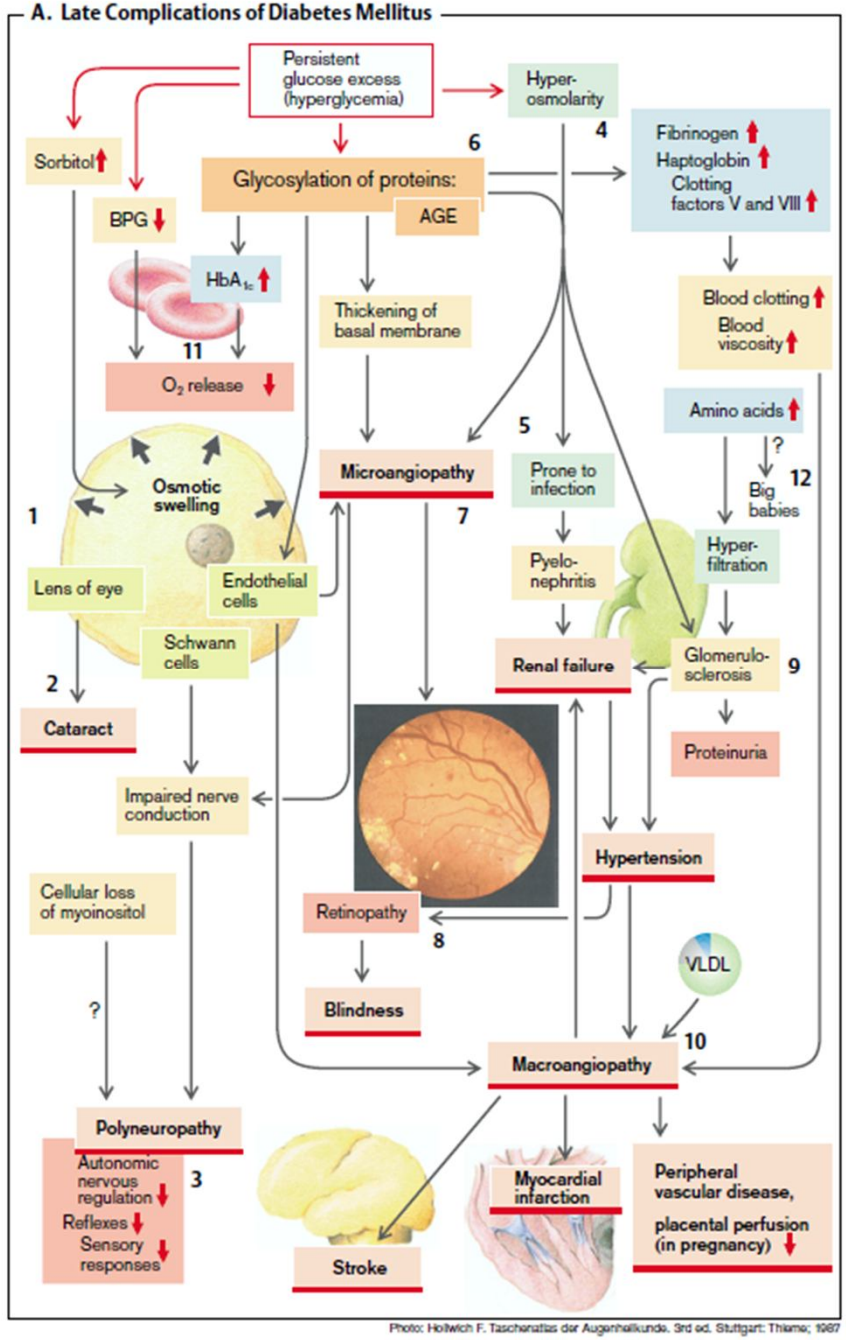
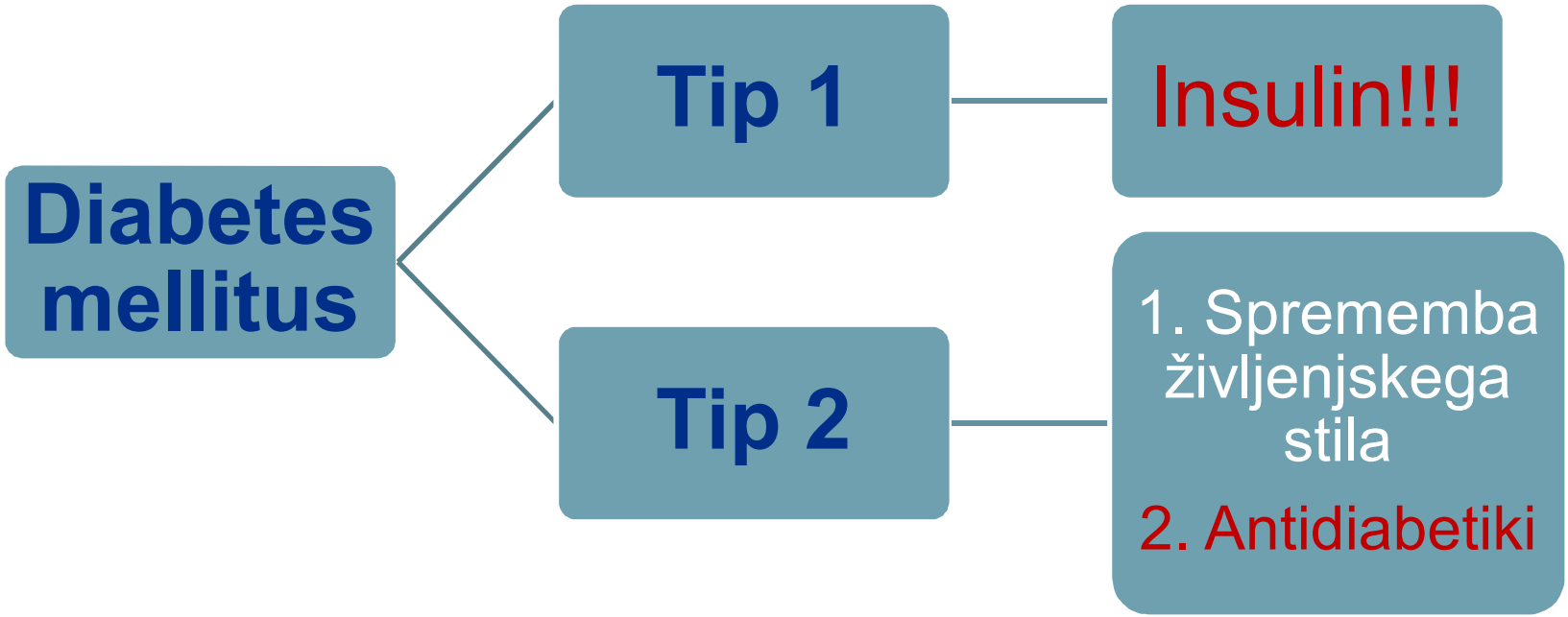


Photo: Hollwich F. Taschenatlas der Augenheilkunde. 3rd ed. Stuttgart: Thieme; 1987

Metabolni sindrom

- povišan krvni sladkor
- hiperlipidemija
- debelost
- znižani nivoji HDL
- hipertenzija

Terapija diabetesa



Terapija diabetesa

- Antagonisti glukagona
- Sulfonilsečnine
- Glinidi (meglitinidi)

Insulinski sekretagogi

- Gliptini

Inhibitorji DPP-4

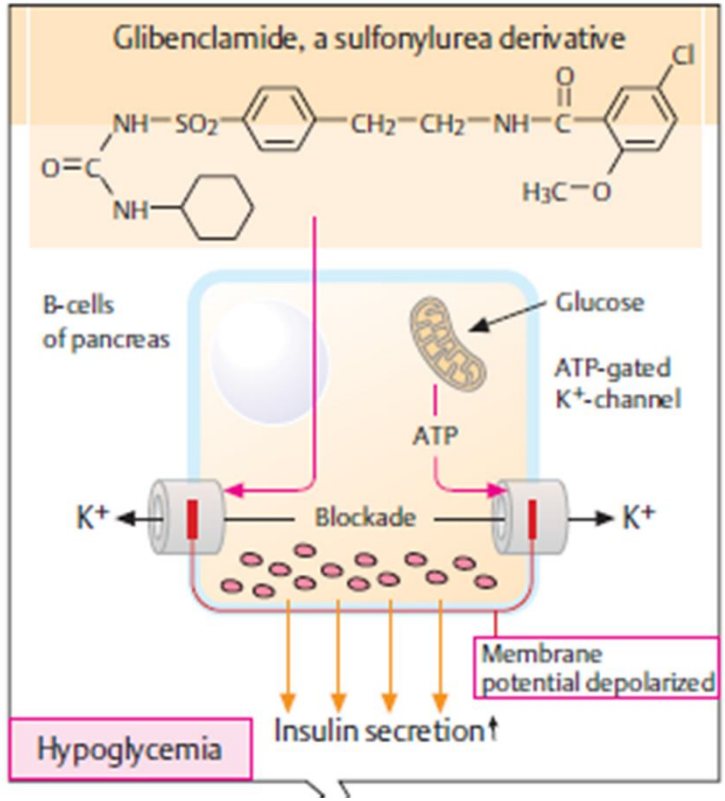
- Bigvanidi
- Glitazoni
- Glitazarji

Povečana občutljivost na insulin

- Inhibitorji α-glukozidaze

Sulfonilsečnine

- Mehanizem delovanja – zaviranje ATP-odvisnih K+ kanalčkov
- Sprememba mirovnega potenciala β-celic trebušne slinavke – vstop Ca2+, izločanje insulina
- Hipoglikemija!

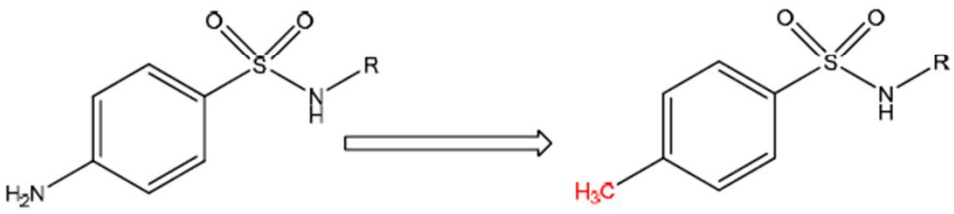


Sulfonilsečnine

- nastanek

Razvojna pot do sulfonilsečnin:

Sulfonamidi kot kemoterpevtiki tudi znižujejo Koncentracijo glukoze v plazmi:



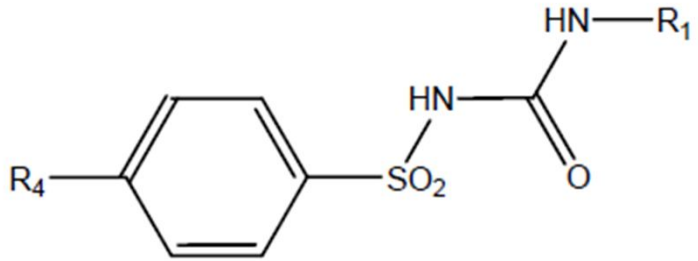
Kemoterapevtik z antidiabetičnim delvanjem

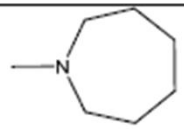
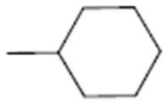
Samo antidiabetični učinek

Sulfonilsečnine

- 1. generacija

Sulfonil sečnine: PRVA GENERACIJA

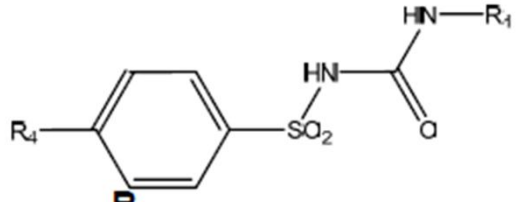


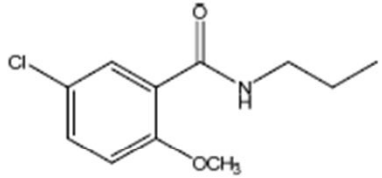
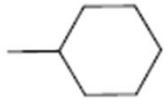
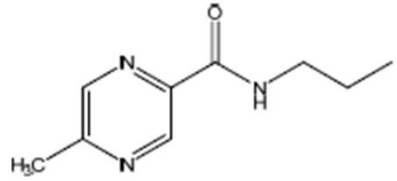
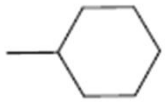
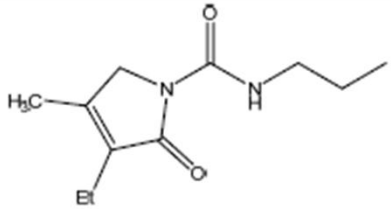
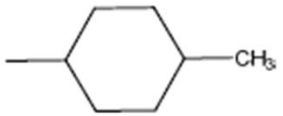
Ime	R_4	R_1	ODMEREK/mg
TOLBUTAMID	$-CH_3$	$-CH_2CH_2CH_2CH_3$	500-3000
KLORPROPAMID	-Cl	$-CH_2CH_2CH_3$	250
TOLAZAMID	$-CH_3$		250
ACETOHEKSAMID	$-CO-CH_3$		500

Sulfonilsečnine

- 2. generacija

Sulfonil sečnine: DRUGA GENERACIJA



Ime	R_4	R_1	odmerek/mg
GLIBURID			5
GLIPIZID			5
GLIMEPIRID			1-8

Sulfonilsečnine

- SAR

Sulfonilsečnine

Selektivnost – stranski učinki?

- Sulfonilsečnine delujejo na SUR1 (t. slinavka), SUR2A (kardiomiociti, povečan influks Ca2+; preobremenitev srca, tudi smrt miocitov) in SUR2B (žile; povečan tonus žil)
- Selektivnost dosežemo z lipofilnimi substituenti (cikloheksil, butil, propil)

Sulfonilsečnine

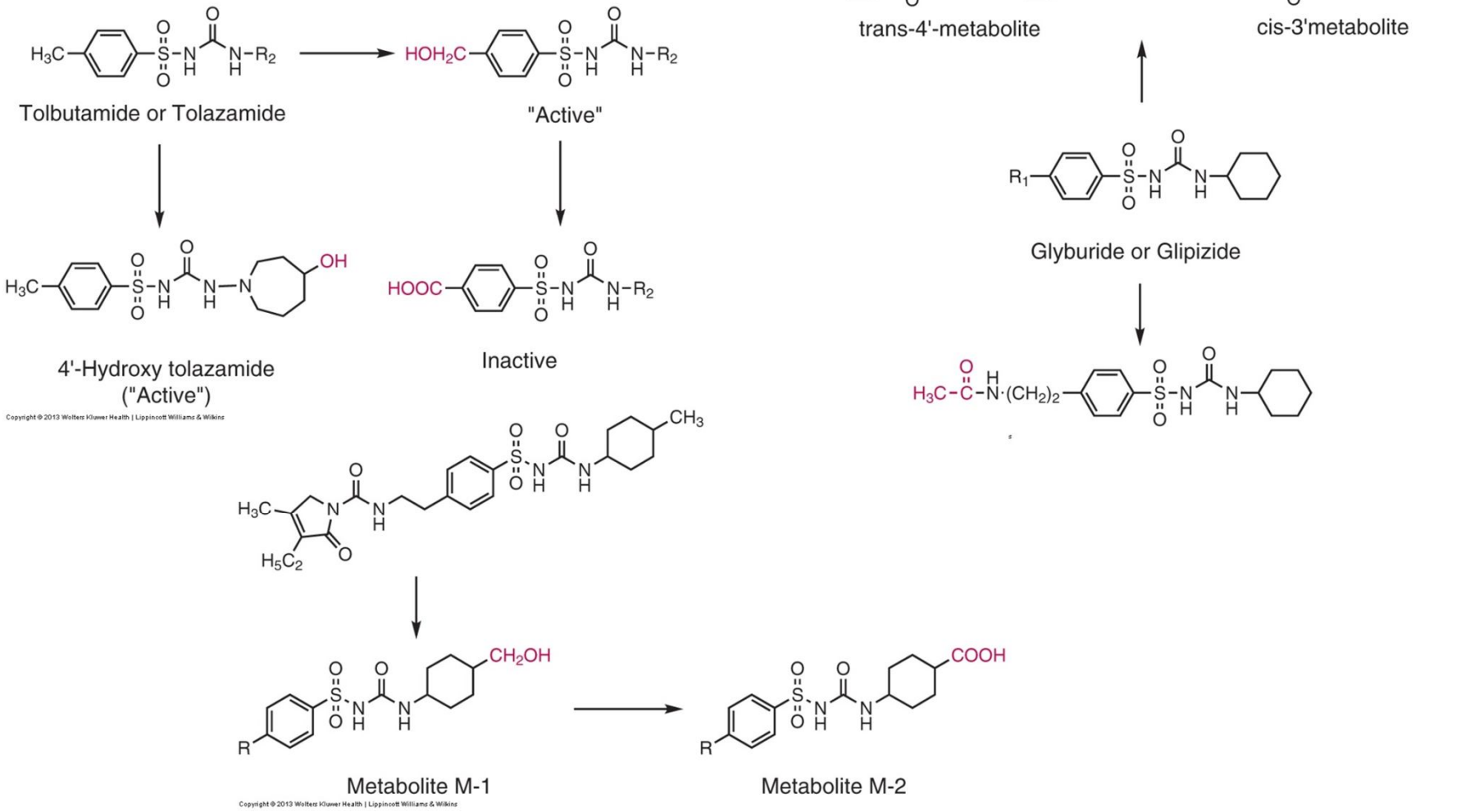
FK lastnosti

TABLE 27.7 Pharmacokinetic Properties of the Sulfonylureas

Drug (sulfonylureas)	Equivalent Dose (mg)	Serum Protein Binding (%)	Half-Life (hours)	Duration (hours)	Renal Excretion (%)
Tolbutamide	1,000	95–97	4.5–6.5	6–12	100
Chlorpropamide	250	88–96	36	Up to 60	80–90
Tolazamide	250	94	7	12–14	85
Acetohexamide	500	65–88	6–8	12–18	60
Glyburide	5	99	1.5–3.0	Up to 24	50
Glipizide	5	92–97	4	Up to 24	68
Glimepiride	2	99	2–3	Up to 24	40

Sulfonilsečnine

Metabolizem



Glinidi (meglitinidi)

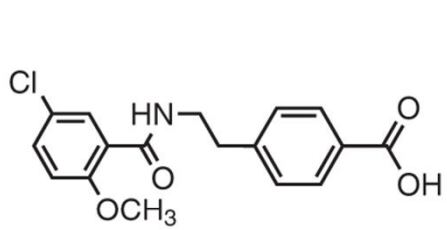
Mehanizem delovanja

- Kratkotrajni sekretagogi, delujejo podobno kot sulfonilsečnine – zaviranje ATP odvisnih K+ kanalčkov
- Vezava na drugo vezavno mesto
- Možna hipoglikemija!

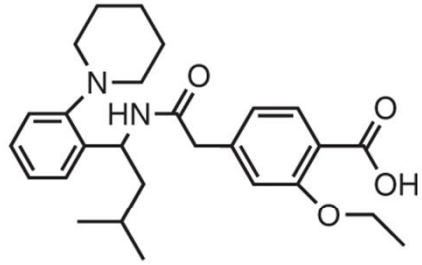
Glinidi (meglitinidi)

- Predstavniki

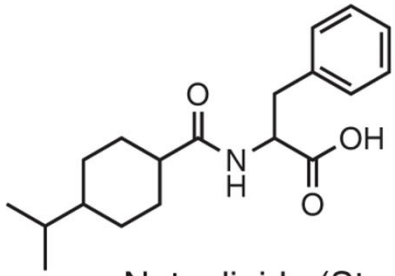
Glyburide/glibenclamide



Meglitinide



Repaglinide (Prandin)

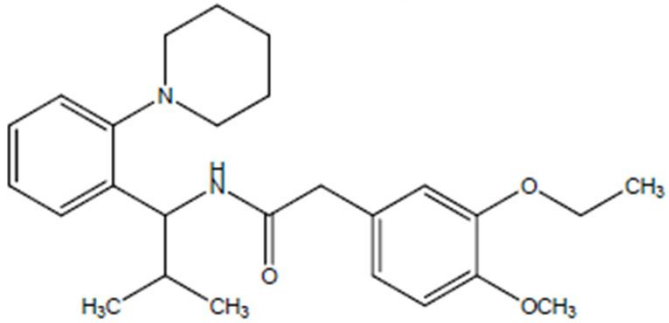


Nateglinide (Starlix)

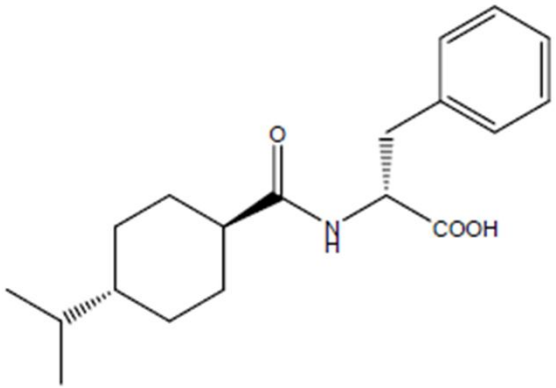
Glinidi (meglitinidi)

- Predstavniki

GLINIDI, sekretagogi inzulina, D2



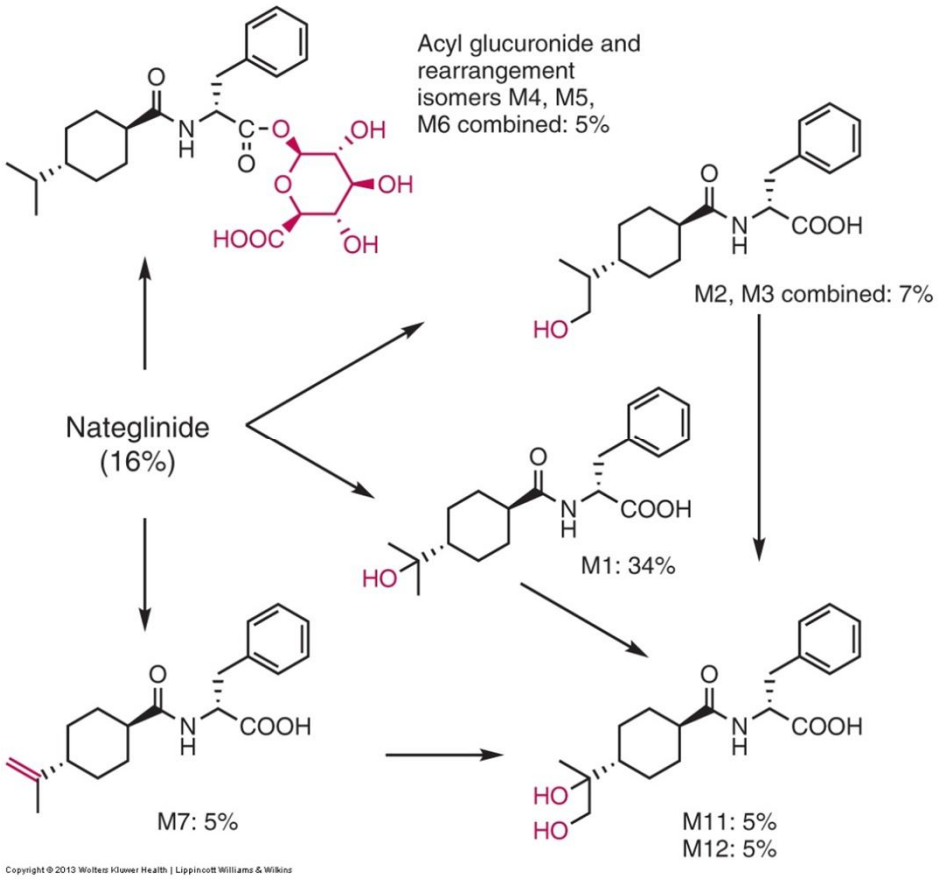
REPAGLINID
0,5-4 mg; 4 x na dan



NATEGLINID
60-120 mg; 3 x na dan

Glinidi (meglitinidi)

- Predstavniki



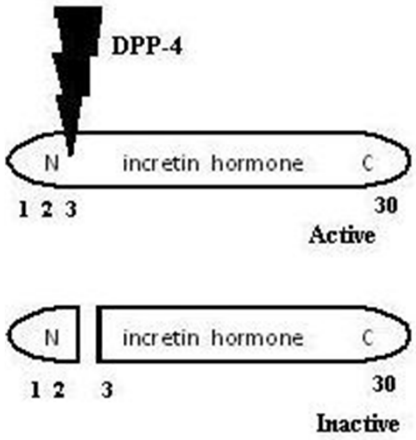
Gliptini

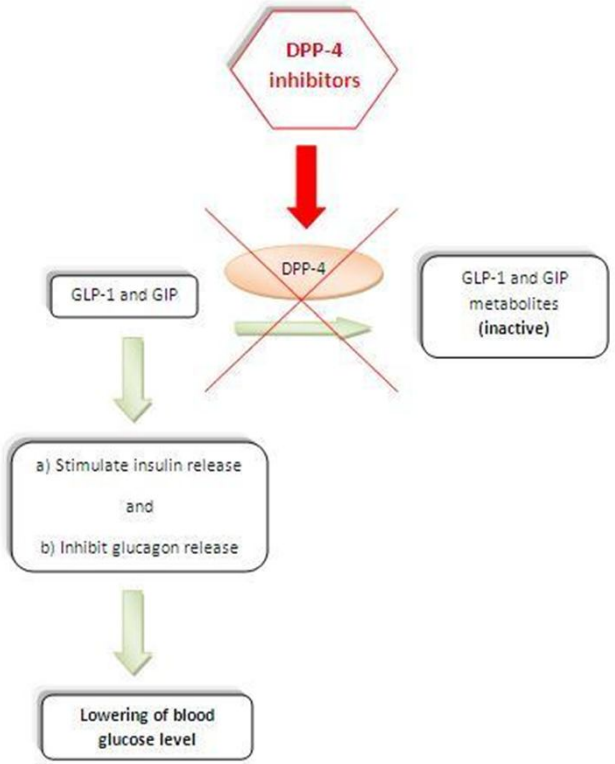
Mehanizem delovanja

- Inkretini – endogeni peptidi, insulinski sekretagogi: glukagonu podoben protein-1 (GLP-1), gastrični inhibitorni protein (GIP)
- Inkretini – sekrecija insulina, zaviranje sekrecije glukagona
- Inkretine presnavlja dipeptidil peptidaza 4 (DPP-4)
- Zaviranje DPP-4; podaljšanje življenjske dobe inkretinov

Gliptini

Mehanizem delovanja

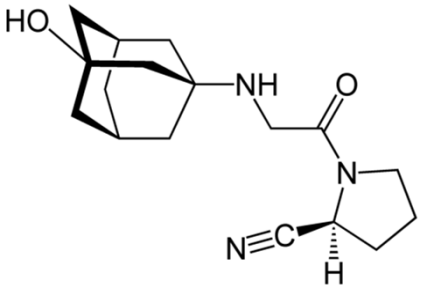




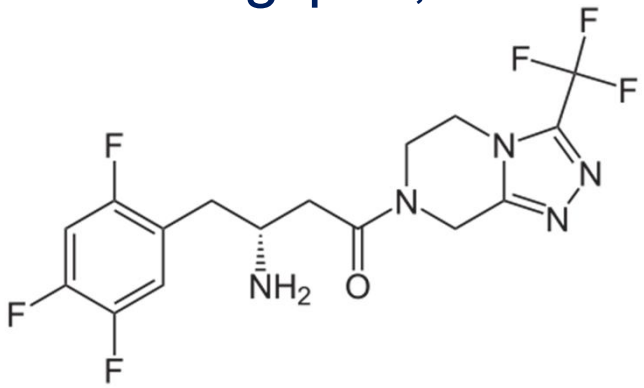
Gliptini

Predstavniki

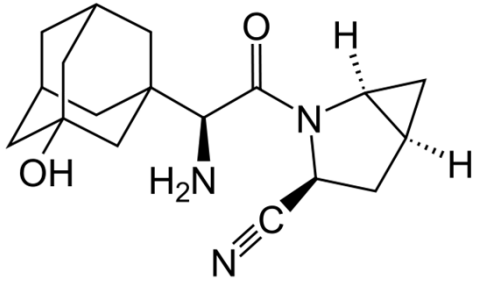
Vildagliptin, 2008



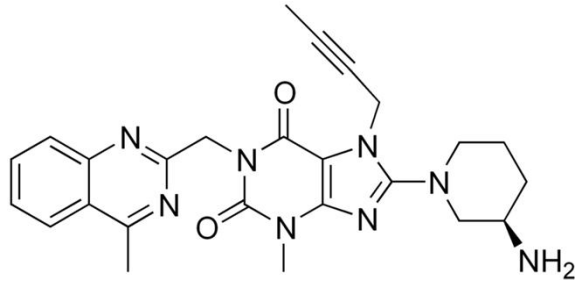
Sitagliptin, 2006

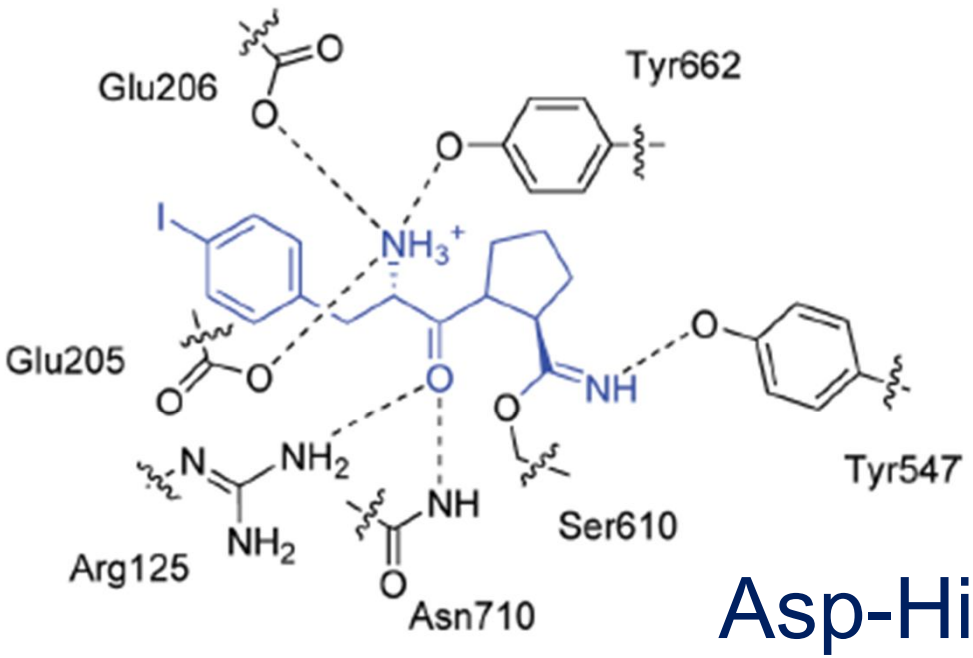


Saksagliptin, 2008



Linagliptin, maj 2011





Asp-His-Ser

Figure 17. Representation of the crystal structure of a pyrrolidine nitrile bound to DPP-IV. It is predicted that vildagliptin and other pyrollidine nitriles bind in a similar fashion.

Bigvanidi

Mehanizem delovanja

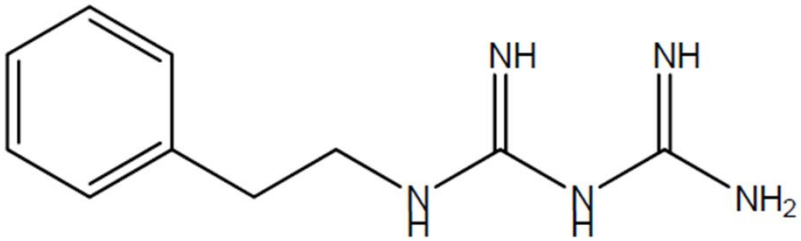
- Ni popolnoma razjasnjen
- Zaviranje glukoneogeneze
- Povečanje občutljivosti na insulin

Ne delujejo preko izločanja insulina:

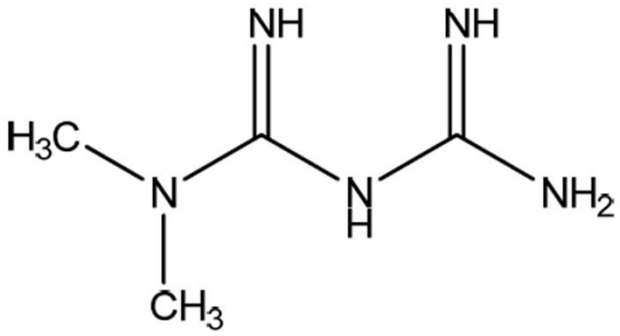
- Ne povzročajo hipoglikemije!
- Ni rejenja/debelosti
- Znižujejo trigliceride
- Delujejo vazoprotektivno

Bigvanidi

Predstavniki



FENFORMIN



METFORMIN

- Presenetljivo: BU 50-60%
- pKa = 11,5, 2,8
- Izločanje?

Bigvanidi

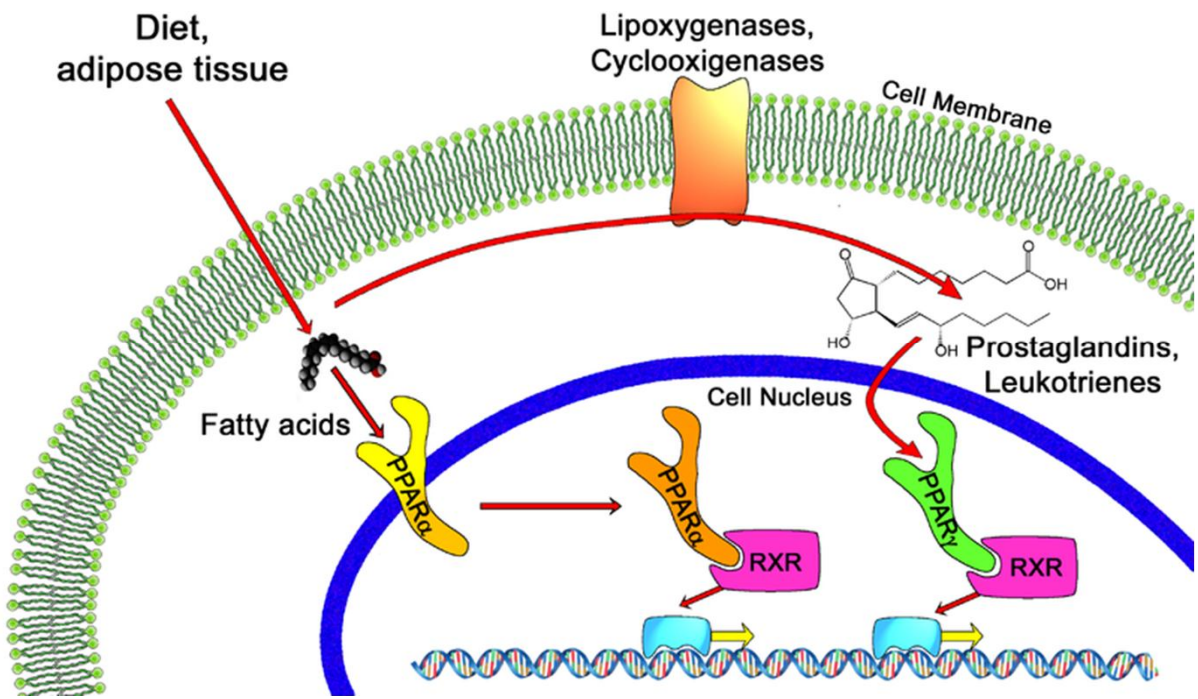
Stranski učinki

- Pospešujejo razgradnjo glukoze – oksidativno in neoksidativno
- Metabolična acidoza!

Glitazoni

Mehanizem delovanja

- Aktivatorji predvsem PPAR-γ, manj PPAR-α
- PPAR = s peroksisomskim proliferatorjem aktiviran receptor



Glitazoni

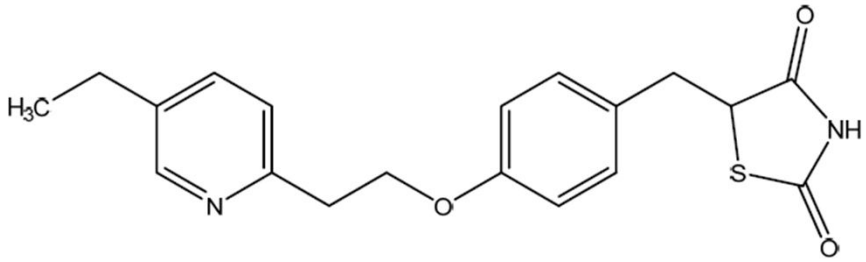
Mehanizem delovanja

- PPAR = metabolna tipala; metabolizem CH, lipidov
- PPAR-γ poveča ekspresijo glukoznega prenašalca GLUT-4
- Modulatorji PPAR-α – hipolipemiki, modulatorji PPAR-γ – antidiabetiki
- Ligandi za PPAR-α – levkotrien B4, za PPAR-γ – prostaglandin PGJ_2

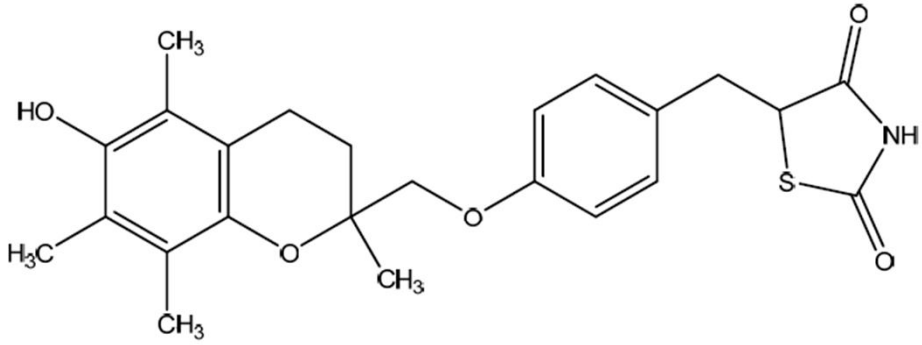
Glitazoni

- Predstavniki

Tiazolidindion – pKa ~ 6,5



PIOGLITAZON
15-45 mg/dan



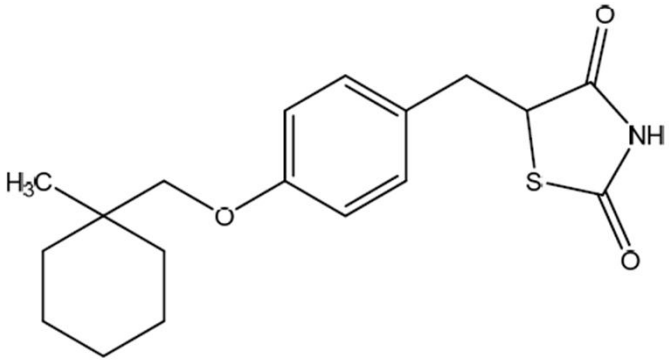
TROGLITAZON:

Antidiabetik in protivnetna uč.

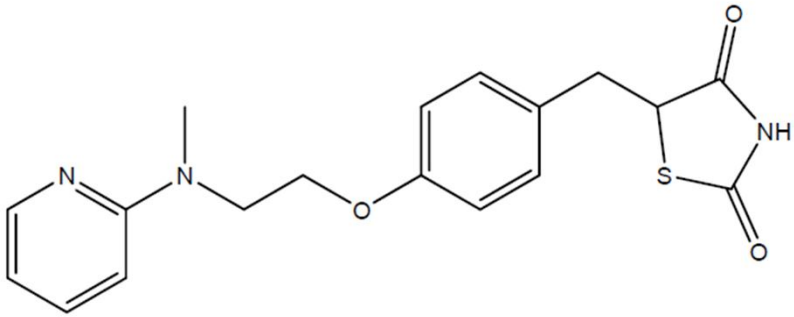
1997: začetek
2000: konec

Glitazoni

- Predstavniki



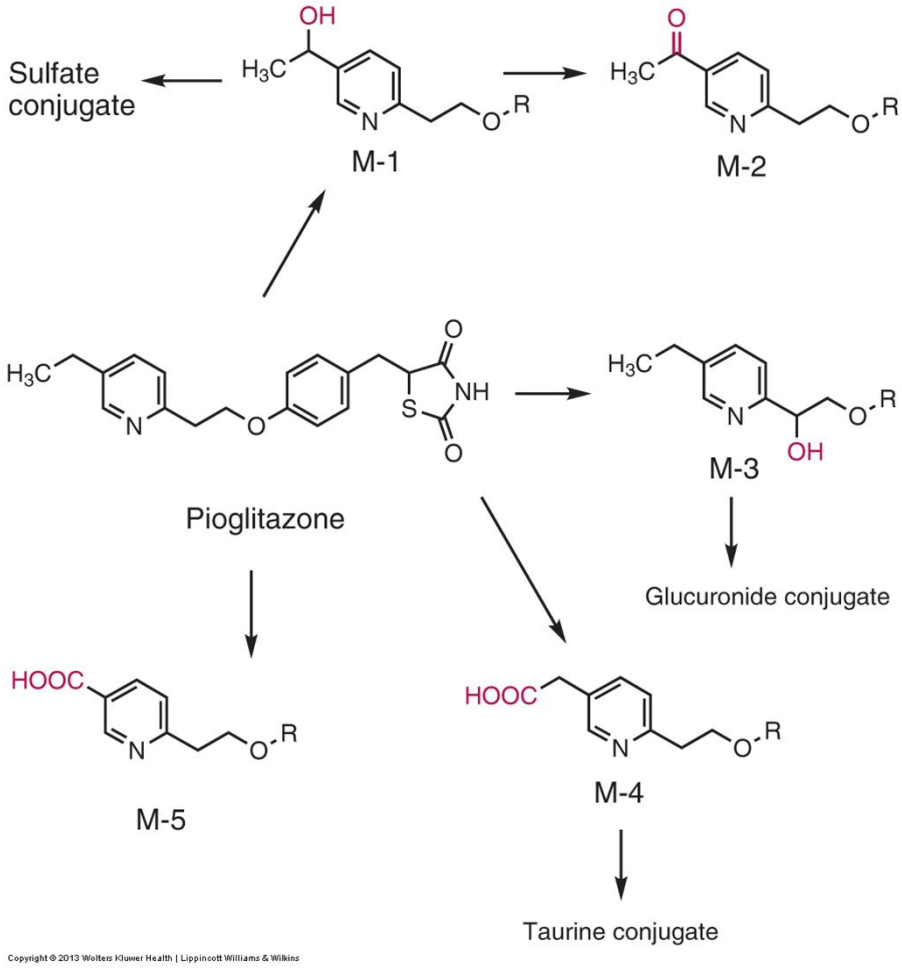
CIGLITAZON



ROZIGLITAZON
4-8 mg/dan

Glitazoni

- Pioglitazon – edini „preživeli“



Glitazarji

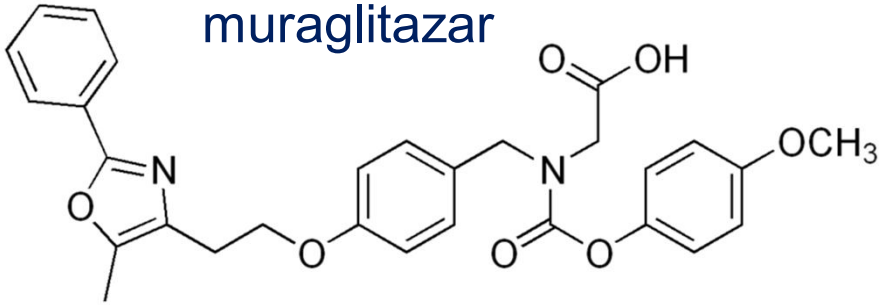
Mehanizem delovanja

- Aktivatorji tako PPAR-γ, kot PPAR-α
- Novejše učinkovine
- Terapija metabolnega sindroma!

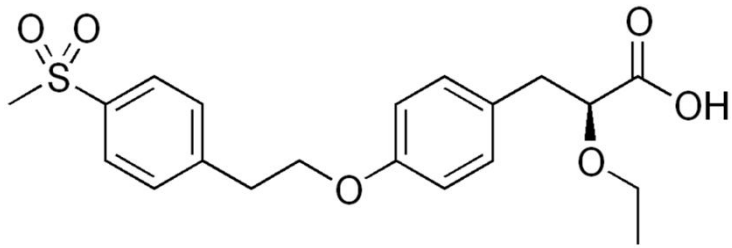
Glitazarji

- Predstavnika

muraglitazar



tesaglitazar



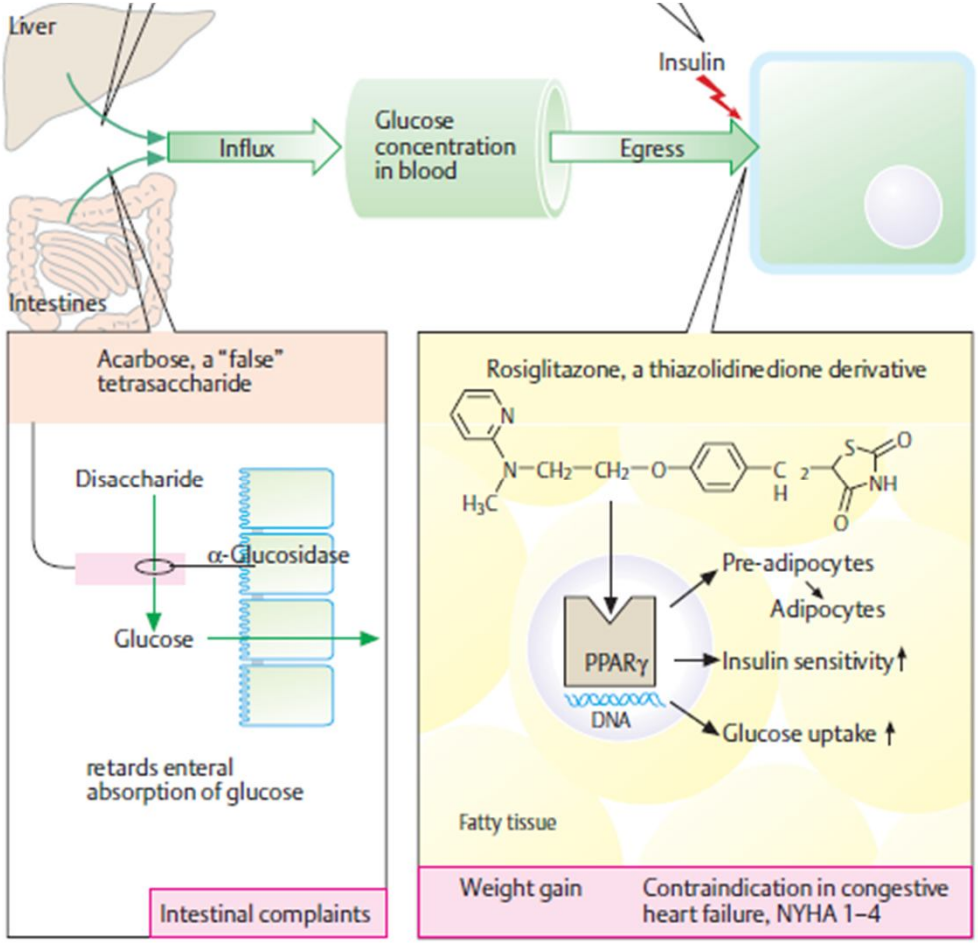
Oba prestala 3. fazo kliničnih testiranj, nista na trgu

Inhibitorji α-glukozidaze

- Mehanizem

Delovanja

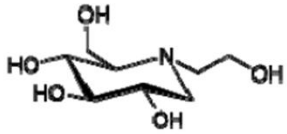
- Encim v steni prebavnega trakta – enterociti
- Cepi disaharide v glukozo + monosaharid



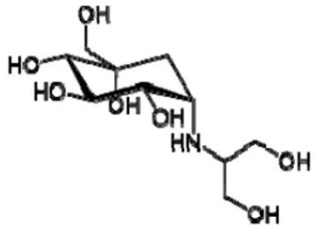
Inhibitorji α-glukozidaze

Inhibitorji α-glikozidaze

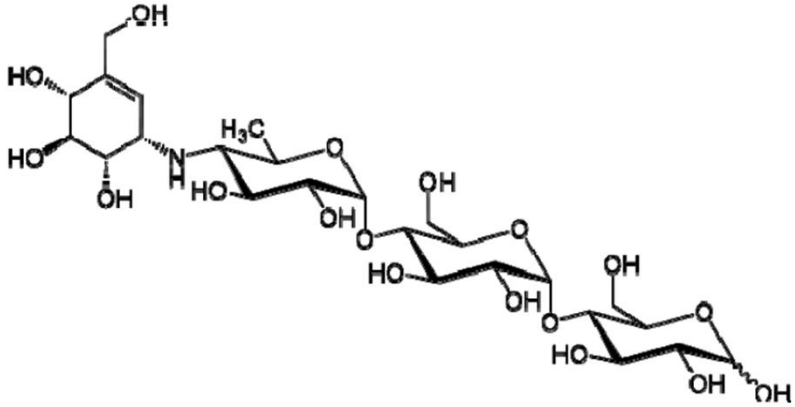
- **miglitol**



- **vogliboza**

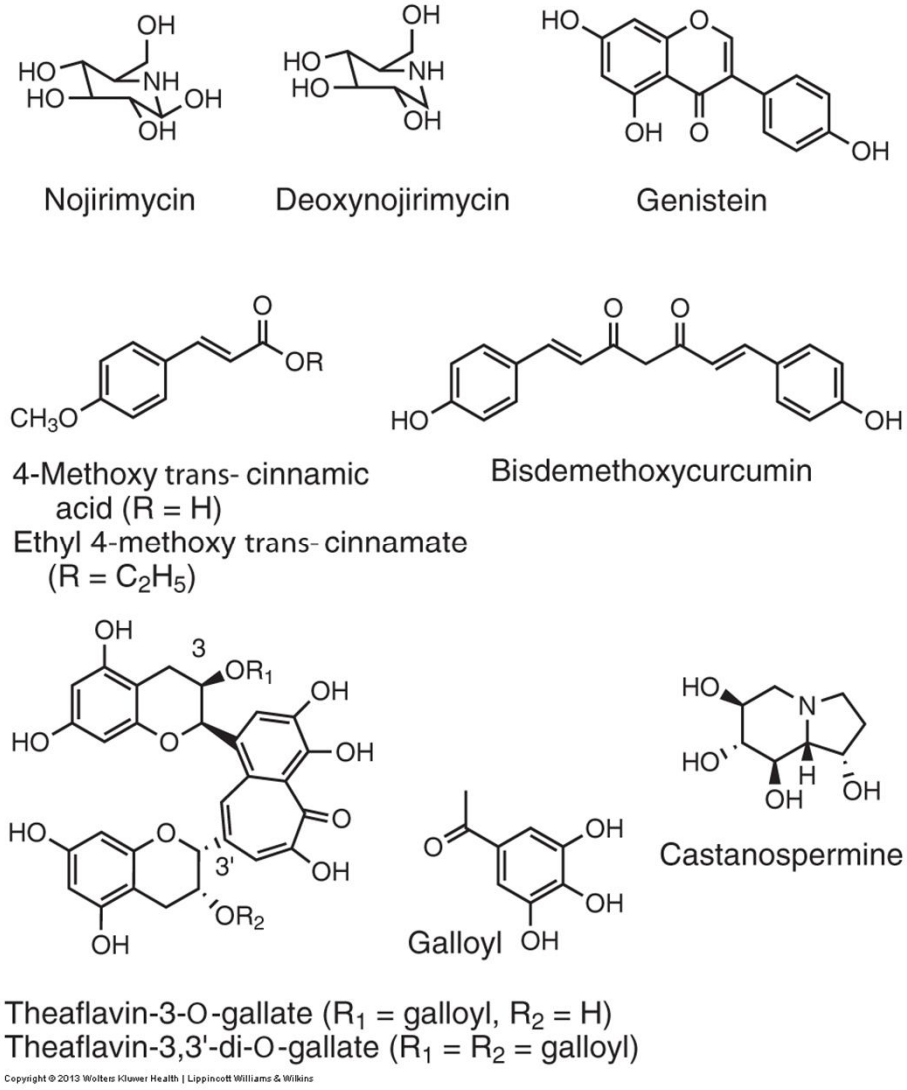


- **akarboza**



Inhibitorji α-glukozidaze

- Lahko pojeste vse, a se ne boste zredili…???



Literatura predavanj

Foye's Principles of Medicinal Chemistry, 6. izdaja:

- 32. poglavje

Foye's Principles of Medicinal Chemistry, 7. izdaja:

- 27. poglavje

Izpiti

Spomladansko izpitno obdobje

- 21. junij 2013
- 5. julij 2013

Jesensko izpitno obdobje

- 23. avgust 2013
- 17. september 2013

Izpiti

Vidimo se na izpitu!