

## Timeline:

- Arateus 80 a.c.: mellitu(m) ‘dolce come il miele’, deriv. di mēl mēllis ‘miele’ (Areteo di Cappadocia)
- 1500 a.c.: egizi consideravano condizione rara quella in cui una persona urinava molto e perdeva peso.
- 1776: Matthew Dobson misurò la concentrazione di glucosio nelle urine di questi pazienti e la trovò aumentata.

**Table 1. Nobel Prizes for Diabetes-Related Research.**

Year	Category	Recipient	Contribution
1923	Medicine	F.G. Banting and J.J.R. Macleod	Discovery of insulin
1947	Medicine	C.F. Cori and G.T. Cori	Discovery of the course of the catalytic conversion of glycogen
1947	Medicine	B.A. Houssay	Discovery of the role of hormones released by the anterior pituitary lobe in the metabolism of sugar
1958	Chemistry	F. Sanger	Work on the structure of proteins, especially insulin
1971	Medicine	E.W. Sutherland	Discoveries concerning the mechanisms of action of hormones
1977	Medicine	R. Yalow	Development of radioimmunoassays for peptide hormones
1992	Medicine	E.H. Fischer and E.G. Krebs	Discoveries concerning reversible protein phosphorylation as a biologic regulatory mechanism

**The Past 200 Years in Diabetes**

New Engl J Med, october 4, 2012, 367 (14), 1332

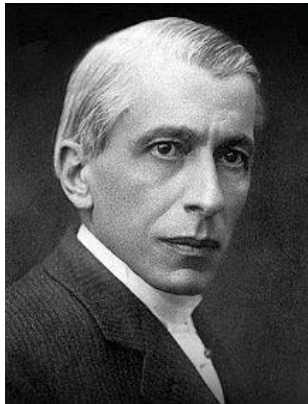
## Successful Drug Discovery-2015

3- Insulin Analogs Improving the Therapy of Diabetes

5- Dapagliflozin, A Selective SGLT2 Inhibitor

7-Discovery of Linagliptin for the Treatment of Type 2 Diabetes

- 1916. professor Nicolae Paulescu (Fisiologia all'Università di Medicina e Farmacia di Bucarest) → pancreas (cane) → pancreatina (brevetto 1922).
- 1922: Frederick Grant Banting & John James Richard Macleod (Università di Toronto-Canada) → estratto dal pancreas purificato dai sali e dai grassi che causano le forti reazioni allergiche osservate durante i primi trattamenti → insulina
- 1923: Frederick Grant Banting & John James Richard MacLeod: Nobel Fisiologia e Medicina.
- 1971: Comitato del Premio Nobel riconosce tardivamente la precedenza di Nicolae Paulescu.



Nicolae Paulescu



Banting (a destra)  
Charles Herbert Best

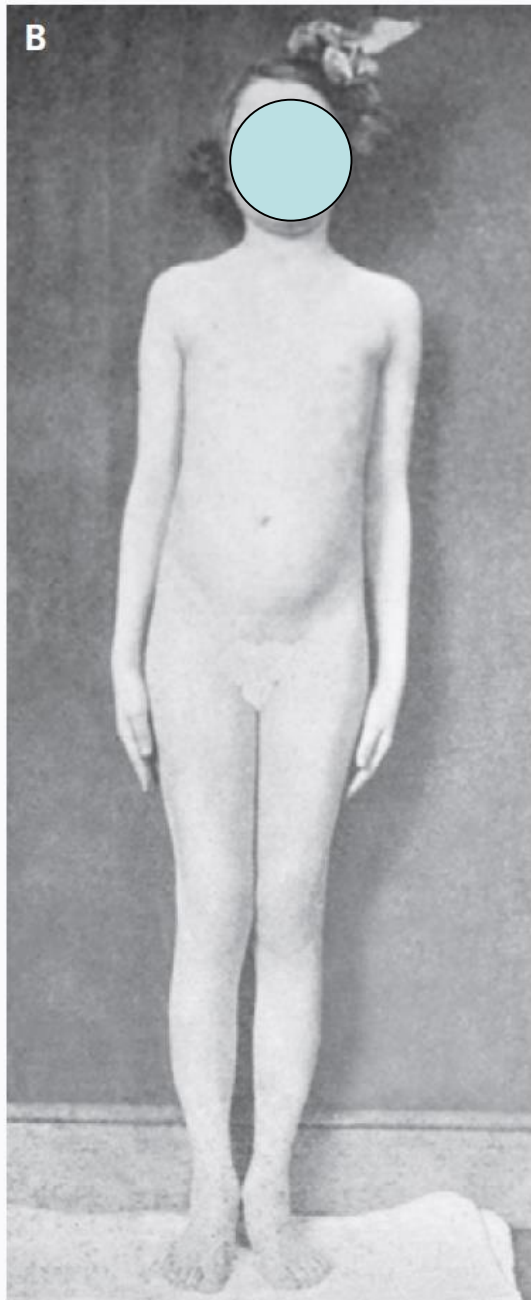
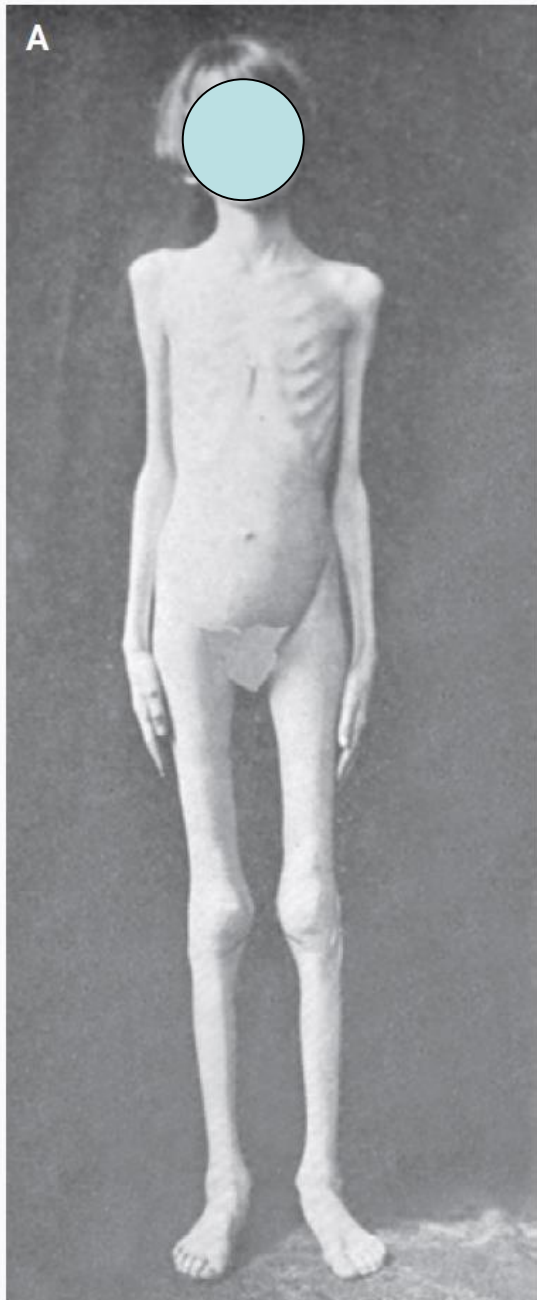


John James  
Richard Macleod



James Bertram Collip,

Toronto group

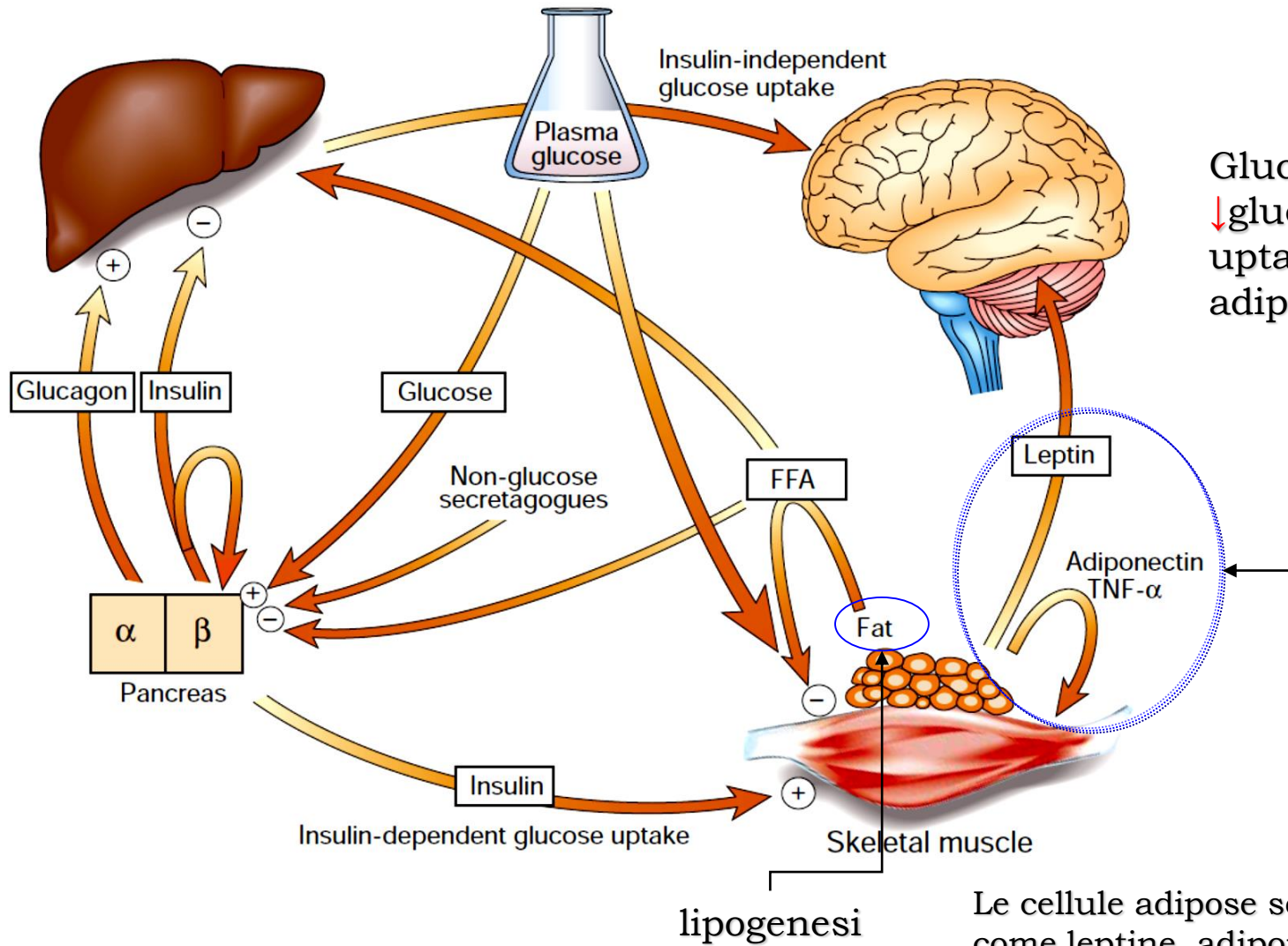


## Effects of Insulin Therapy.

These photographs from 1922, in a case described by Geyelin, show a young girl with insulin-deficient diabetes before treatment with insulin (Panel A) and after treatment (Panel B).



FFA= Acidi grassi liberi (free fatty acids)

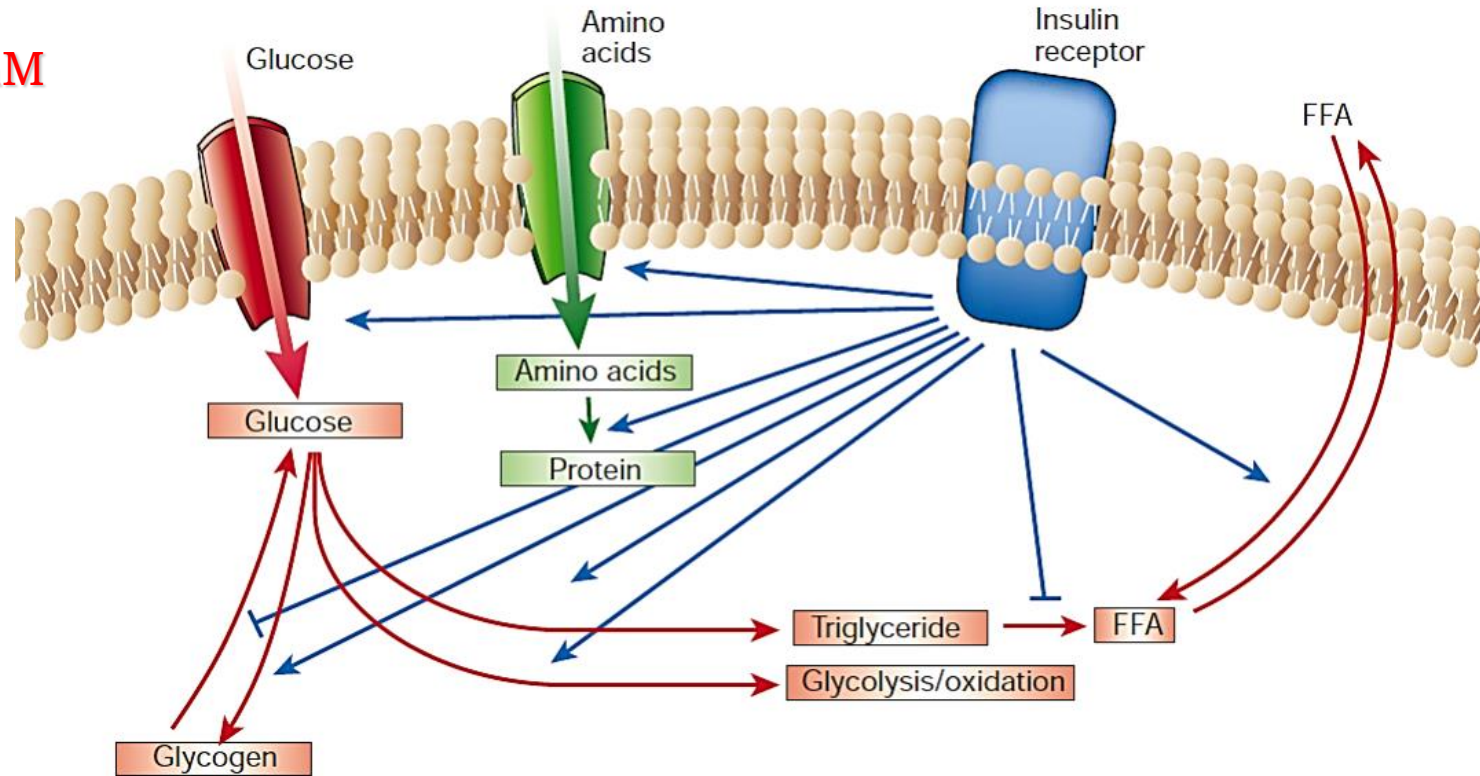


Glucosio → insulina →  
↓ glucosio epatico →  
uptake ↑ → deposito  
adipe muscoli ↑

Le cellule adipose secernono adipochine come leptine, adiponectine e TNF che regolano sazietà, dispendio energetico e sensibilità all'insulina.

# Insulina: regolazione metabolica

4-7 mM



L'Insulina stimola la crescita e la differenziazione cellulare, promuove il deposito di substrati nel tessuto adiposo, fegato e muscoli stimolando la lipogenesi, la sintesi di glicogeno e di proteine, inibendo la lipolisi, glicogenolisi e degradazione proteica. La resistenza o un deficit di insulina genera una profonda disregolazione di questi processi e conseguente incremento della concentrazione plasmatica di glucosio e dei lipidi sia a digiuno che dopo un pasto.

- The number of people with diabetes has risen from **108 million in 1980 to 422 million in 2014**.
- The global prevalence of diabetes\* among adults over 18 years of age has risen from **4.7% in 1980 to 8.5% in 2014<sup>1</sup>**.
- Diabetes prevalence has been rising more rapidly in middle- and low-income countries<sup>1</sup>.
- Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation<sup>1</sup>.
- In 2012, an estimated **1.5 million deaths were directly caused by diabetes and another 2.2 million deaths were attributable to high blood glucose**.
- Almost half of all deaths attributable to high blood glucose occur before the age of 70 years. WHO projects that diabetes will be the 7th leading cause of death in 2030.
- Healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use are ways to prevent or delay the onset of type 2 diabetes.

# Italy

Total population: 59 798 000

Income group: High

## Mortality

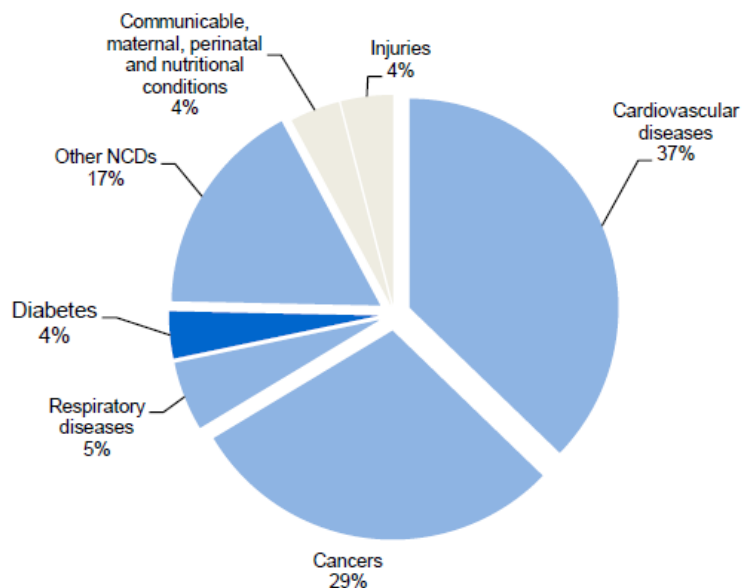
### Number of diabetes deaths

	<i>males</i>	<i>females</i>
ages 30–69	1 820	940
ages 70+	7 150	10 800

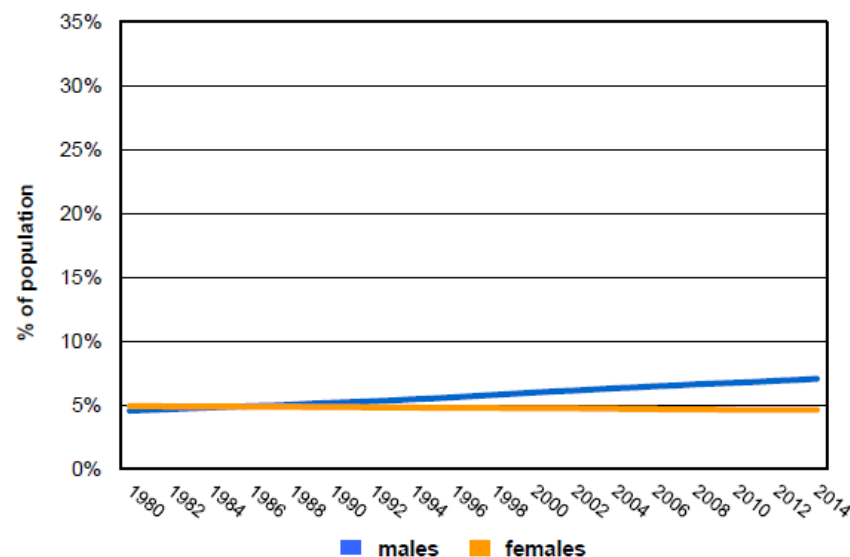
### Number of deaths attributable to high blood glucose

	<i>males</i>	<i>females</i>
ages 30–69	3 250	1 280
ages 70+	13 600	18 700

## Proportional mortality (% of total deaths, all ages)



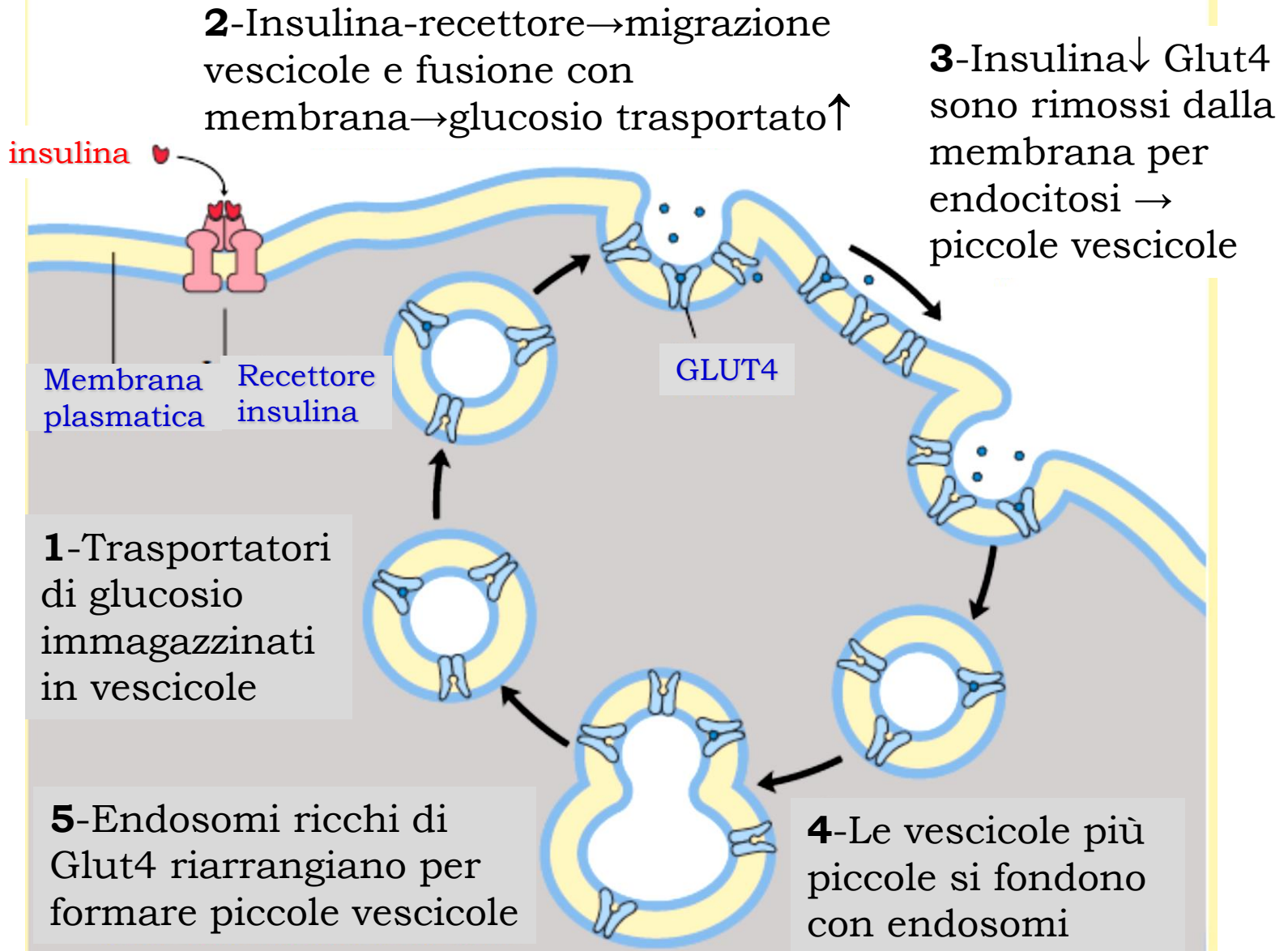
## Trends in age-standardized prevalence of diabetes



## Prevalence of diabetes and related risk factors

	<i>males</i>	<i>females</i>	<i>total</i>
Diabetes	9.6%	7.4%	8.5%
Overweight	68.7%	59.5%	64.0%
Obesity	22.5%	24.8%	23.7%
Physical inactivity	30.0%	41.3%	35.9%

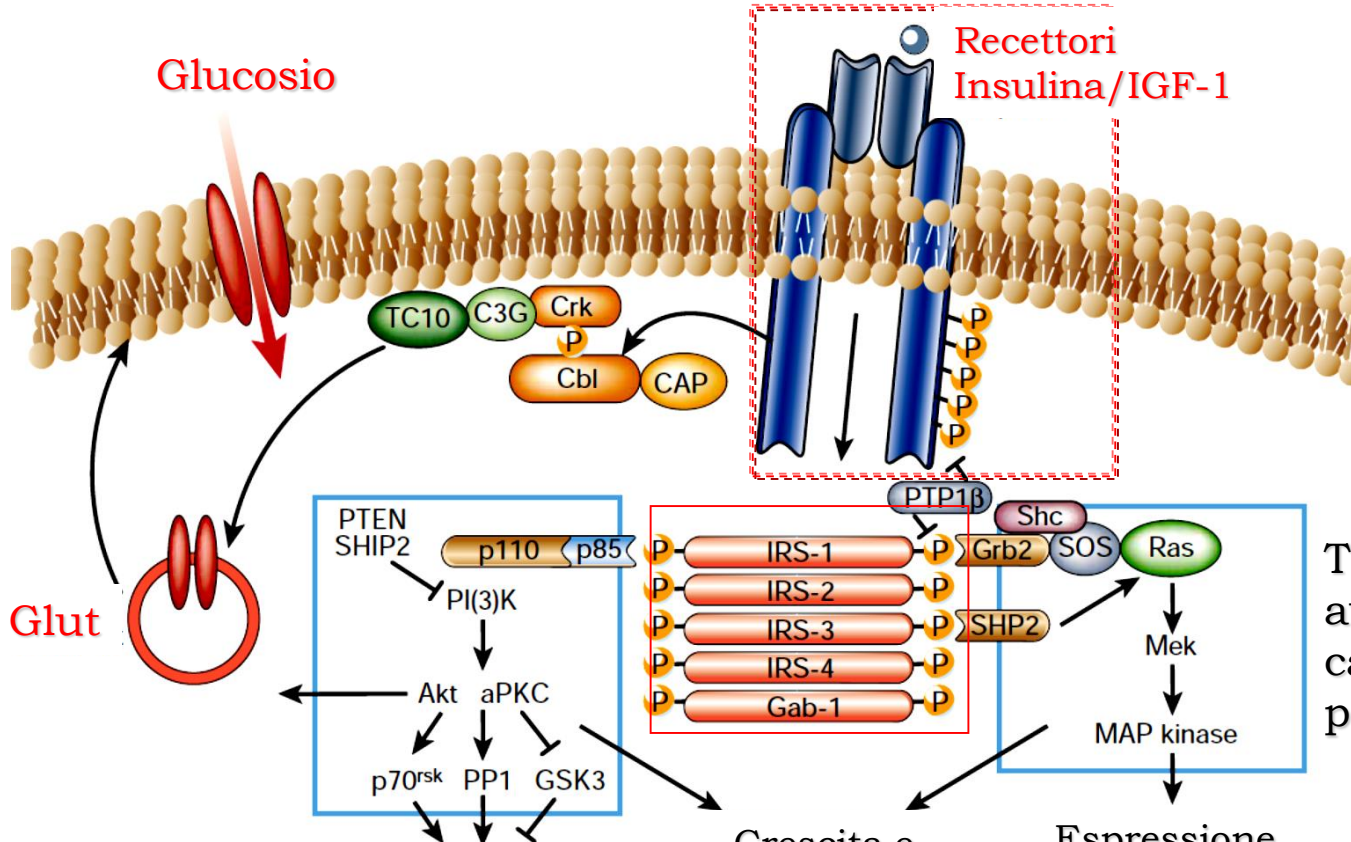
# Miociti cardiaci e scheletrici





# Insulina: trasduzione del segnale

recettore dell'insulina (IR) appartiene alla famiglia dei recettori tirosin chinasi che sono in generale recettori per i fattori di crescita



Tirosin chinasi promuove auto fosforilazione e catalizza fosforilazione proteine cellulari (IRS)

Metabolismo del glucosio-sintesi di glicogeno/lipidi/proteine-specifica espressione genica

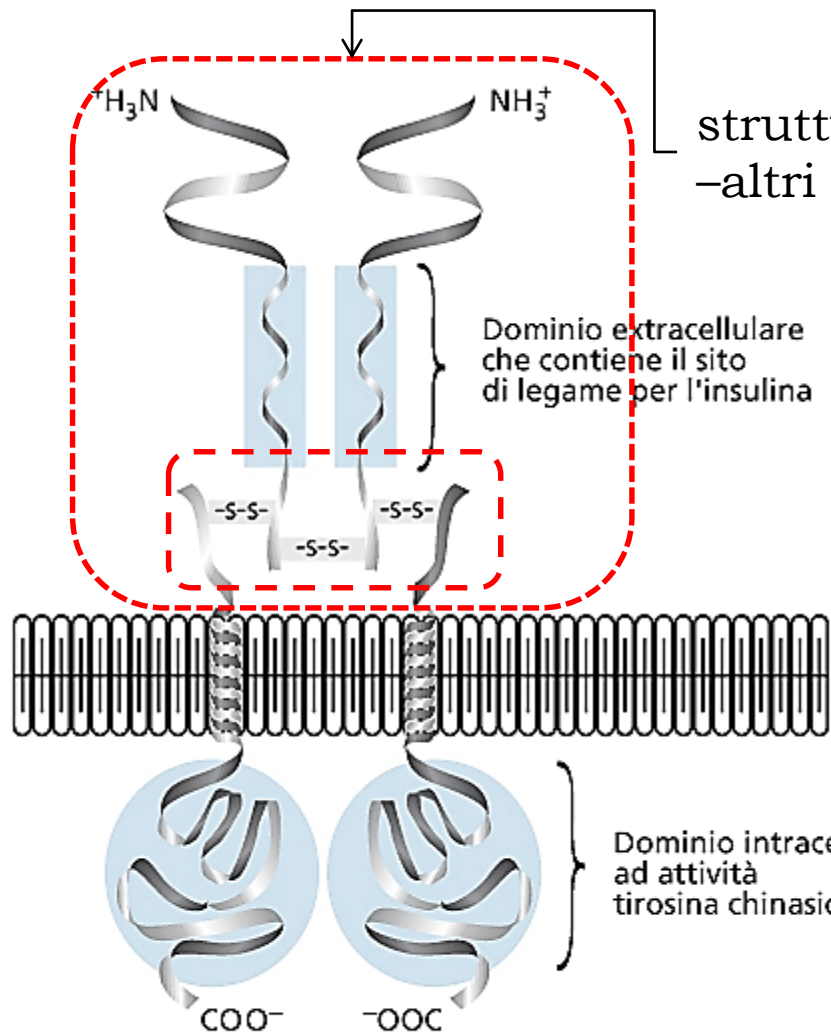
Crescita e differenziazione cellulare

Espressione genica generale

Proteina IRS (Insulin Receptor Substrate)

Questi meccanismi di trasduzione del segnale (metabolismo glucidico, lipidico e proteico) agiscono in modo concertato, regolando il movimento di vescicole, sintesi proteica, attivazione ed inattivazione enzimatica ed espressione genica.





struttura dimerica covalente di tipo  $\alpha_2\beta_2$  (IGF)  
 -altri rec TyrK dimerizzano/oligomerizzano

$\alpha$ -dominio globulare (Cys)

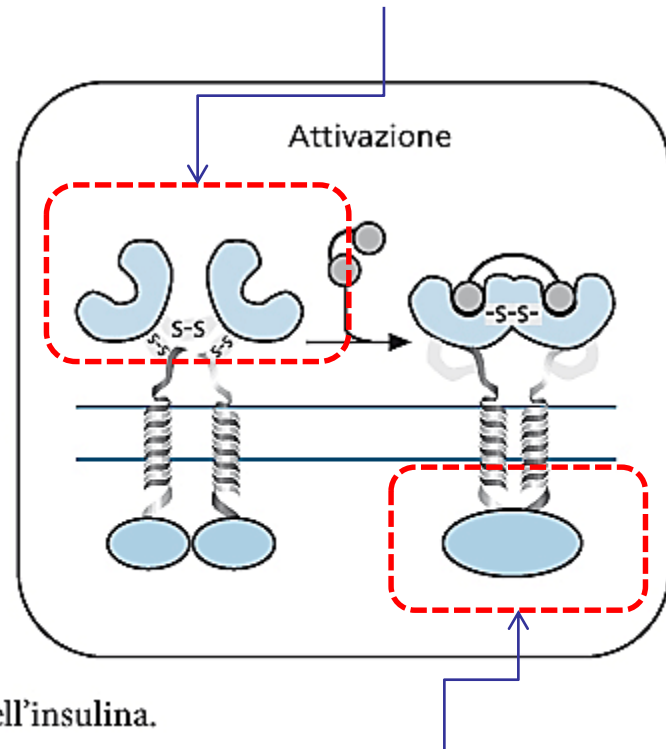
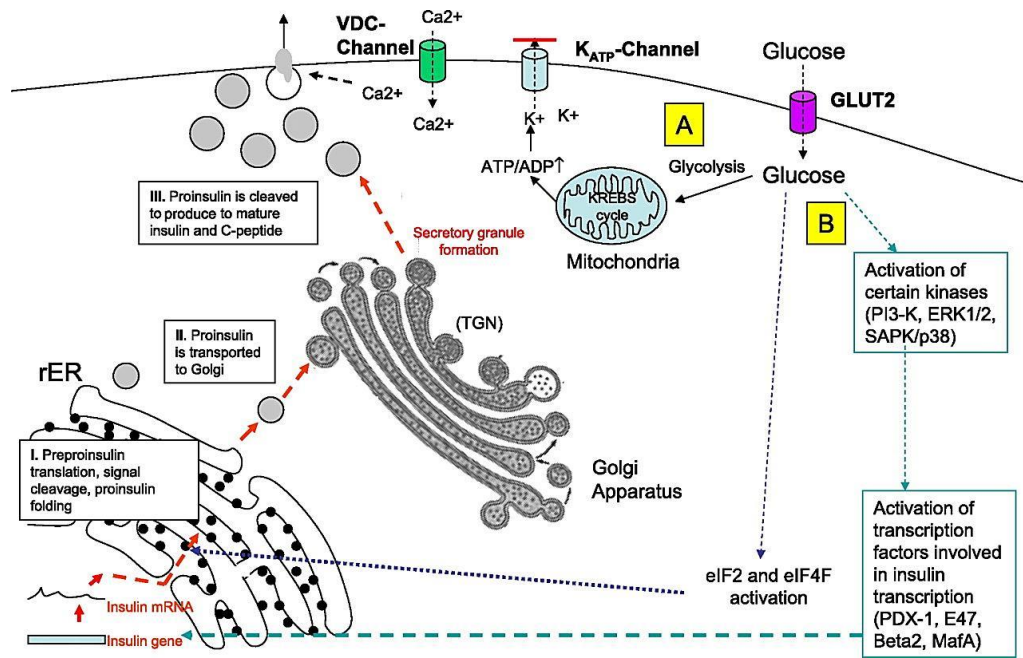


FIGURA 41.3 Il recettore dell'insulina.

$\beta$ -dominio catalitico (chinasico)



**Preproinsulina** (110 aa, sequenza “pre” aminoterminale (peptide-segnale; 24 aa), che consente la secrezione della proteina; sequenza centrale “pro” (peptide C; 35 aa) che determina il corretto ripiegamento del filamento polipeptidico

→ enzima taglia i 24 aminoacidi aminoterminali, rilasciando la proinsulina che si piega consentendo la formazione dei ponti disolfuro tra residui di cisteina.

→ **Proinsulina** (86 aa) vescicole dell'apparato di Golgi, dove il peptide C viene rimosso

→ La proinsulina è convertita in insulina da enzimi proteolitici che rimuovono il peptide di connessione (C) e le sequenze di aminoacidi basici lisina-arginina (Lys-Arg) e arginina-arginina (Arg-Arg). La molecola dell'insulina consiste delle catene A e B legate da un ponte disolfuro.

**Insulina (51 aa)**

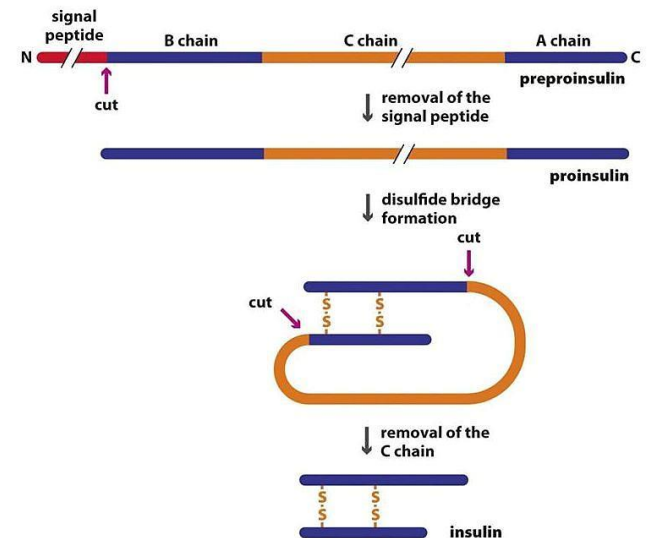
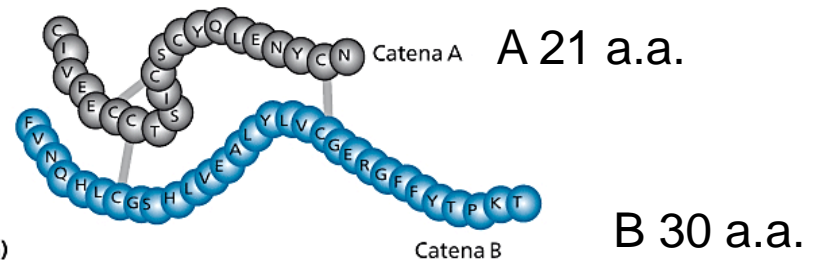


Figure 8.24 Introduction to Genetics (© Garland Science 2012)



a.a. (A) 8,9,10 e (B)30  
Caratteristici di specie

TABELLA 41.2 Insulina umana e animale

Origine	Catena A	Catena B
Umana	Thr-8 Ile-10	Thr-30
Porcina	Thr-8 Ile-10	Ala-30
Bovina	Ala-8 Val-10	Ala-30

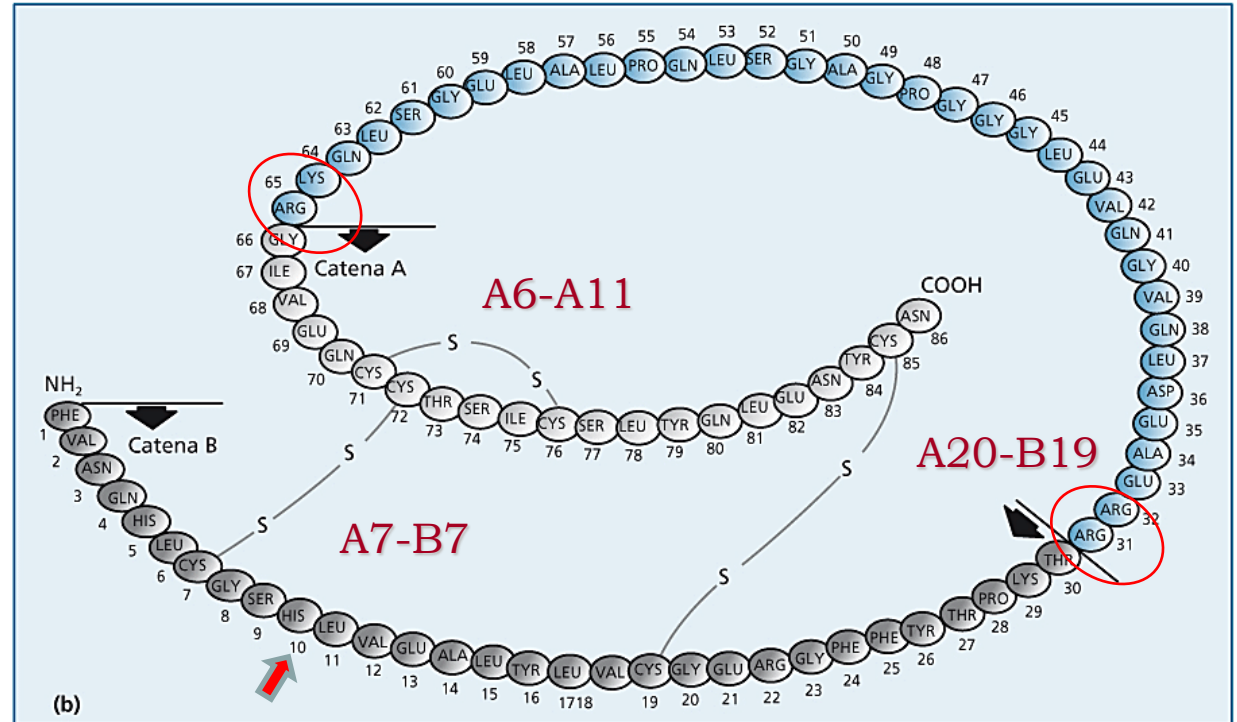
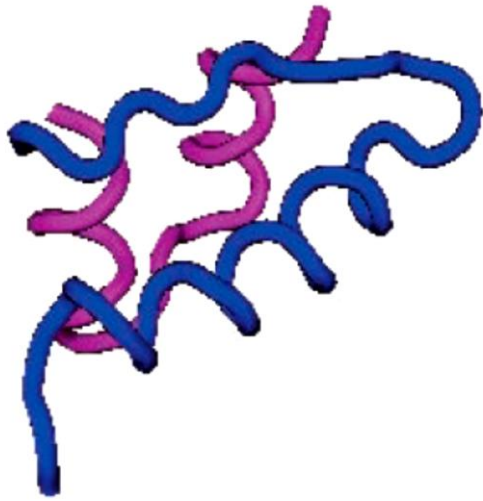


FIGURA 41.1 (a) Insulina in forma attiva. (b) Struttura primaria della proinsulina (86 aa) con indicazione dei siti della scissione enzimatica che determina perdita del peptide C (aa 33-63) e di 4 amminoacidi basici.

## Struttura della of Proinsulina Umana.

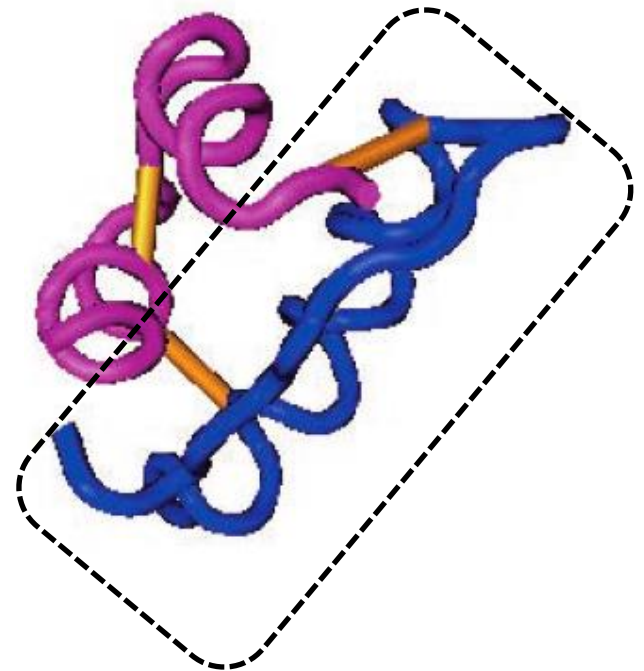
convertita in insulina da enzimi proteolitici che rimuovono il peptide di connessione (C) e le sequenze di aminoacidi basici lisina-arginina (Lys-Arg) e arginina-arginina (Arg-Arg).



### **catena A catena B**

struttura terziaria della **catena A**; si formano due sezioni ad alfa elica, che delimitano una parte centrale  $\beta$ -sheet la **catena B** presenta una sezione maggiore ad alfa elica e si piega a gomito, “avvolgendo” la catena A.

Struttura terziaria stabilizzata da **ponti disolfuro** La parte esterna della molecola è principalmente polare, quella interna è per lo più apolare.

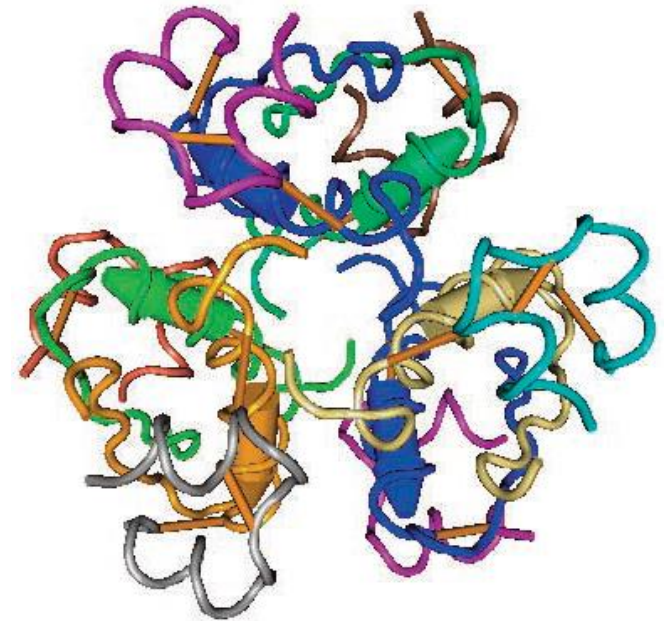


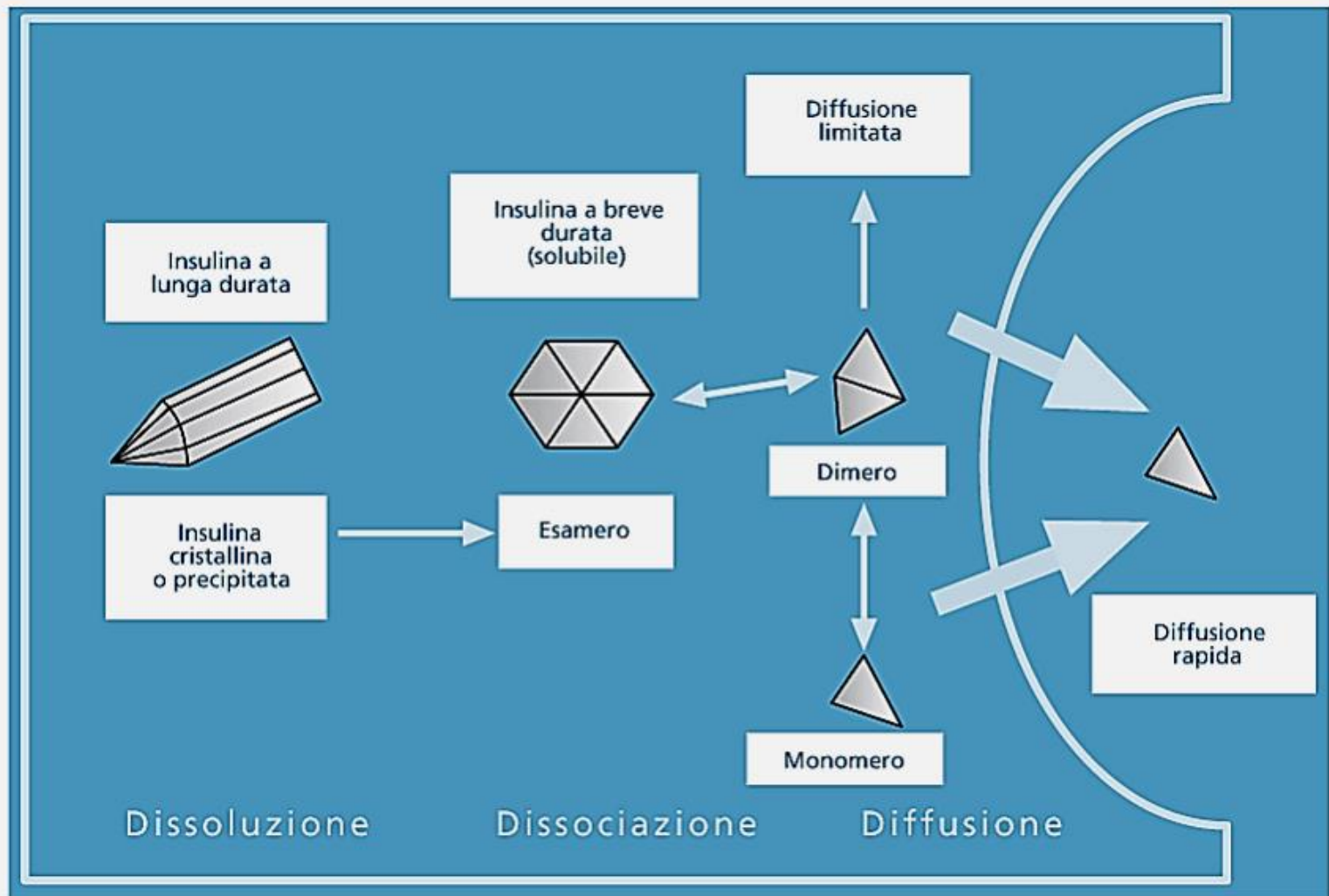




**Dimero di insulina**, struttura quaternaria, l'insulina in soluzione tende a formare dimeri, per l'instaurarsi di ponti idrogeno tra le estremità C-terminali della catena B.

**Esamero di insulina** In presenza di ioni zinco può formare esameri; ne risulta una forma toroidale (“a ciambella”) con la quale l'insulina è immagazzinata nelle cellule  $\beta$  e secreta nel flusso sanguigno. In ogni caso la forma attiva è costituita da un singolo monomero.

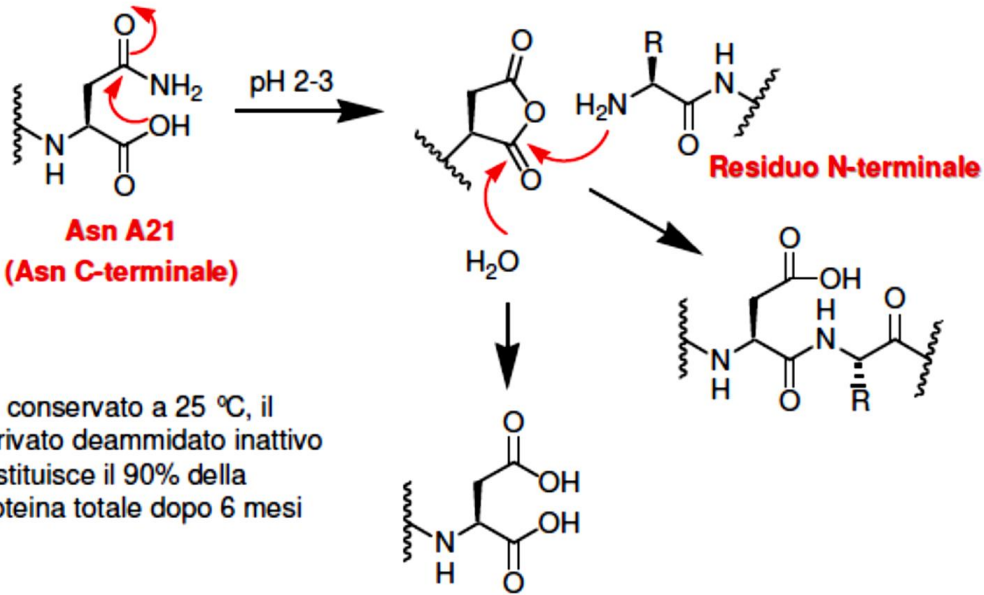




**FIGURA 41.2** Rappresentazione schematica dei processi di dissoluzione, dissociazione e assorbimento dell'insulina dopo somministrazione sottocutanea di sospensioni o soluzioni.



## Degradazione chimica (pH 2-3)



Deamminazione di asparagina e glutamina: la più comune modifica post-traslazionale non enzimatica; può influenzare struttura, stabilità, folding ed aggregazione delle proteine (amiloidi).  
(cfr insulina **Glargine**)

In soluzione neutra il fenolo ritarda la velocità di deamidazione riducendo la flessibilità conformazionale del segmento B1-B6. I prodotti di deamidazione conservano l'attività senza immunogenicità avversa.  
(cfr insulina **Glulisina**)

**TABELLA 41.1** Meccanismo d'azione delle principali classi di farmaci antidiabetici

	Correzione della deficienza di insulina	Stimolazione della secrezione di insulina	Diminuzione della produzione di glucosio epatico	Aumento dell'utilizzo di glucosio	Riduzione dell'assorbimento dei carboidrati
Insulina ed analoghi	→ X				
Solfoniluree e glinidi		→ X			
Farmaci attivi sul sistema incretinico		→ X			
Biguanidi			→ X	→ X	
Tiazolidindioni			→ X	→ X	
Inibitori dell' $\alpha$ -glucosidasi					→ X

Insulina umana:

- half-life 4-6 min;
- concentrazione plasmatica variabile (deposito sottocutaneo, pH, cationi metallici bivalenti, aggregati dimerici/esamerici (Zn));
- oltre duecento formulazioni

Analogue	Modification	Mechanism
A		
Lispro (Humalog®) Eli Lilly and Co	Pro <sup>B28</sup> → Lys Lys <sup>B29</sup> → Pro	IGF-I-related motif impairs dimerization
Aspart (NovoLog®) Novo-Nordisk	Pro <sup>B28</sup> → Asp	Charge repulsion at dimer interface
Glulisine (Apidra®) Sanofi-Aventis	Asn <sup>B3</sup> → Lys Lys <sup>B29</sup> → Glu	Decreased zinc-free self-association
B		
Glargine (Lantus®) Sanofi-Aventis	Arg <sup>B31</sup> -Arg <sup>B32</sup> tag Asp <sup>A21</sup> → Gly	Shift in pI to pH 7 leads to isoelectric precipitation on injection
Detemir (Levemir®) Novo-Nordisk	Modification of Lys <sup>B29</sup> by a tethered fatty acid	Stabilization of hexamer and binding to serum albumin

## Tappe fondamentali delle formulazioni di Insulina.

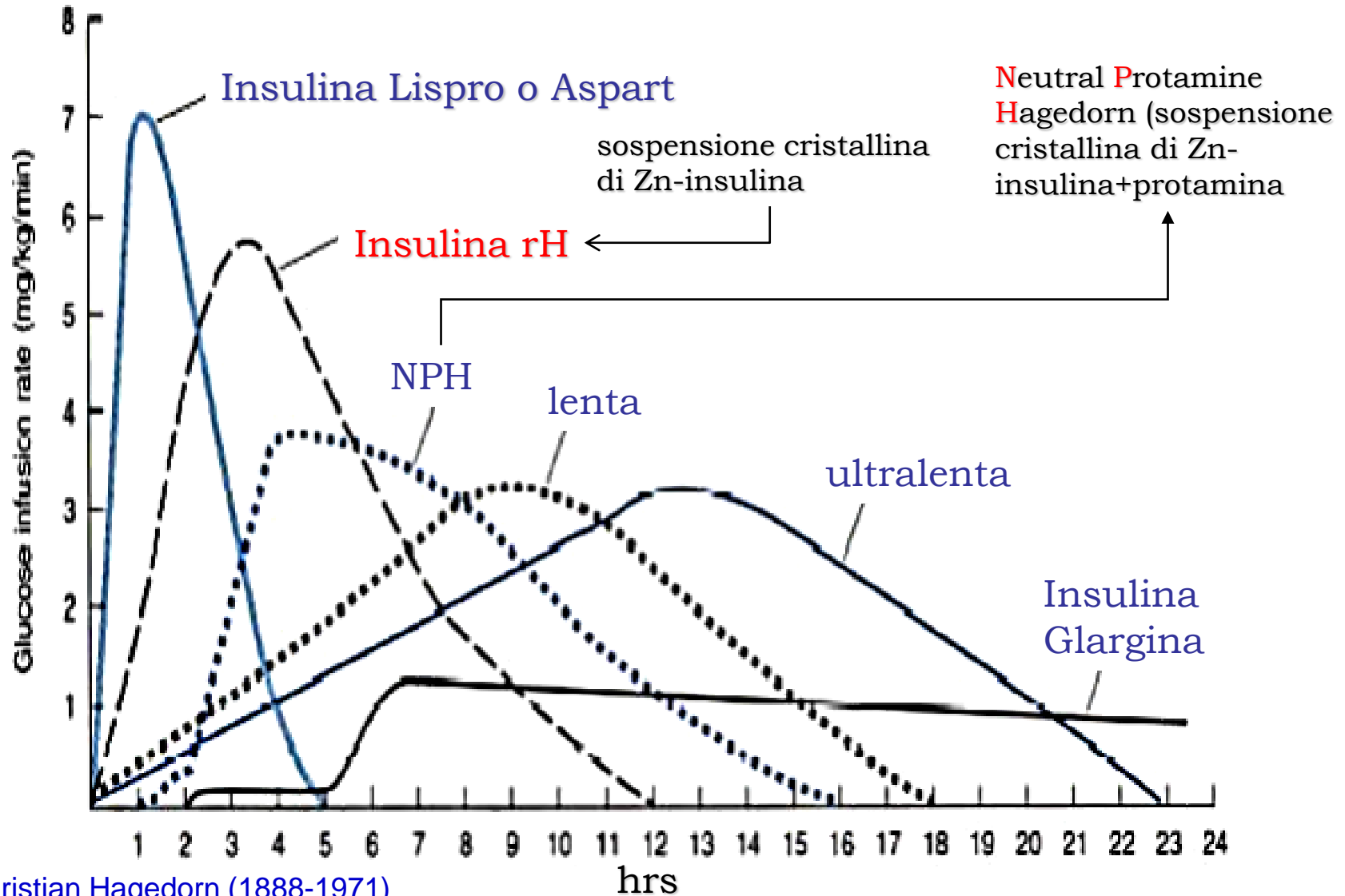
- anni '20-insulina di origine animale (porcina, bovina);
- anni '40-insulina NPH;
- 1953-insuline lente ed ultralente;
- anni '80-insulina ricombinante umana (rDNA);
- anni '90-insulina Lispro (azione breve);
- 2000-insulina Glargine (azione lenta);
- formulazioni non iniettabili;
- formulazione per inalazione spray

Neutral Protamine Hagedorn

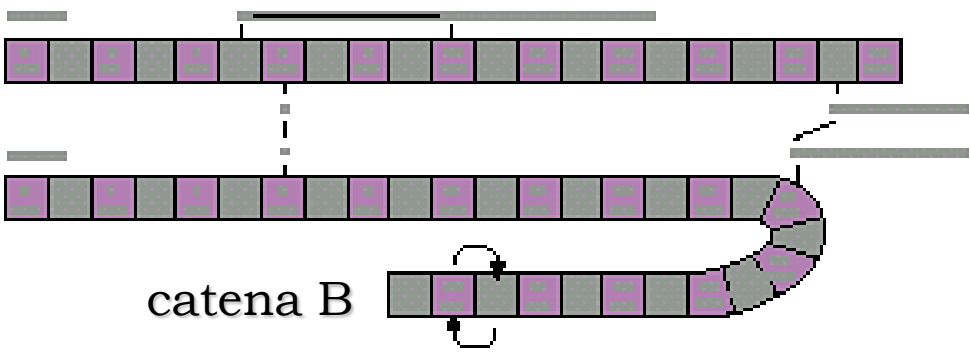
(sospensione cristallina di Zn-insulina+protamina)

### 3 criteri funzionali:

1. compatibilità con binding ad alta affinità vs recettore;
2. conservazione dell'attività biologica in vivo;
3. idonea formulazione



**AMINOACID SEQUENCE OF THE INSULIN MOLECULE**



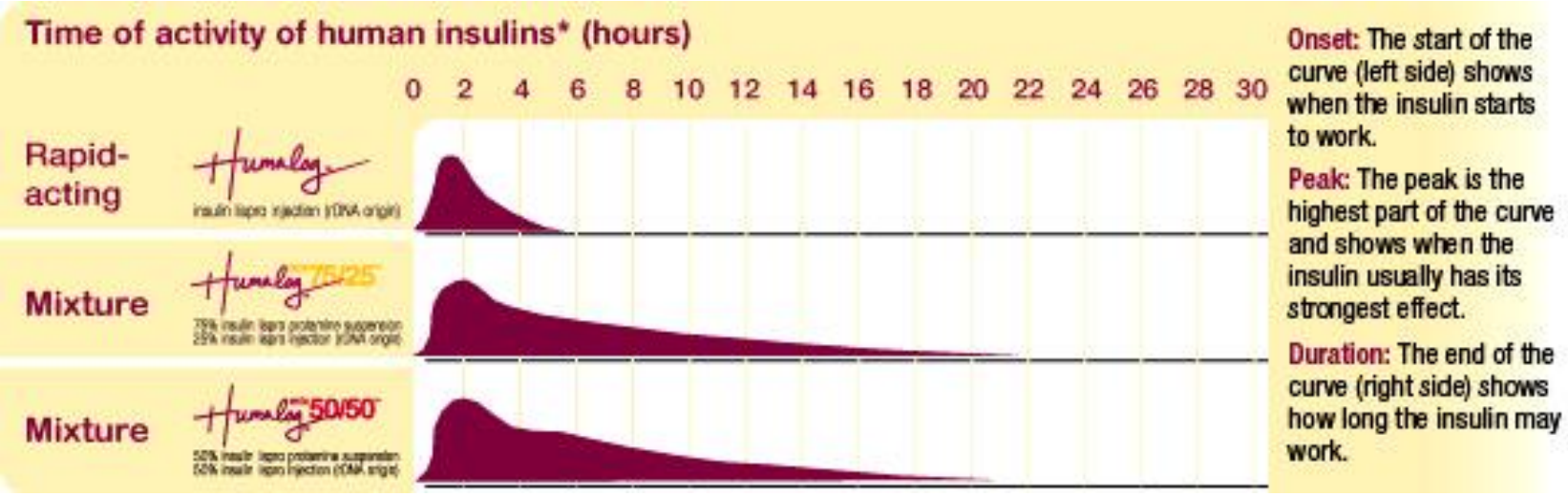
**Analoghi Insulina Azione Rapida**

Livelli glicemici prossimi a quelli della popolazione non-diabetica, senza aumentare il rischio d'ipoglicemia.

Lys28 ↔ Pro29

**EFFETTI COMPARATI FRA L'INSULINA REGOLARE E LISPRO**

Tipo	Inizio dell'azione	Picco massimo	Durata
Regolare	1/2 - 1 ora	2 - 3 ore	3 - 6 ore
<b>Lispro</b>	<b>5 Minuti</b>	<b>1 ora</b>	<b>2 - 4 ore</b>

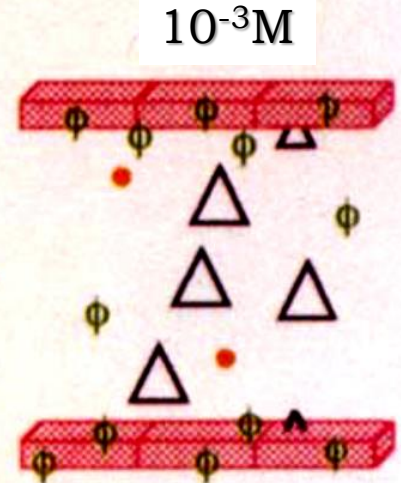
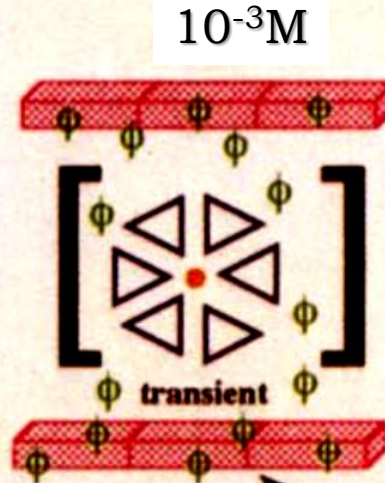




# Analoghi Insulina **Azione Rapida**

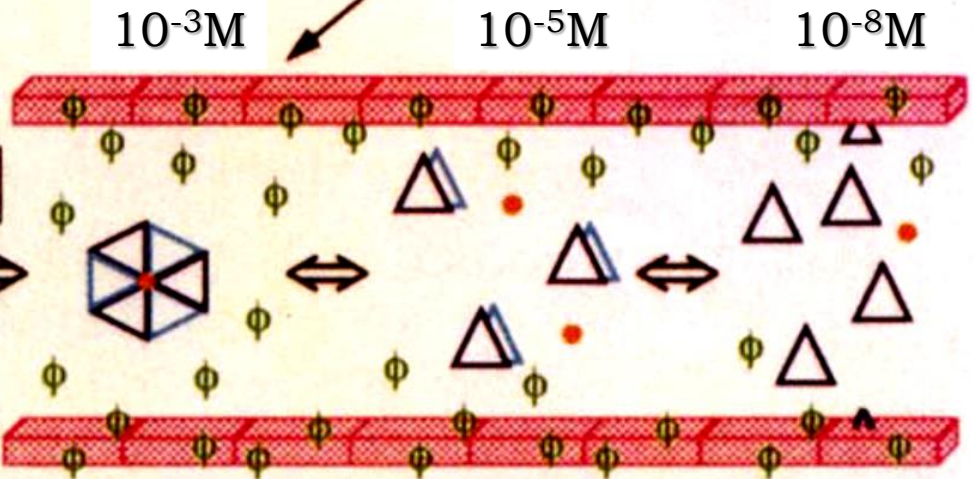
**Lys<sup>R28</sup>Pro<sup>R29</sup>-human insulin**

~ concentration (M)  $10^{-3}$



**Human insulin**

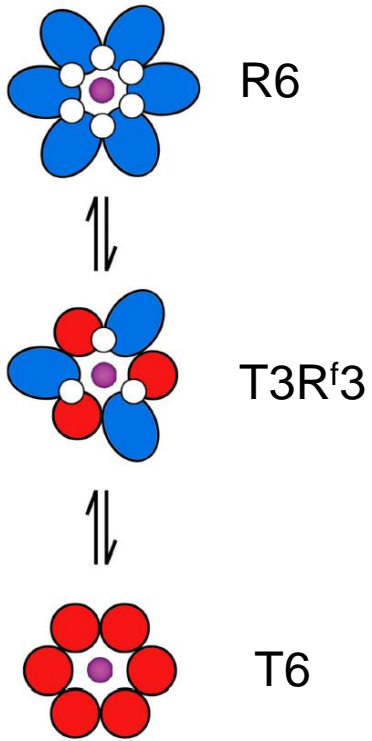
~ concentration (M)  $10^{-3}$



**subcutaneous tissue**

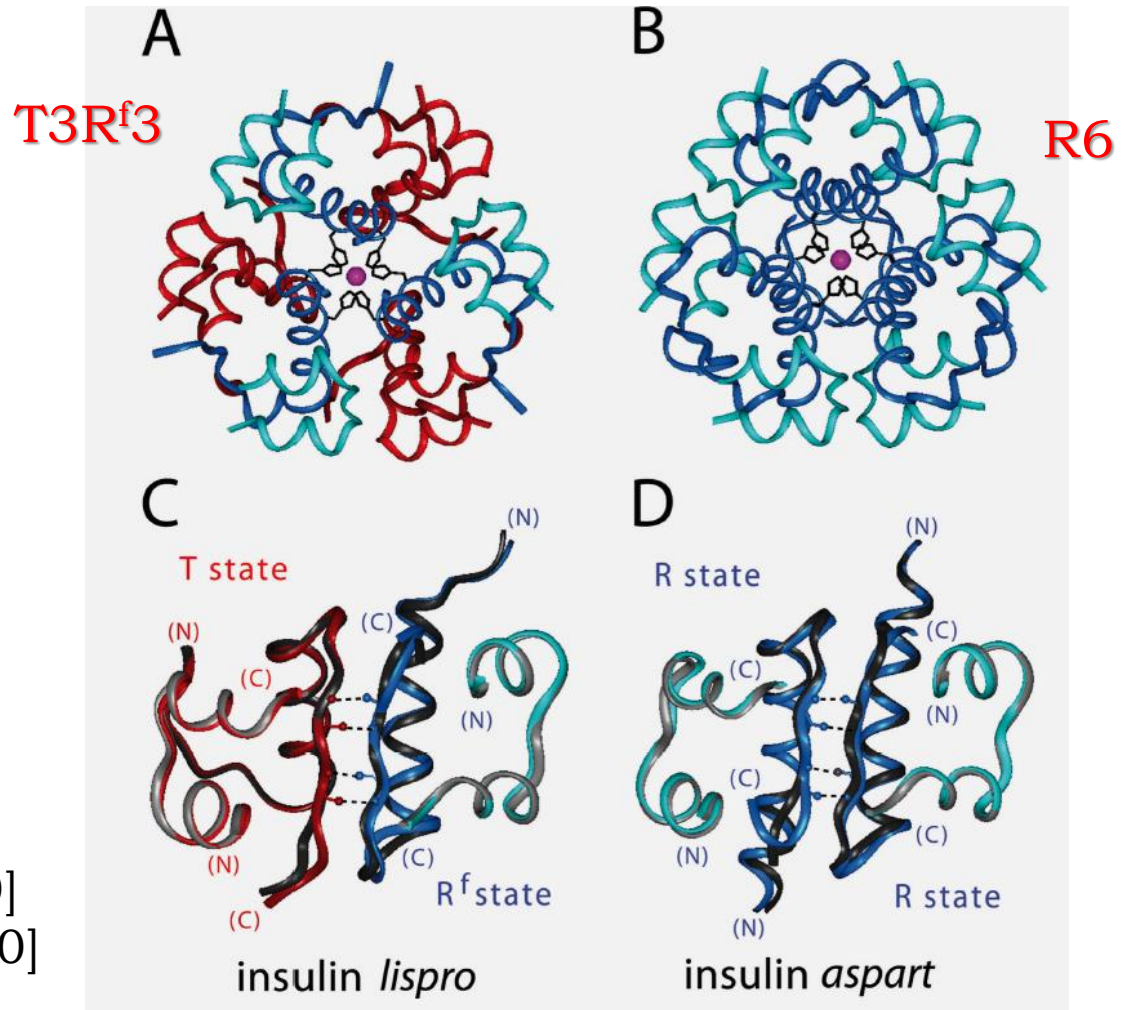
$10^{-5}M$

$10^{-8}M$



des-tripeptide [B28–B30]  
 des-tetrapeptide [B27–B30]  
 des-pentapeptide [B26–B30]

### Struttura crx

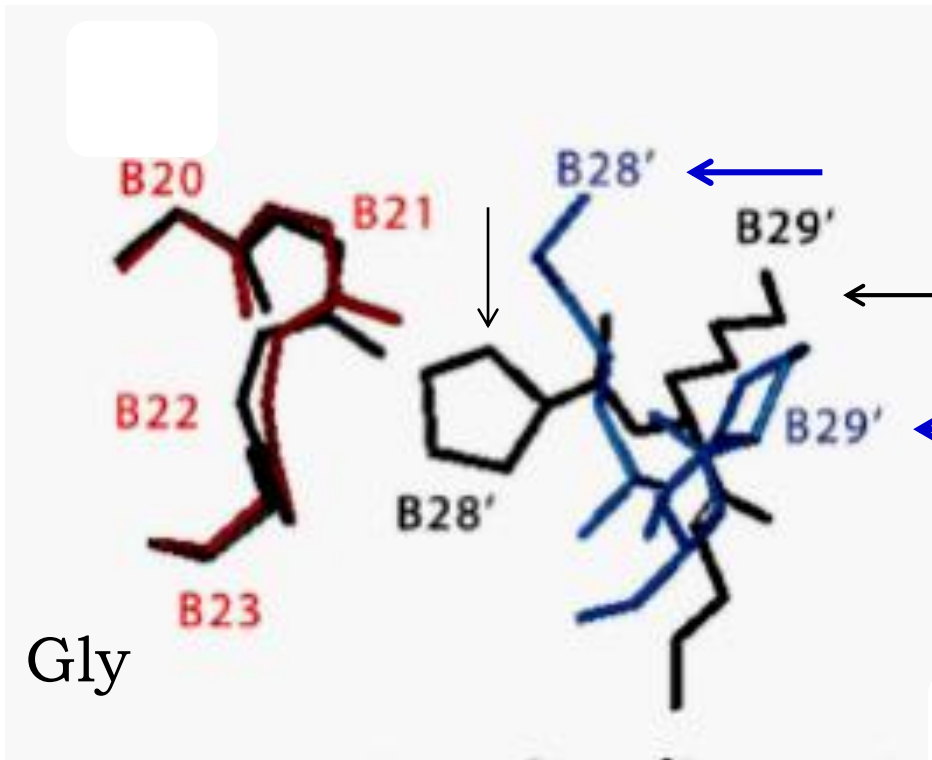


(R6 in soluzione)

Lys28 ⇌ Pro29

Pro28 → Asp28

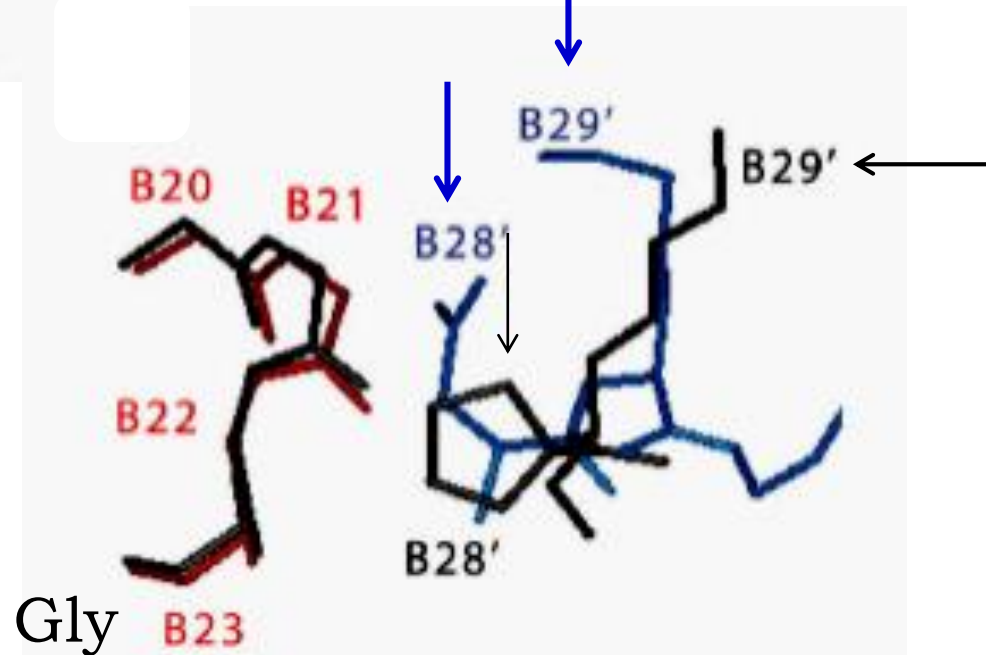
# Interfaccia dimero



Lispro T3Rf3

Gly

Aspart R6



Gly



# Analoghi Insulina **Azione Rapida**

## Insulina Glulisina (*Apidra*®)

>A chain GIVEQCCTSICSLYQLENYCN

>B chain FV**K**QHLCGSHLVEALYLVCGERGFFYTP**E**T

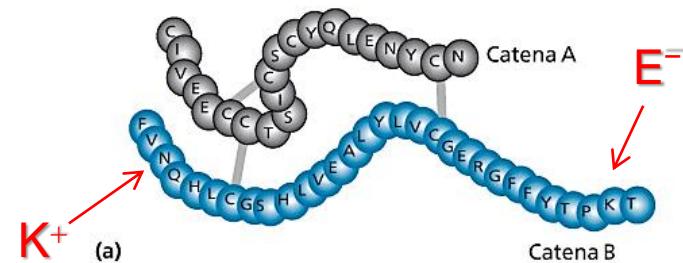
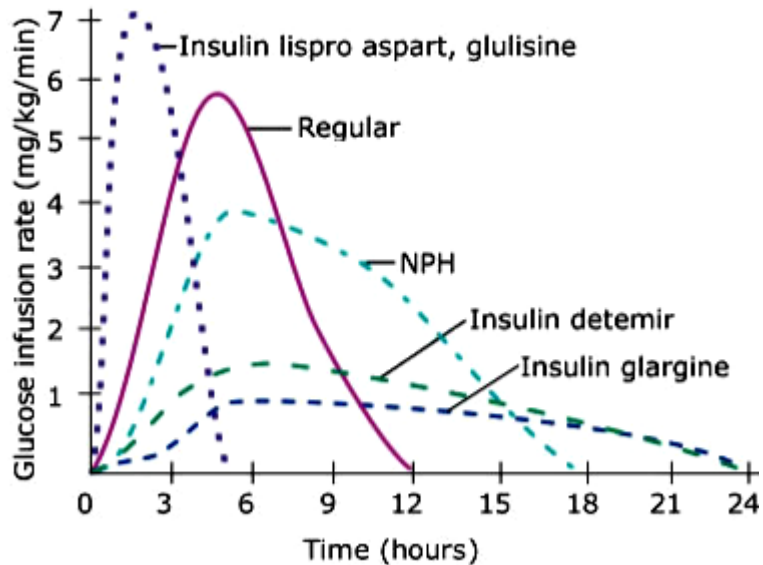
Asn3 →<sup>!</sup> Lys3

Lys29 →<sup>!</sup> Glu29

>A chain GIVEQCCTSICSLYQLENYCN

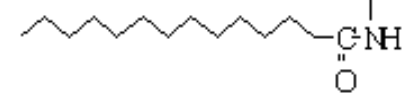
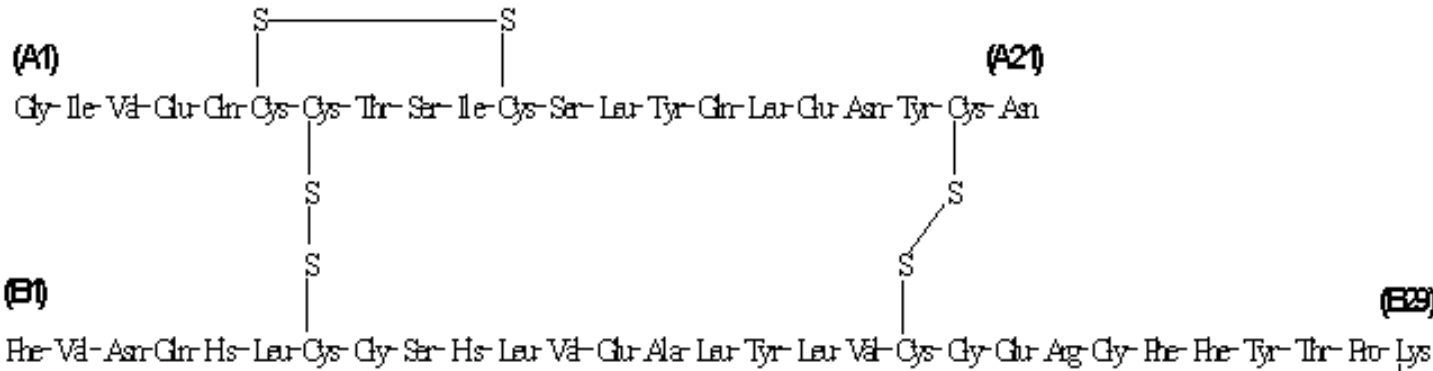
>B chain FV**N**QHLCGSHLVEALYLVCGERGFFYTP**K**T

Insulina ricombinante regolare



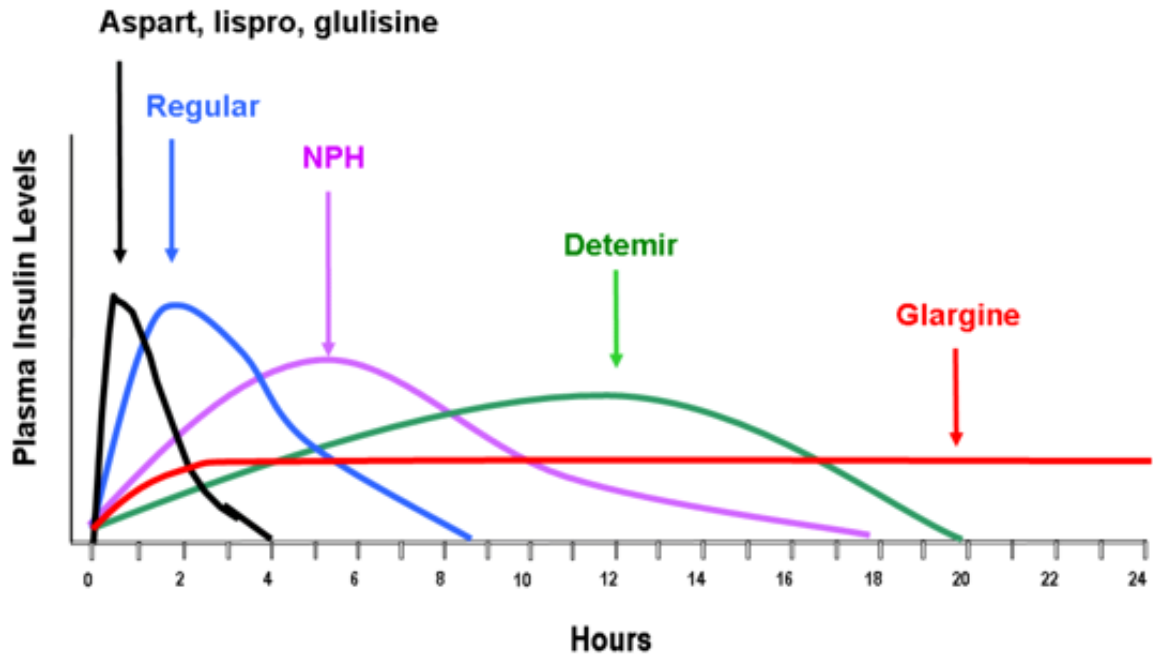
# Insulina Detemir (*Levermir*®)

## Analoghi Insulina **Azione Lenta**



acido miristico (14C)

Incrementa l'autoassociazione ed il binding all'albumina (> 98%)



# Insulina Glargine (*Lantus*®)

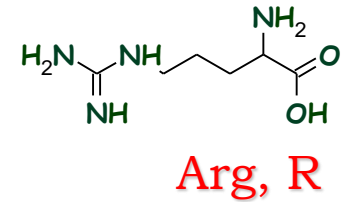
## Analoghi Insulina **Azione Lenta**

>A chain GIVEQCCTSI**C**SLYQLENY**C****G**

>B chain FVNQHLCGSHLVEALYLVCGERGFFYTPK**T****RR**

**A** Asn21  $\leftarrow$  Gly21

**B** + Arg31-Arg32

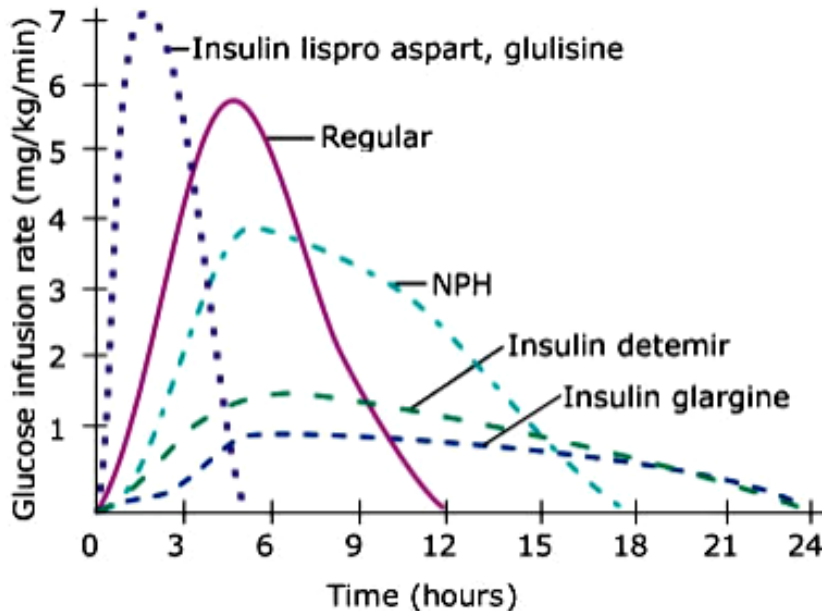


Insulina Glargine

>A chain GIVEQCCTSI**C**SLYQLENY**C****N**

>B chain FVNQHLCGSHLVEALYLVCGERGFFYTPK**T****--**

Insulina ricombinante regolare



- Gly21Asn, Arg31 e Arg32 aumentano il pHi 5.4→6.7;
- Glargine è formulata a pH 4 (formazione di microprecipitati a pH 7.4);
- La lenta dissoluzione di questi ppt produce genera una conc costante di insulina in circolo per un periodo particolarmente lungo.



## **How Inhaled Insulin Works**

The idea of inhaling insulin has been around for decades. However, it wasn't until the 1990s that researchers made it possible. First, insulin is made into a powder form. Insulin particles are delivered through an [inhaler](#) much like the type used by people with [asthma](#). The powder is then inhaled into the lungs and enters the bloodstream through tiny blood vessels.

## **Inhaled Insulin and Exubera**

The FDA approved the first inhaled insulin, called [Exubera](#), in September 2006. People who have either type 1 or [type 2 diabetes](#) could use Exubera.

The drug's maker, Pfizer, took Exubera off the market in October 2007 for financial reasons. The drug was expensive and didn't seem to catch on with patients. In 2008, the FDA also expressed concern that Exubera could be linked to lung toxicities and [lung cancer](#).

## **The Future of Inhaled Insulin**

The withdrawal of Exubera from the U.S. market hasn't ended the quest for inhaled insulin. There are other versions of the drug and inhalers currently in development for both type 1 and type 2 diabetes.

One is [Afrezza](#), made by California-based MannKind Corporation. Afrezza is pre-metered ultra rapid acting mealtime insulin. The drug is designed for people with type 1 or type 2 diabetes. However, the **FDA declined to approve Afrezza in early 2011 and asked the makers to provide more study data.**

U.S. Department of Health and Human Services

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**FDA News Release**

**FDA approves Afrezza to treat diabetes**

For Immediate Release June 27, 2014

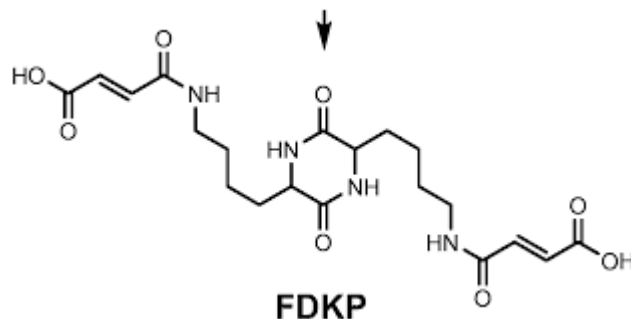
**Inquiries**

**Media**

✉ Andrea Fischer  
☎ 301-796-0393

**Consumers**

Technosphere technology: fumaryl diketopiperazine (FDKP), water and the non-ionic surfactant polysorbate 80 are mixed and crystallised into uniform particles of 2 microns in diameter in combination with recombinant human insulin



PNAS, March 17, 2015

# Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery

Jicheng Yu<sup>a,b</sup>, Yuqi Zhang<sup>a,b</sup>, Yanqi Ye<sup>a,b</sup>, Rocco DiSanto<sup>a,b</sup>,  
Frances S. Ligler<sup>a</sup>, John B. Buse<sup>c</sup>, and Zhen Gu<sup>a,b,c,1</sup>

Author Affiliations [▲](#)

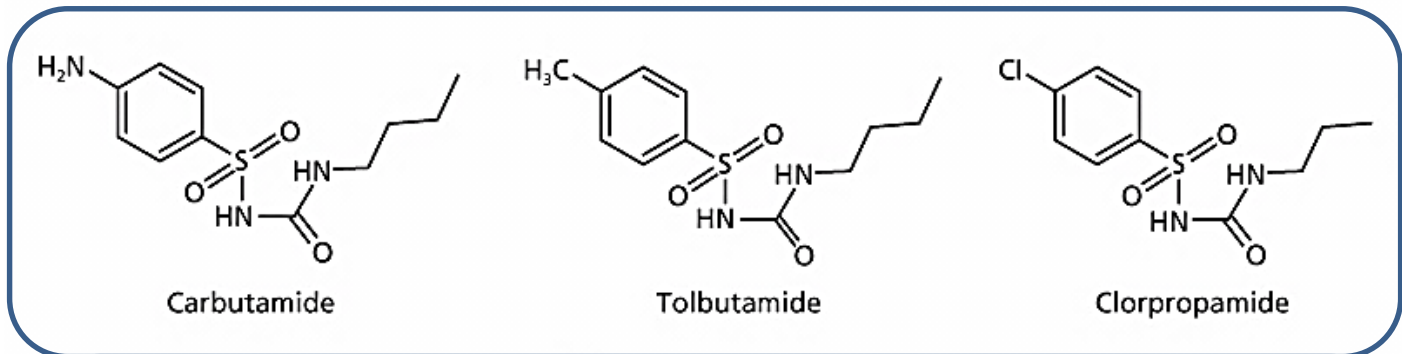
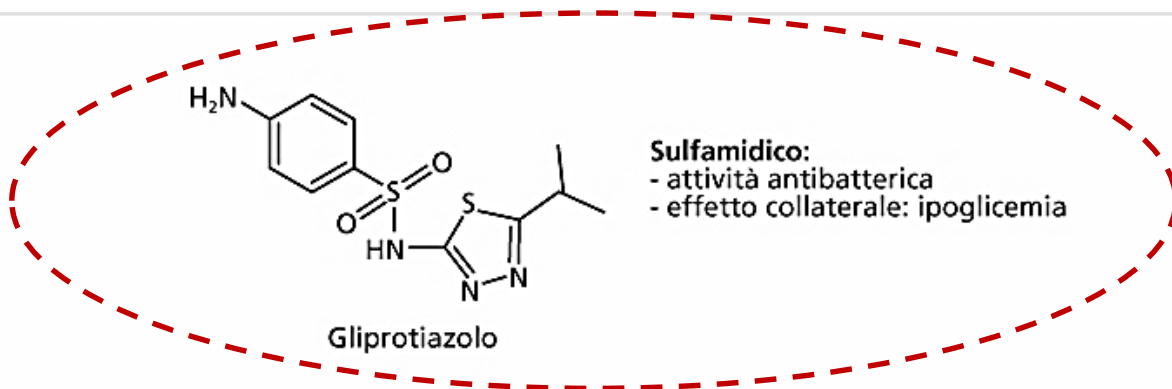
Edited by Dean Ho, University of California, Los Angeles, CA, and accepted for review March 17, 2015)



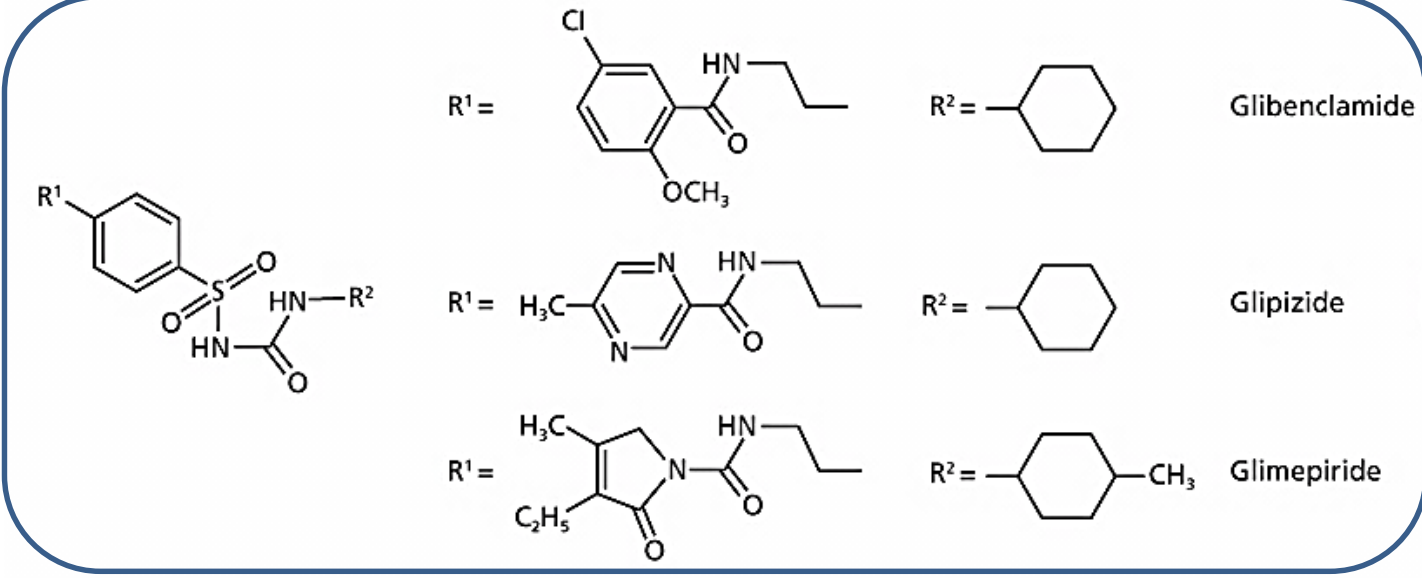
[Abstract](#) [Authors & Info](#) [SI](#) [Metrics](#) [Related Content](#) [PDF](#) [PDF+SI](#)

## Significance

For exploiting synthetic glucose-responsive insulin delivery systems, challenges remain to demonstrate a strategy that would combine (*i*) fast responsiveness, (*ii*) ease of administration, and (*iii*) excellent biocompatibility. We have developed a novel glucose-responsive insulin delivery device using a painless microneedle-array patch containing hypoxia-sensitive hyaluronic acid-based vesicles. The vesicles quickly dissociate and release encapsulated insulin under the local hypoxic environment, caused by the enzymatic oxidation of glucose in the hyperglycemic state. This "smart insulin patch" with a new enzyme-based glucose-responsive mechanism can regulate the blood glucose of type 1 diabetic mice to achieve normal levels, with faster responsiveness compared with the commonly used pH-sensitive formulations, and can avoid the risk of hypoglycemia.



Solfoniluree di I generazione



Solfoniluree di II generazione

FIGURA 41.4 Struttura delle solfoniluree di I e II generazione.

**La curieuse histoire de la découverte  
des sulfamides hypoglycémiants  
(premiers antidiabétiques actifs  
par voie buccale) \***

par Philippe DECOURT \*\*

*L'histoire n'a pas encore été publiée complètement et ce qu'on en a dit est souvent erroné. Elle commença en 1941 quand l'auteur tenta de trouver une thérapeutique de la fièvre typhoïde. Des accidents, parfois mortels, firent apparaître la forte activité hypoglycémiante inattendue qui conduisit à la découverte de la thérapeutique antidiabétique aujourd'hui la plus répandue. Erreur de la Société industrielle qui en empêcha l'usage pendant longtemps.*

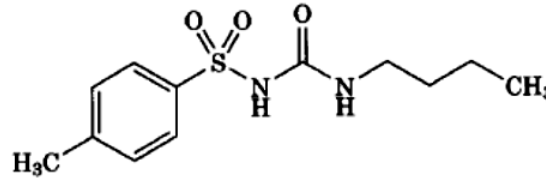
Communication présentée à la séance du 26 janvier 1985 de la Société française d'histoire de la médecine.

# Ipoglicemizzanti: Agenti Insulinotropici → Sulfoniluree (I generazione)

Jambon S, Chaptal J, Vedel A, Schaap J (1942) Accidents hypoglycémiques graves par un sulfamido-thiadiazol. *Montpell Med* 21: 441-445

## Tolbutamide (1956)

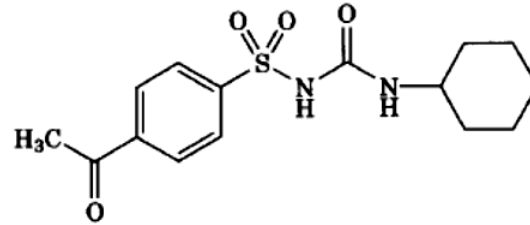
N-(butilcarbamoil)-4-metilbenzenesulfonamide



Dose giorn.	tmax	t½	durata
0.25-3G	3-4	4.5-6.5	6-12

## Acetoexamide

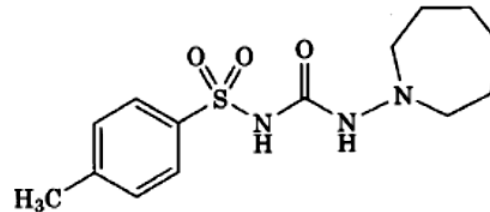
4-acetil-N-(cicloesilcarbamoil)benzenesulfonamide



0.25-1.5G	2-5	3.7-6.4	12/18
-----------	-----	---------	-------

## Tolazamide

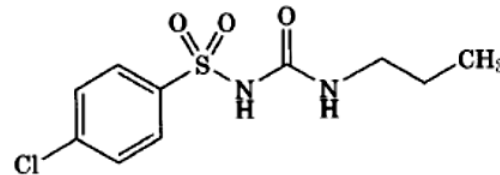
N-(azepan-1-ylcarbamoil)-4-metilbenzenesulfonamide



0.1-1G	3-4	7	12-24
--------	-----	---	-------

## Clorpropamide

4-cloro-N-(propilcarbamoil)benzenesulfonamide



0.1-0.75G	2-4	36	60
-----------	-----	----	----

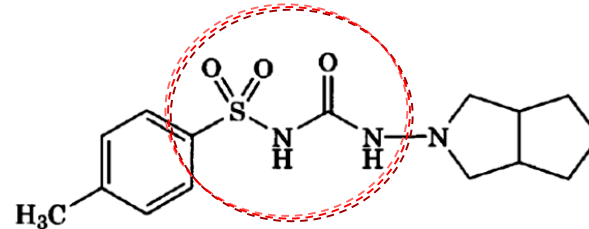
**Agenti Insulinotropici:** stimolano direttamente il rilascio di insulina dalle cellule  $\beta$ -pancreatiche (trattamento per diabete mellito non insulino dipendente, NIDDM); Agiscono chiudendo canali ionici di membrana K-ATP (cellule-beta) → depolarizzazione e apertura canali ionici  $\text{Ca}^{++}$  voltaggio dipendenti. L'influsso di  $\text{Ca}^{++}$  attiva l'esocitosi dell'insulina.

# Ipoglicemizzanti: Agenti Insulinotropici → Sulfoniluree (II generazione)

**Dose giorn. tmax t½ durata**

## Gliclazide

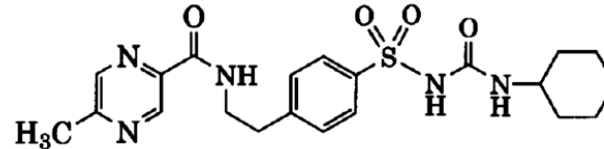
N-(esaidrociclopenta[c]pirrol-2(1H)-ylcarbamoil)-4-metilbenzenesulfonamide  
pKa 4.07 (drugbank, comp.)



0.05-0.32 4-6 10-12

## Glipizide

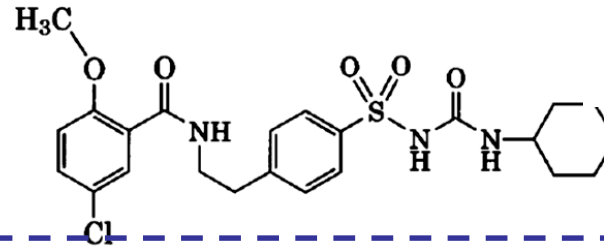
pKa 5.9 (drugbank, exp)



0.025-0.04 1-3 2-4 12-24

## Glyburide (Glibenclamide)

pKa 4.3 (drugbank, comp.)

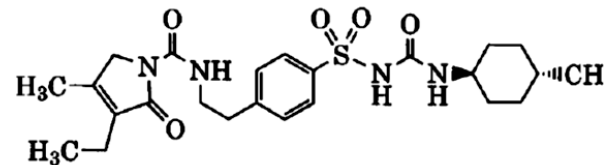


0.001-0.02 2-4 4-10 16-24

**Gliben, Gliboral, Daonil, Euglucon**

## Glimepiride

pKa 4.3 (drugbank, comp.)

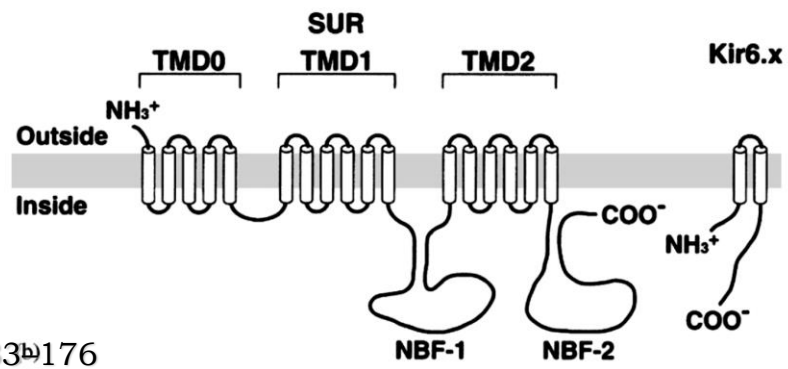
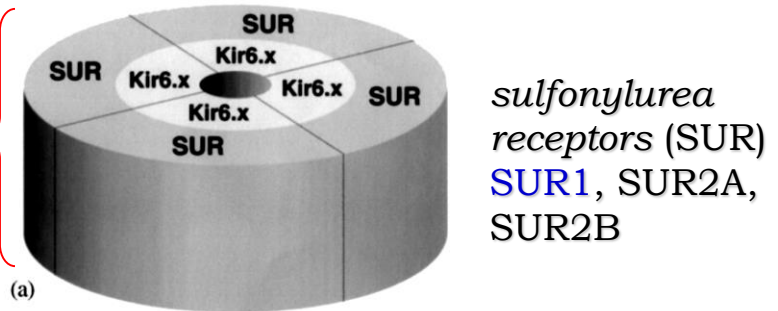
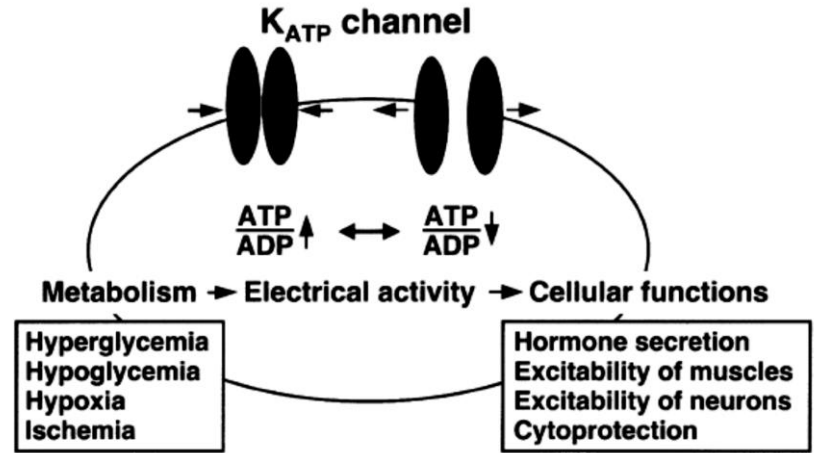
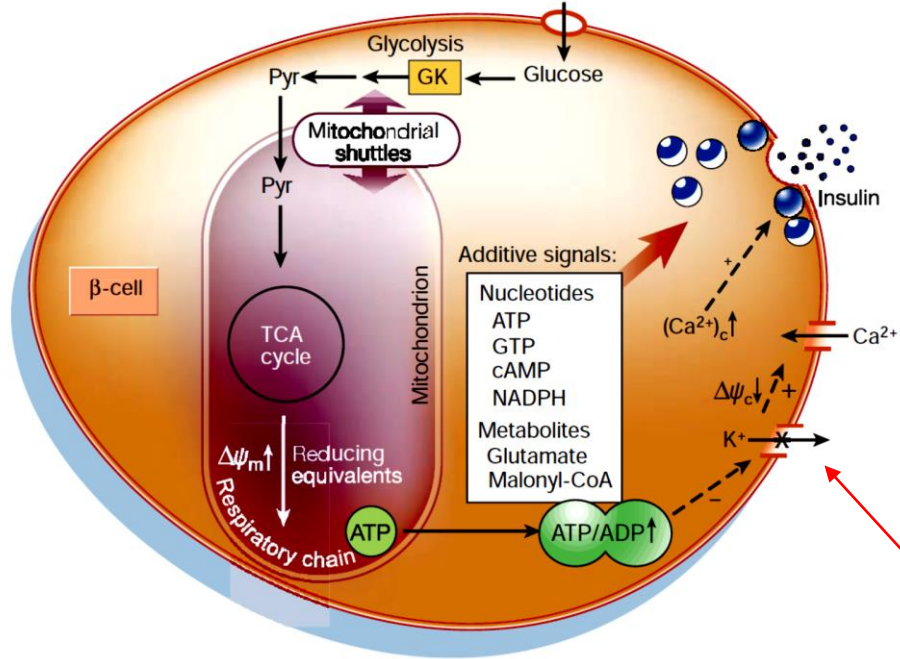


0.001-0.008 2-3 9 16-24

(III generazione)



# Insulina: metabolismo del glucosio e rilascio dalle cellule beta (sistema accoppiato metabolismo-secrezione)

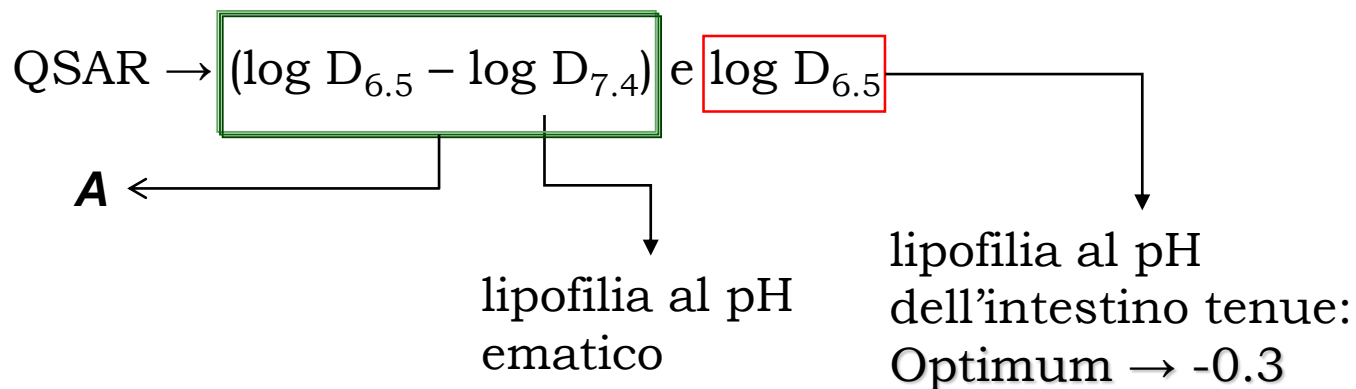


I canali K-ATP sono sensori metabolici che svolgono un ruolo importante in vari tessuti in seguito a stati di alterato metabolismo (iperglicemia, ipoglicemia, ischemia, ipossia).

NATURE, DECEMBER 2001, VOL 414 (13), 807

Progress in Biophysics & Molecular Biology 81 (2003) 133-176

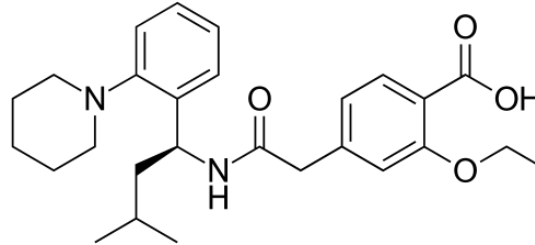
## Proprietà chimico-fisiche delle solfoniluree



# Ipoglicemizzanti: Agenti Insulinotropici → Glinidi

## Repaglinide (*Prandin*)

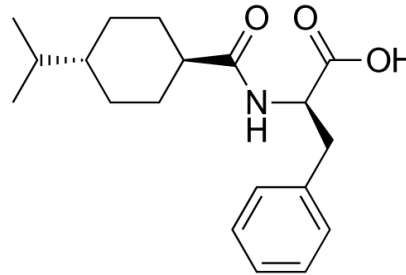
Acido (S)-(+)-2-etossi-4-[2-(3-metil-1-[2-(piperidin-1-il)fenil]butilammino)-2-oxoetil]benzoico



**Dose giorn.** 0.0005-0.004  
x3/4     **t<sub>max</sub>** 1     **t<sub>1/2</sub>** 1-1.4     **durata** 4-6

## Nateglinide (*Starlix*)

Acido 3-fenil-2-[(4-propan-2-ilcicloesancarboneil)ammino]propanoico



0.12x3     <1     1.4

- meccanismo simile a quello delle sulfoniluree;
- minore durata d'azione ma effetto più rapido (o.s.);

**Table 1.5 Binding Parameters for Sulfonylureas and Glinides with HEK EBNA[Human SUR1] Cell Membranes**

	$K_i$ nM (SEM)	Hill Coefficient (SEM)
Glyburide	2.3 (0.4)	1.0 (0.05)
Glimepiride	4.5 (0.9)	1.1 (0.13)
Glipizide	100 (24)	0.82 (0.12)
Repaglinide	240 (38)	0.90 (0.07)
Nateglinide	1300 (110)	0.80 (0.05)
Tolbutamide	270,000 (17,000)	1.05 (0.09)

p-disostituito\*

4 C, N in 3<sup>^</sup>/4<sup>^</sup> posiz.

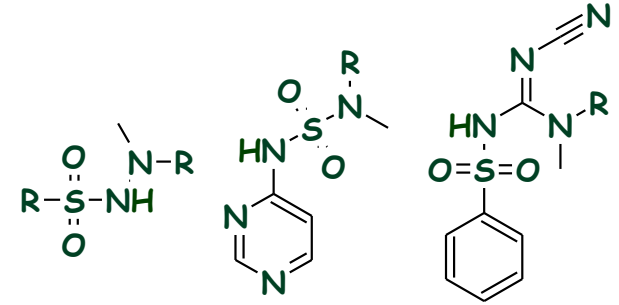
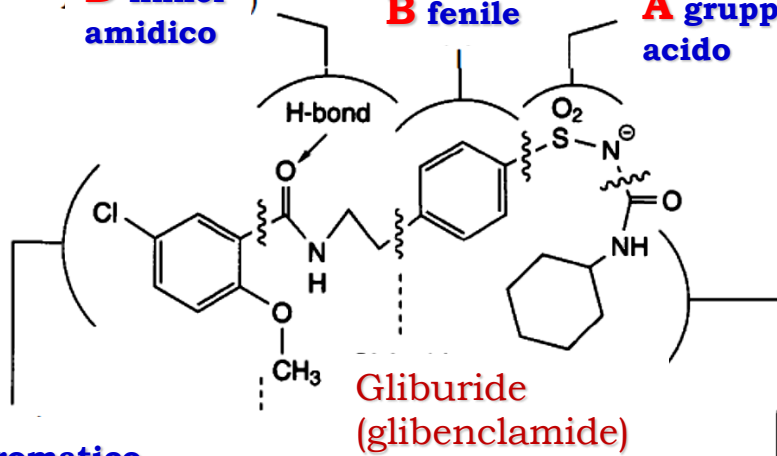
**D linker amidico**

**B fenile**

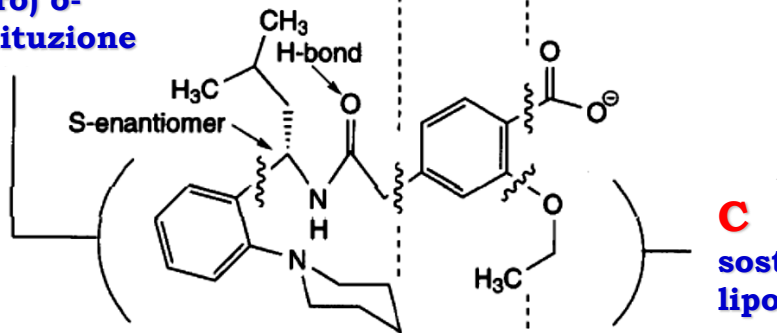
**A gruppo acido**

**← Essenziale per l'attività**

(propionato, carbossilato, sulfonilsemicarbazi, sulfonilaminopirimidine, sulfonilcianoguanidine)



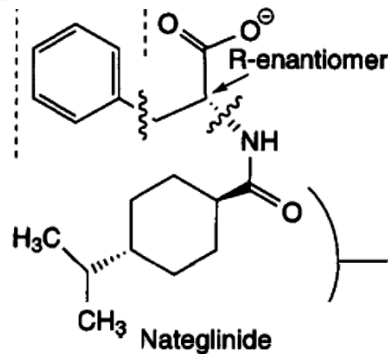
**E aromatico (etero) o-sostituzione**



**C sostituyente lipofilo**

propile, butile (I gen.)  
cicloalchili (II gen.)  
>> affinità SUR1  
>> selettività for SUR1/SUR2A (cuore, muscolo scheletrico)  
>> selettività for SUR1/SUR2B (muscolo liscio)

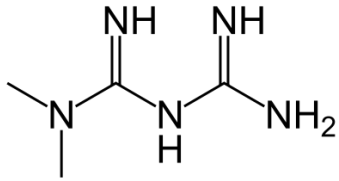
**Repaglinide**



- metile, acetile, cloro (I generazione);
- sostituzione con gruppi più ingombranti (aromatici etero) aumenta la potenza (II generazione)



# Ipoglicemizzanti: Agenti *Insulin-Sensitizing* → **Biguanidi**



*Glucophage, Metbay, Metfonorm, Metforal, Metformina (eq).....*

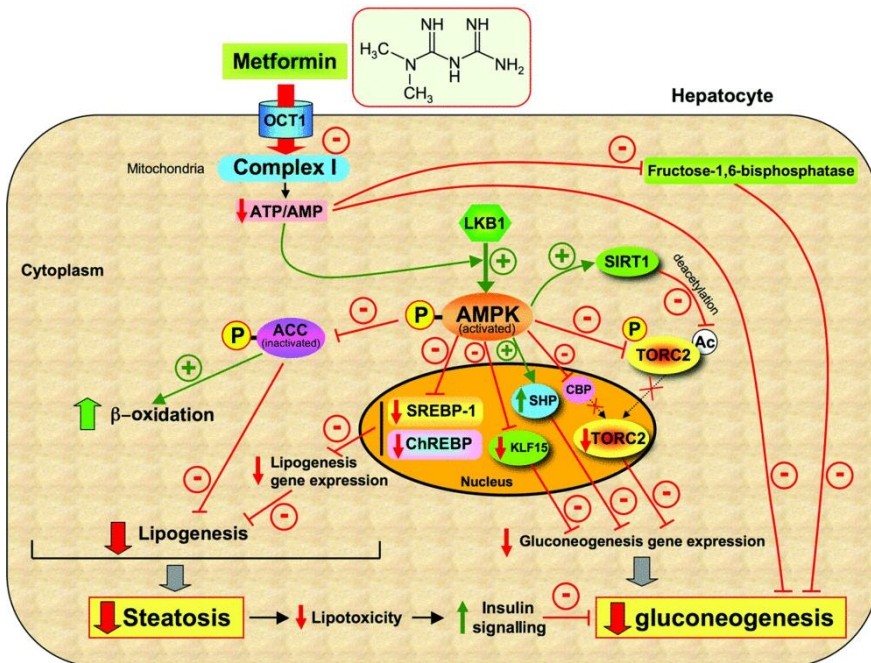
**Metformina (1950)**

Dose giorn.	tmax	t½	durata
5-2.5	2-4	6.2	>3-4 wk

Biguanide

## OCT1

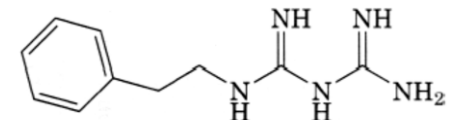
Organic cation transport proteins



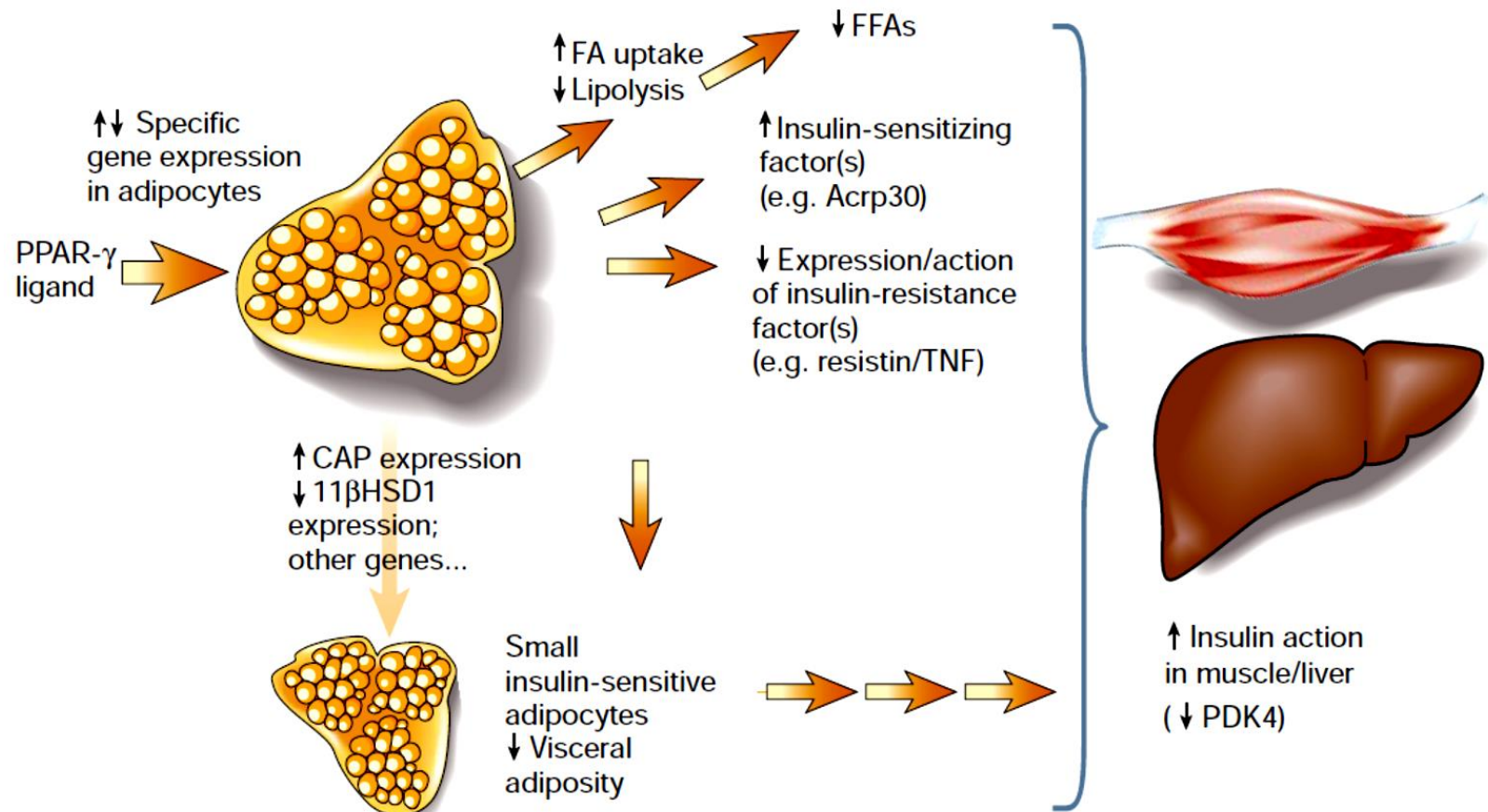
Trasportata nell'epatocita da OCT1→mitocondrio  
Metformina riduce i livelli di glucosio ematico:

- 1) << produzione epatica;
  - 2) << l'assorbimento intestinale;
  - 3) migliorando la sensibilità all'insulina (>> assorbimento e utilizzo periferico del glucosio).
- Effetti mediati da **protein kinasi-AMP-attivata** (enzima epatico **mitocondriale**) Metformina aumenta l'attività di AMPK nel muscolo scheletrico.

fenformina

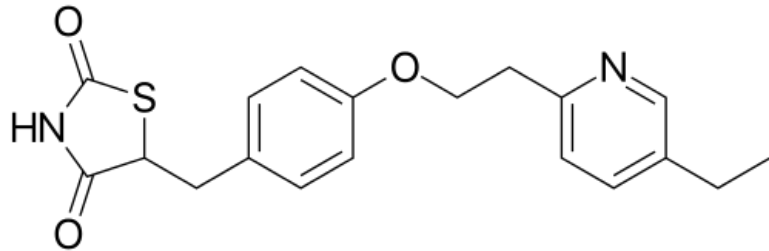
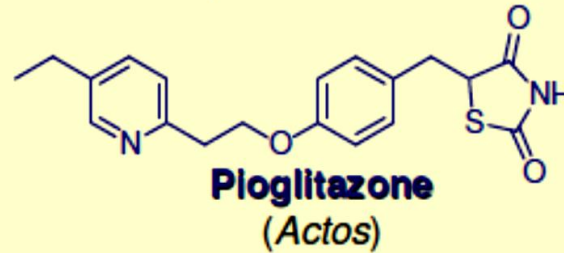
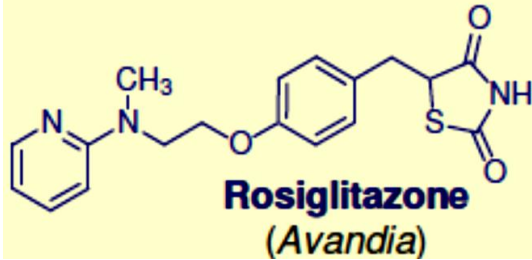
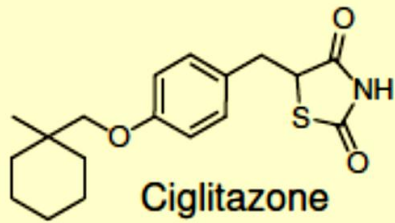






PPAR $\gamma$  (peroxisome proliferator-activated receptor  $\gamma$ ) : >> espressi nel tessuto adiposo; attivazione (ligandi specifici: )  $\rightarrow$  modifica espressione genica (es. *fatty-acid transporter 1* << FFAs  $\rightarrow$  >> sensibilità all'insulina (fegato e muscoli).

# Ipoglicemizzanti: Agenti *Insulin-Sensitizing* → **Tiazolidindioni**



## **Pioglitazone**

(Actos, Competact e Glubrava (+metformina), Tandemact (+glipiride), Incresync (+alogliptin)  
(RS)-5-(4-[2-(5-etilpiridin-2-yl)etossi]benzil) tiazolidin-2,4-dione

Scoperta casuale in ricerca su ipolipidemici (Takeda);  
>> sensibilità all'insulina,  
<< [glucosio]<sub>plasmatico</sub> FFAs, TG

**AIFA 18-03-2016.** Il rischio di carcinoma della vescica legato all'utilizzo di pioglitazone è stato oggetto di ampio dibattito a livello europeo, nel corso del quale sono stati presi in considerazione tutti i dati a disposizione (sia quelli epidemiologici che quelli derivanti da meta-analisi di studi clinici randomizzati).

Al termine della revisione, il Comitato per i Medicinali per uso umano (CHMP) dell'Agenzia Europea dei Medicinali (EMA), nell'ottobre 2011, ha confermato che il profilo beneficio-rischio del pioglitazone rimane favorevole se il farmaco è utilizzato come trattamento di seconda e terza linea.

Lo studio TOSCA.IT (Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents Intervention Trio/), ha ad oggetto gli effetti sull'incidenza di eventi cardiovascolari dell'aggiunta di pioglitazone o di una sulfonilurea alla metformina in pazienti con diabete mellito di tipo 2 in monoterapia non adeguatamente compensati (2008-2018).

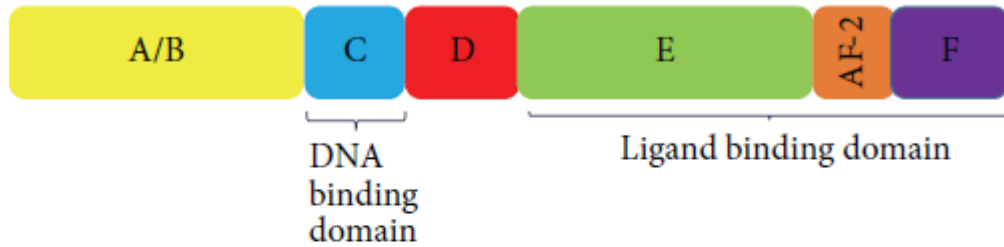
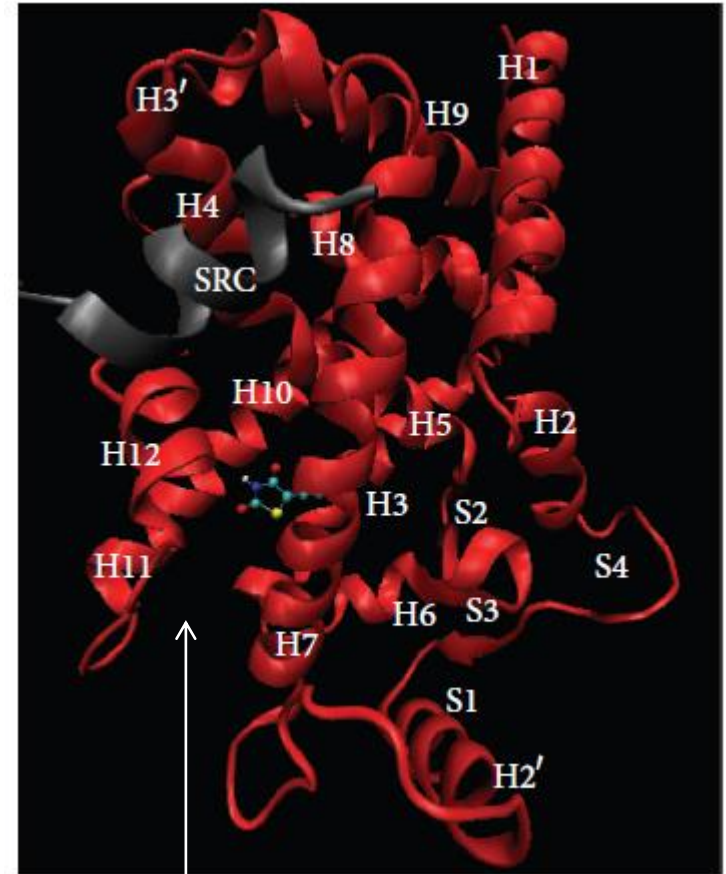


FIGURE 2: Main functional domains of nuclear PPARs. All three isotypes of PPAR have 4 main functional domains: A/B, which is the activation function 1 (AF-1); C, or DNA binding domain; D, which serves as a hinge between C and E/F; and E/E, which includes AF-2, a ligand binding dimerization transactivation domain.

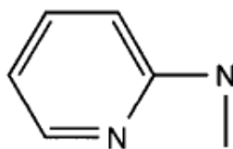
LBD contains a **large binding pocket** that allows a wide range of ligands searching for their proper conformations in order to form ligand-receptor complexes.

Natural ligands of PPAR $\gamma$  are **fatty acids**, while synthetic ligands can be classified as either full or partial agonists, such as TZDs, L-tyrosine analogs, and some nonsteroidal anti-inflammatory drugs.

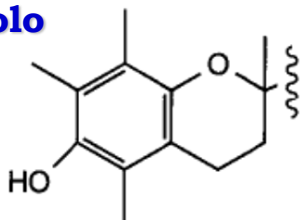


**C** gruppo lipofilo    **B** linker fenossialchilico    **A** funzione acida

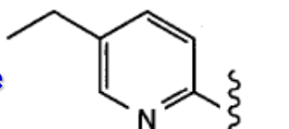
**2-aminopiridile**



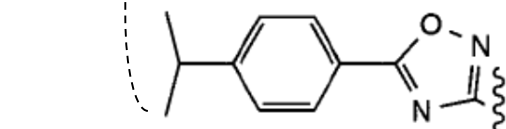
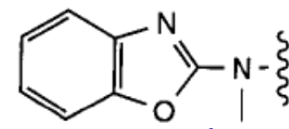
**cromanolo**



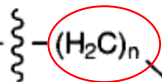
**2-piridile**



**2-aminobenzossazolo**

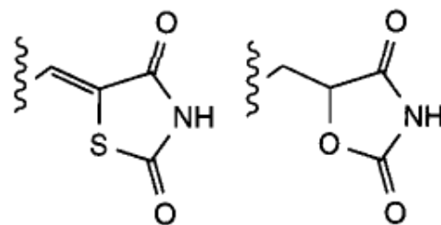
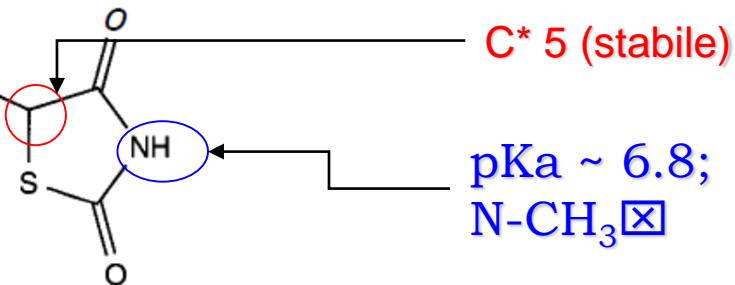


$n=1$

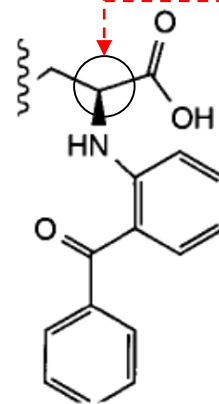
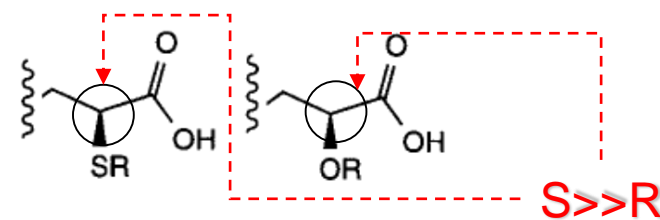


**2-fenilossazolo**

**5-feniloxadiazolo**



oxazolidindioni



logP

# Ipoglicemizzanti: Inibitori $\alpha$ -glucosidasi

**Table 1.9 Structure and Properties of  $\alpha$ -Glucosidase Inhibitors**

USP or Nonproprietary Name	Trade Name	Manufacturer	Chemical Class	Structure	Dose	Duration
<b>Acarbosio</b>	recoce	Bayer	Pseudo tetrasaccaride		25–100 mg 3× daily	Postprandial
<b>Miglitol</b>	Glyset	Pharmacia and Upj	Derivato deossinojirimicina		25–100 mg 3× daily with meals	Postprandial
<b>Voglibose</b>	asen	Takeda			0.2–0.3 mg 3× daily	Postprandial

**Table 1.10  $\alpha$ -Glucosidase Inhibition by Acarbose and Miglitol<sup>a</sup>**

	Acarbose $K_i$ ( $\mu M$ )	Miglitol $K_i$ ( $\mu M$ )
Sucrase	0.086	0.99
Isomaltase	0.36	46.3
Glucoamylase	0.21	0.009

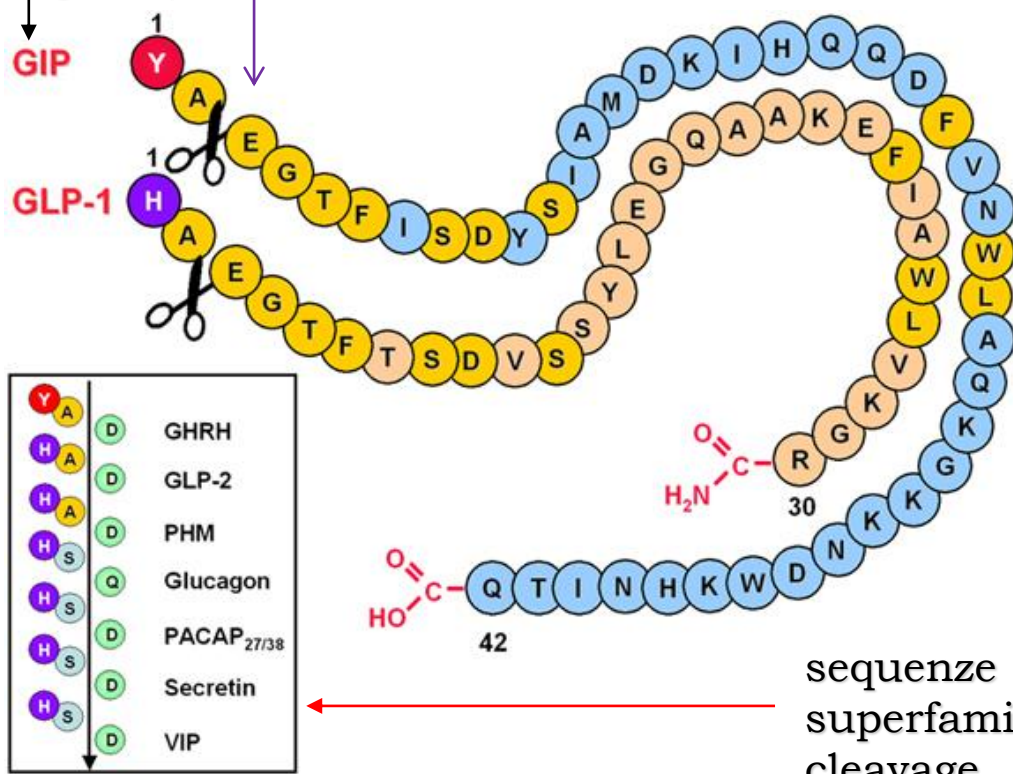
Ritardano la *digestione* dei carboidrati (dieta) in monosaccaridi (assorbiti dal tenue);

Disturbi gastrointestinali (flatulenze, gonfiore, diarrea)



**G**lucose dependent  
**i**nsulinotropic  
**p**olypeptide (cellule K  
 digiuno)

Ipoglicemizzanti: **analoghi GLP1**, Inibitori DPP-4



intero ormoni secreti dal tratto  
 gastrointestinale (incretine) in  
 risposta al pasto (**insulinotropici**)  
 GLP-1 (**glucagon-like peptide**)  
 ileo: **emivita ~ 1min**  
 inattivazione proteolitica ad  
 opera di una famiglia di enzimi:  
 le dipeptidil-peptidasi (DPP)-IV

sequenze (N-terminale) di alcuni membri della  
 superfamiglia glucagone-secretine e loro siti di  
 cleavage

“effetto incretinico” è una glicemia più bassa e una risposta dell’insulinemia superiore di almeno due volte dopo assunzione orale rispetto alla somministrazione endovenosa del glucosio. Dato che l’effetto incretinico sulla secrezione di insulina è glucosio-dipendente, esso non si verifica se la glicemia è normale o ridotta e ciò evita l’ipoglicemia

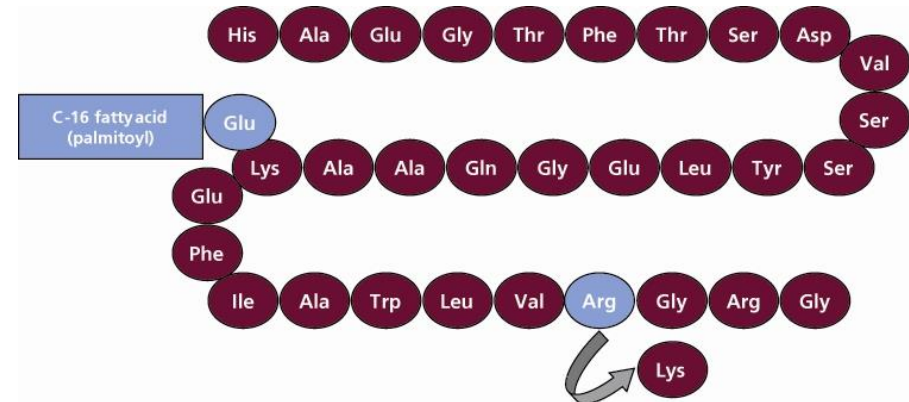
## Ipoglicemizzanti: **analoghi GLP1**, Inibitori DPP-4

### **Exenatide** (*Bydureon, Byetta*)

Derivato (39 a.a.) dalla saliva di mostro di Gila (grossa lucertola, USA-SW), analogo GLP-1

H-His-Gly-Glu-Gly-Thr-Phe-Thr-  
-Ser-Asp-Leu-Ser-Lys-Gln-Met-  
-Glu-Glu-Glu-Ala-Val-Arg-Leu-  
-Phe-Ile-Glu-Trp-Leu-Lys-Asn-  
-Gly-Gly-Pro-Ser-Ser-Gly-Ala-  
-Pro-Pro-Pro-Ser-NH<sub>2</sub>

### **Liraglutide** (*Victoza, penna preriempita*)

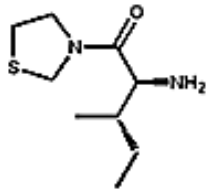


- (**analogo GLP-1 umano**, Arg34  $\leftrightarrow$  Lys34); **agonista acilato GLP-1**;
- unica somministrazione giornaliera (emivita 11-15 ore)

# Ipoglicemizzanti: analoghi GLP1, **Inibitori DPP-4 (dipeptidyl peptidase-4)**

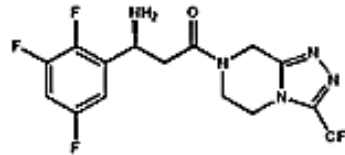
## Dipeptidyl Peptidase IV Inhibitors Used in Preclinical or Clinical Studies

### 1. Reversible Product Analogs



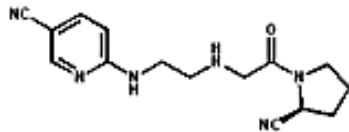
Isoleucine-Thiazolidide  
P32/98 (Probiodrugs)  
 $K_i = 80 \text{ nM}$

### 3. Reversible Non-Peptide Heterocyclic Compounds

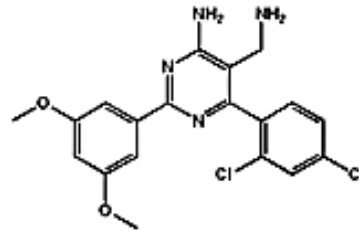


MK-0431  
Sitagliptin  
Januvia (Merck)  
 $IC_{50} = 18 \text{ nM}$

### 2. Covalently Modifying Product Analogs



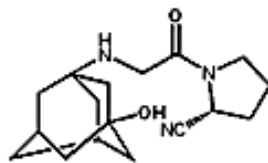
NVP DPP728  
(Novartis)  
 $IC_{50} = 22 \text{ nM}$



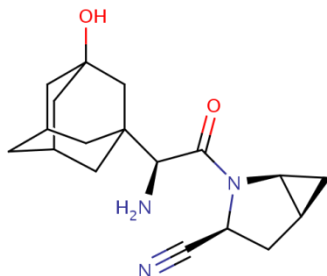
R1438  
Aminomethylpyridine  
(Roche)  
 $K_i = 0.1 \text{ nM}$

### 4. Compounds in Clinical Trials

ABT-279, ABT-341 (Abbott)  
ALS 2-0426 (Alantos/Servier)  
BI 1356 (Boehringer Ingelheim)  
Denagliptin (GSK)  
GRC8200 (Glenmark)  
PSN-9301 (OSI)  
PHX 1149 (Phenomix)  
SSR-162369 (Sanofi-Aventis)  
TS-021 (Taisho)  
Alogliptin (Takeda)  
TA-6666 (Tanabe)

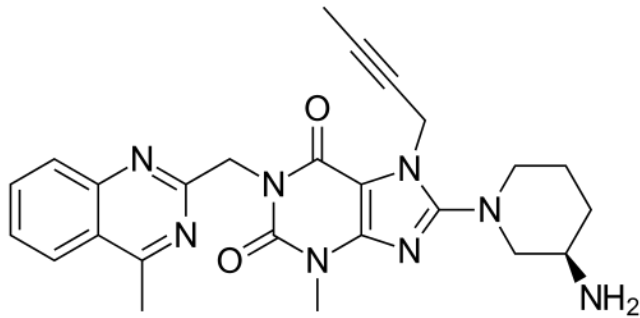


LAF237  
Vildagliptin  
Galvus (Novartis)  
 $IC_{50} = 3.5 \text{ nM}$



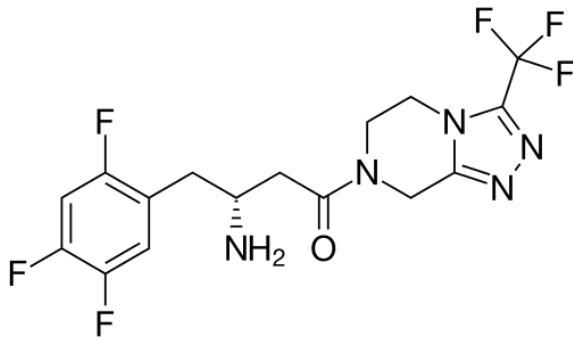
BMS-477118  
Saxagliptin  
(BMS/AstraZeneca)  
 $K_i = 0.45 \text{ nM}$

# Inibitori DPP-4



## Linagliptin (appr FDA 2011) (Trajenta)

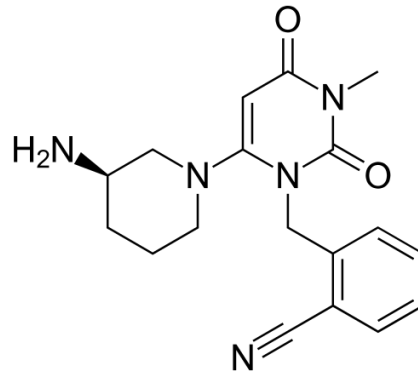
8-[(3R)-3-Aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione



## Sitagliptin (Januvia, Tesavel, Xelevia)

(appr EMEA 2006)

(R)-4-oxo-4-[3-(trifluorometil)-5,6-diidro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-il]-1-(2,4,5-trifluorofenil)butan-2-amine

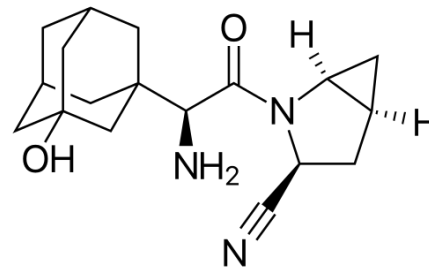


## Alogliptin

(appr FDA 2008-13)

(Vipidia)

2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzonitrile

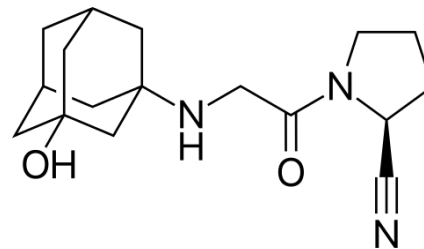


## Saxagliptin

(appr FDA 2008 (2016))

(Onglyza)

(1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile



## Vildagliptin

(Galvus)

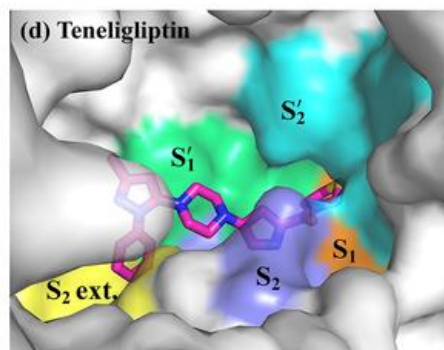
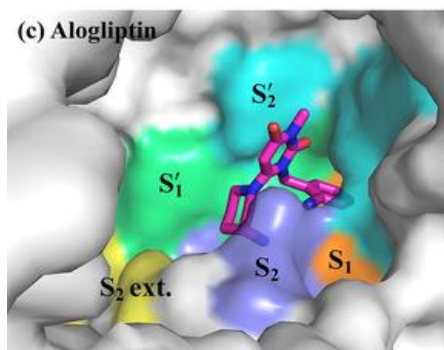
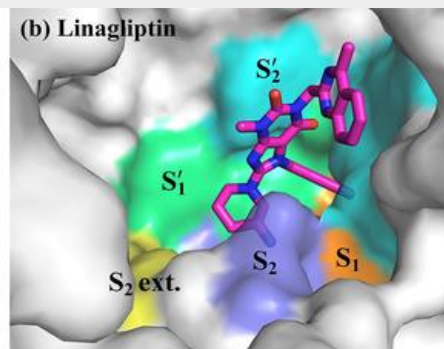
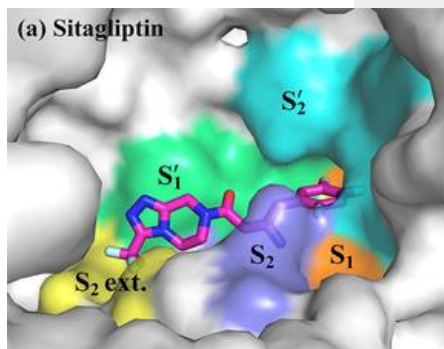
(appr EMEA 2007)

(S)-1-[N-(3-hydroxy-1-adamantyl)glycyl]pyrrolidine-2-carbonitrile



**Table 1.** Experimental Substrates of DPP4

Physiological Substrates	N-Terminal Sequence	Pharmacological Substrates	N-Terminal Sequence
GIP	YAEGTF...	Aprotinin	RPD
GLP-1	HAEGTF...	$\beta$ -Casomorphin	YPFVEPI
GLP-2	HADGSF...	BNP	SPKMVQ...
PYY	YPIKPE...	Chorionic gonadotropin	APD...
SDF-1	KPVSL...	Endomorphin-1	YFFF-NH <sub>2</sub>
SP	RPKQFFGLM...	Endomorphin-2	YVWF-NH <sub>2</sub>
		Enterostatin	VPDPR...
		Eotaxin	GPASVP...
		Erythropoietin	APPRL...
		GCSF	EATPL...
		GCP2	GPVS...
		GHRH44	YADAIF...
		GHRH29	YADAIF...
		GMCSF	APAR...
		GRP (1-27)	VPLPA...
		GRP (3-27)	LPA...
		Glucagon	HSQGT...
		Hemomorphin-7	YVWTRF...
		HMGB1	GKGD...
		IGF-1	GPETLCGA...
		IP-10	VPLSRT...
		Kentsin	TPRK...
		LD78 $\beta$ (CCL3L1)	APLAAD...
		MDC	GPYGAN...
		MiG	TPVVRK...
		Morphiceptin	YVWF-NH <sub>2</sub>
		NPY	YPSKPD...
		Oxyntomodulin	HSQGT...
		PACAP (1-38)	HSEGIF...
		PACAP (1-27)	HSEGIF...
		Promelittin (1-50)	APEPEP...
		Promelittin (5-50)	EPEP...
		Promelittin (3-50)	EP...
		Procalcitonin	APFRSA
		PHM	HADGVF...
		Procolipase	VPDPR...
		Prolactin	FPT...
		Rantes	SPYSSD...
		Secretin	HSDGT...
		SR-17	SAEFPDFY...
		SP (3-11)	KPQFFGLM...
		Trypsinogen propeptide	FPT...
		Tyr-MIF-1	YPLG-NH <sub>2</sub>
		Vasostatin-1	SAEFPDFY...
		VIP (1-59)	HSDAVFTDNY...



Arulmozhiraja S, Matsuo N, Ishitsubo E, Okazaki S, Shimano H, et al. (2016) Comparative Binding Analysis of Dipeptidyl Peptidase IV (DPP-4) with Antidiabetic Drugs – An Ab Initio Fragment Molecular Orbital Study. PLOS ONE 11(11): e0166275.

<https://doi.org/10.1371/journal.pone.0166275>

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0166275>