UNIVERSITÀ DEGLI STUDI FIRENZE

# Metformina: vecchie domande, nuove risposte

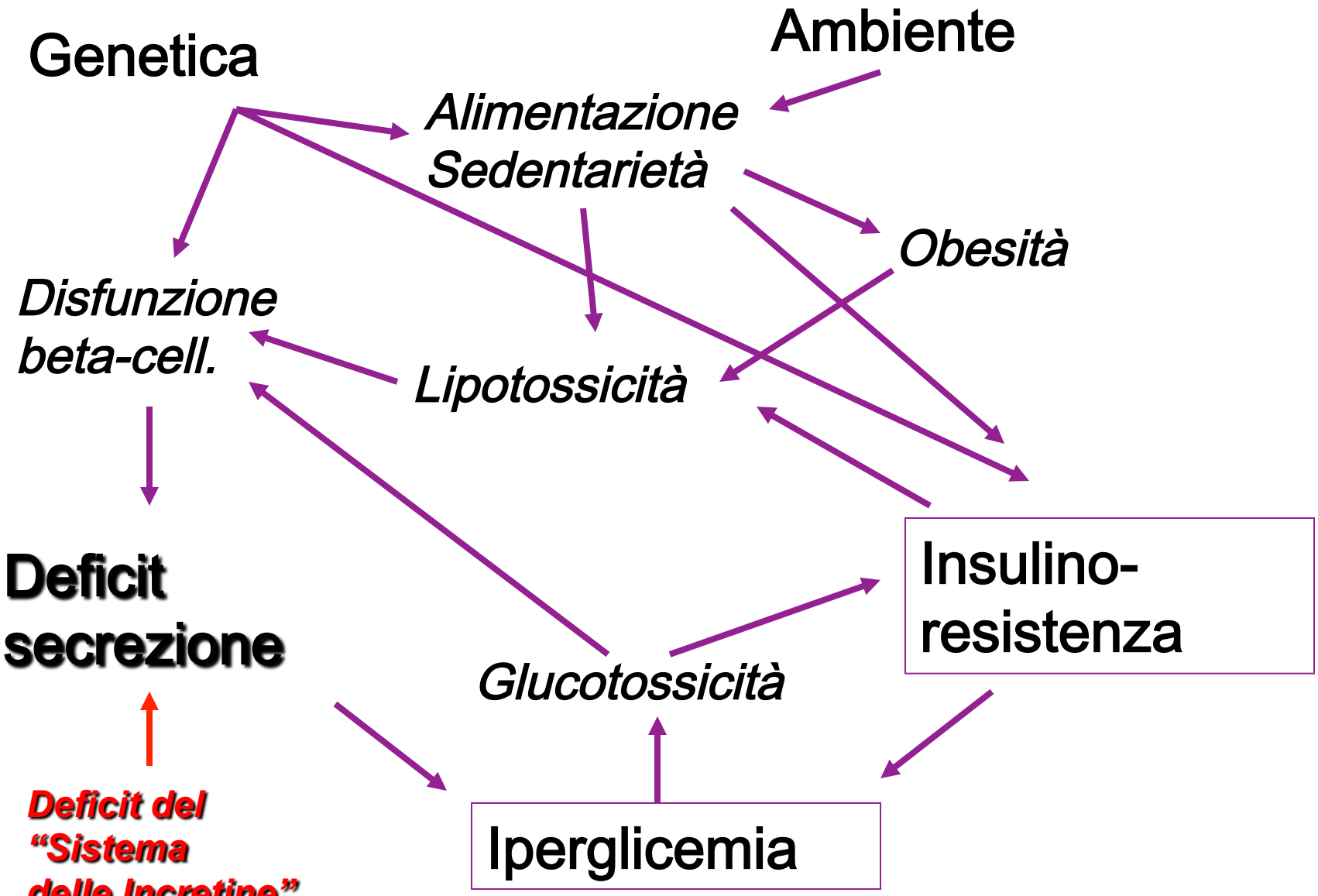
Carlo Maria Rotella

ROMA 11.11.2017

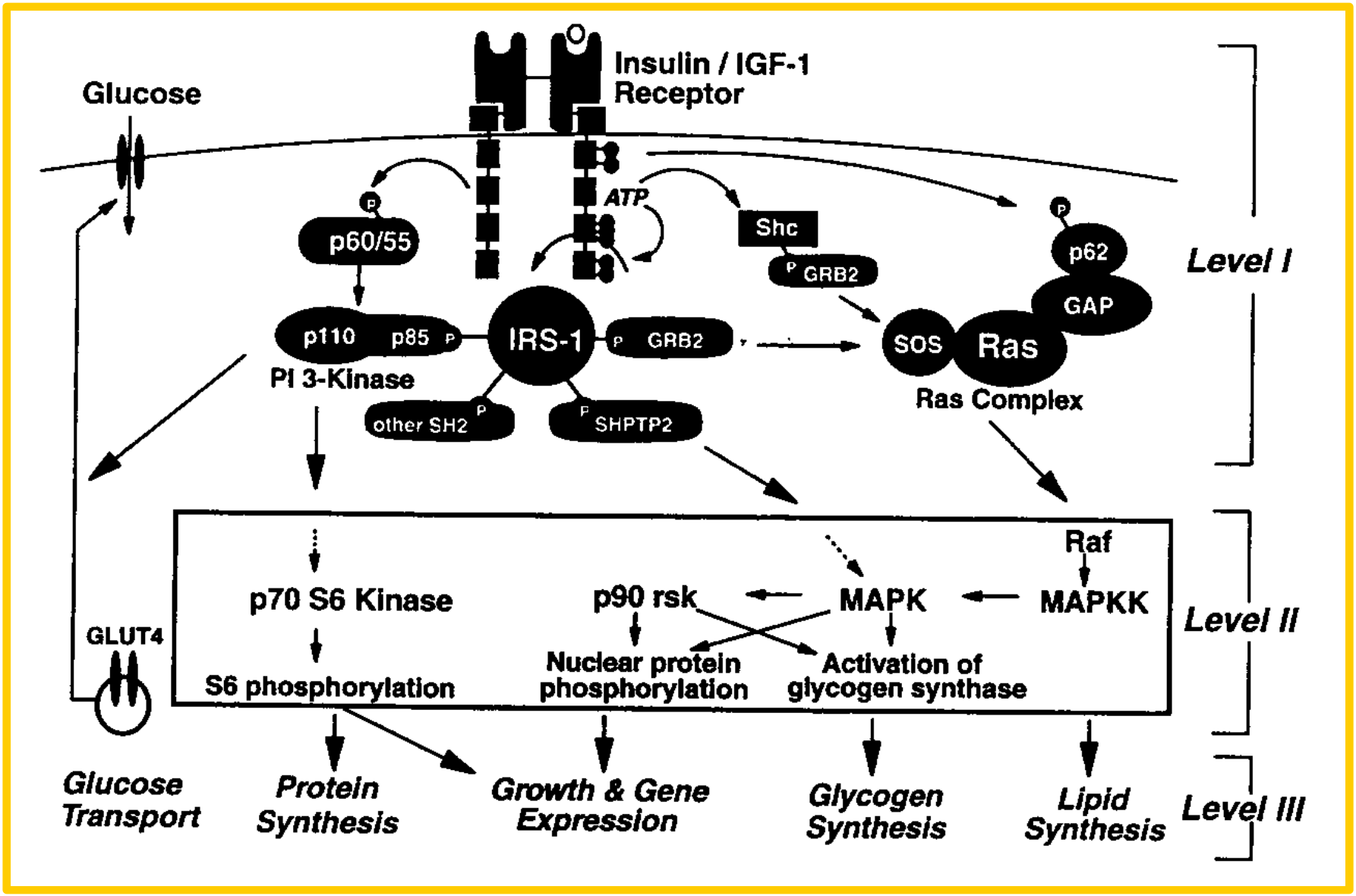
# PATOGENESI DEL DIABETE MELLITO DI TIPO 2

## PERCHE' LA METFORMINA COME FARMACO DI PRIMO IMPIEGO?

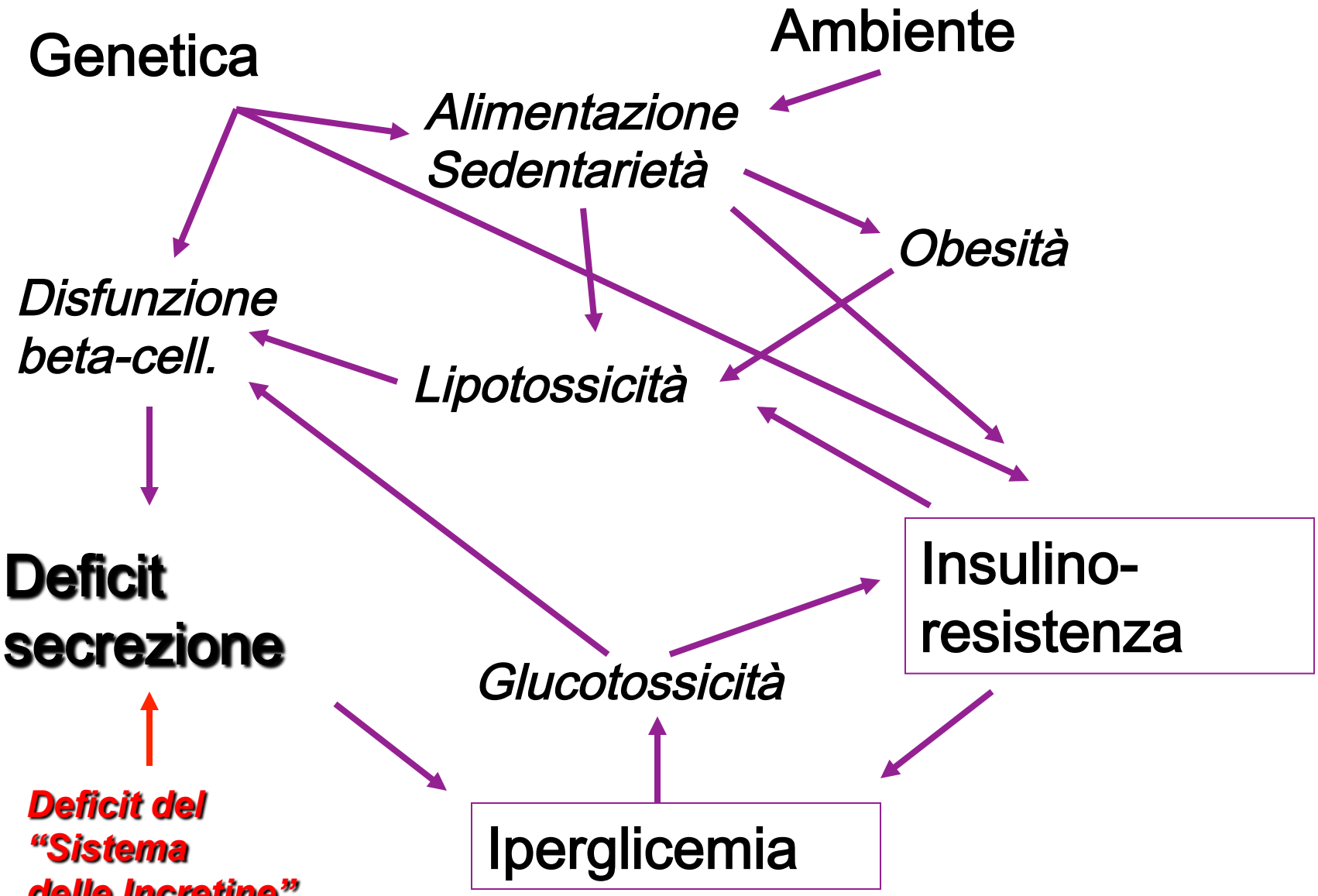
# Patogenesi del diabete tipo 2



# Livelli di azione insulinica



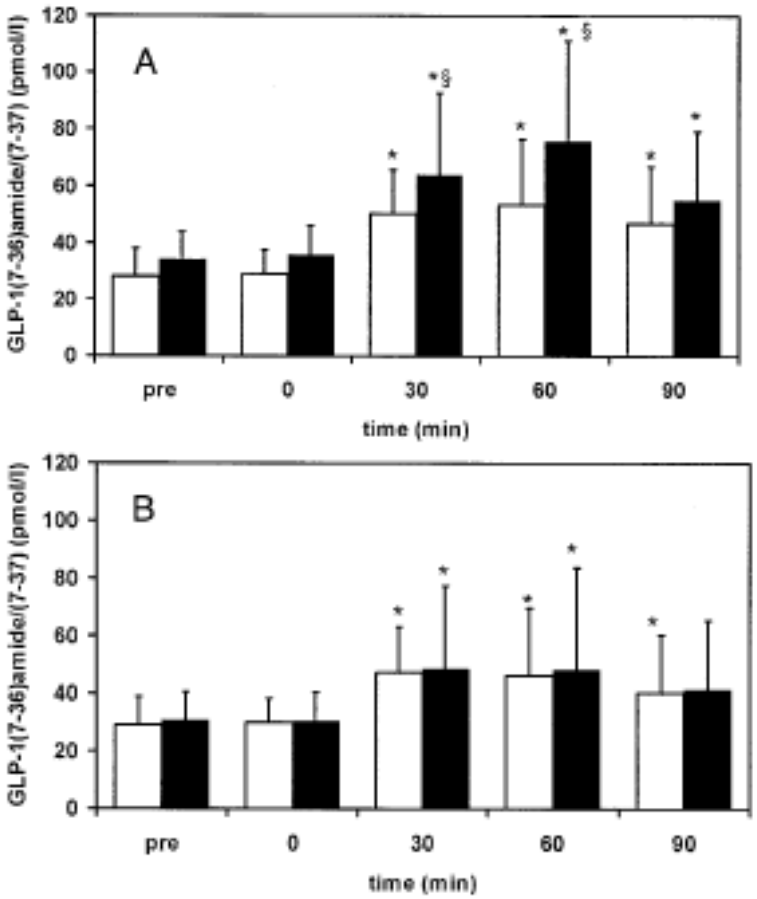
# Patogenesi del diabete tipo 2



# Effect of Metformin on Glucagon-Like Peptide 1 (GLP-1) and Leptin Levels in Obese Nondiabetic Subjects

EDOARDO MANNUCCI, MD[1]
AGOSTINO OGNIBENE, MD[2]
FRANCESCO CREMASCO, MD[1]
GIANLUCA BARDINI, MD[1]
ANTONELLA MENCUCCI, MD[1]
ENRICA PIERAZZUOLI, MD[1]
SILVIA CIANI, BS[1]
GIANNI MESSERI, MS[2]
CARLO M. ROTELLA, MD[1]

Diabetes Care 2001, 24: 489-94


A
B
GLP-1(7-36)amide/(7-37) (pmol/l)
120
100
80
60
40
20
0
pre
0
30
60
90
time (min)
*
*§
*§

# Quando iniziare la terapia con metformina e qual è la durability del farmaco?

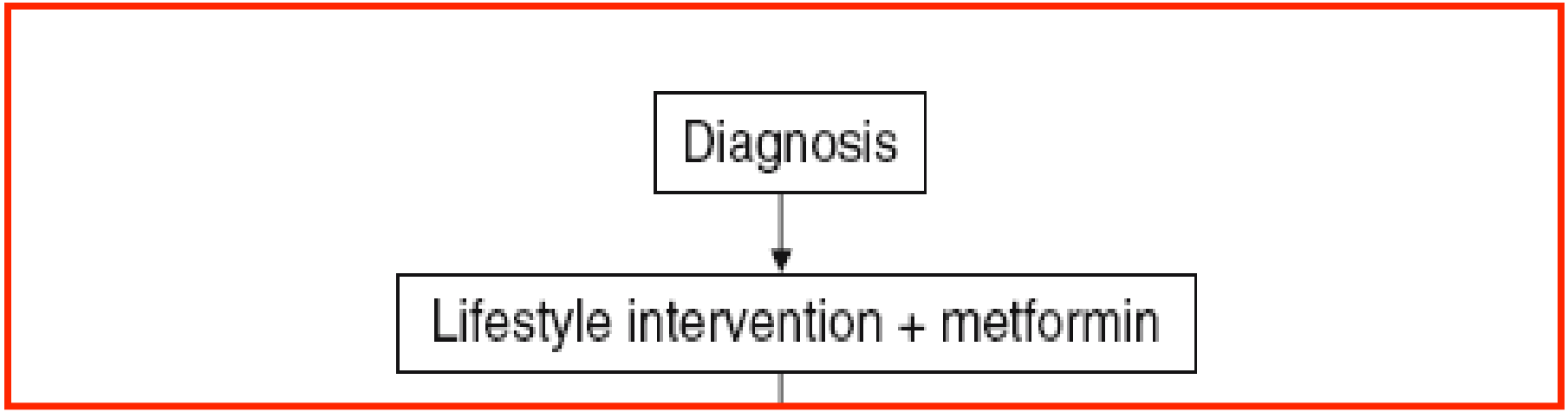


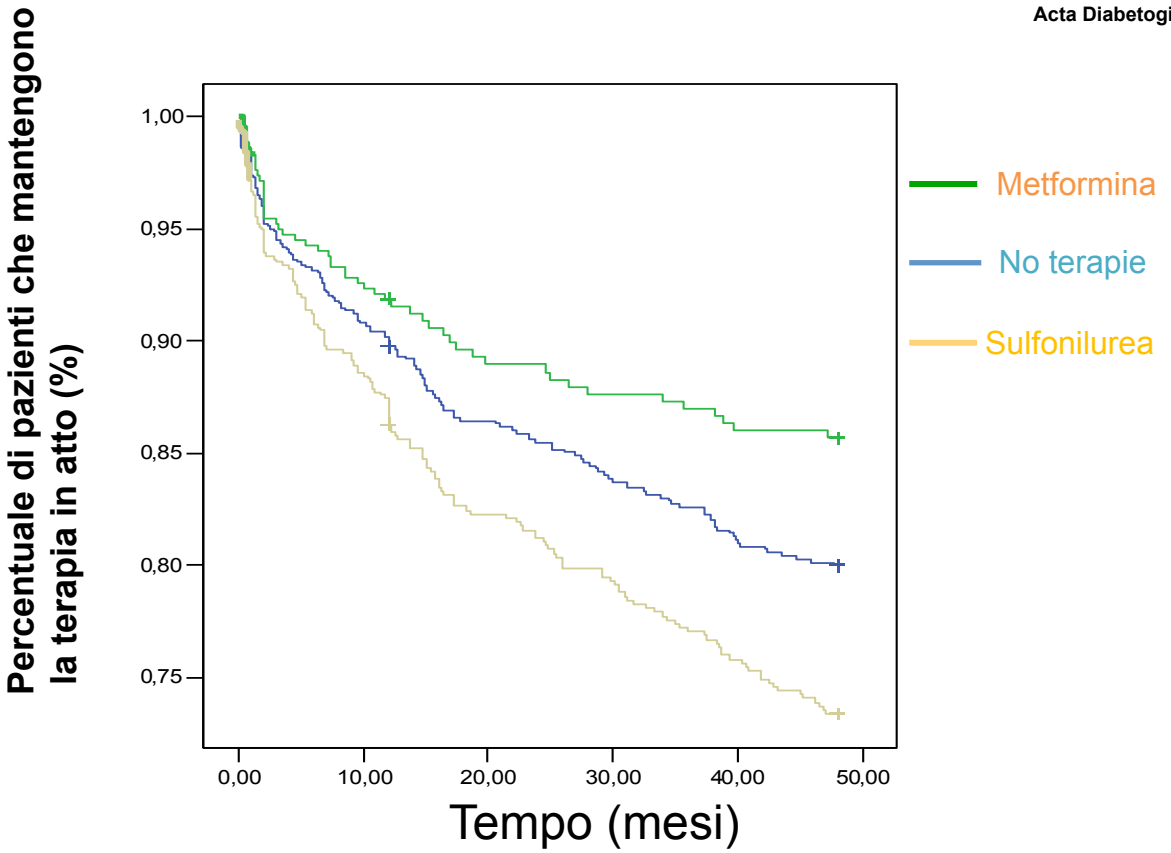

Table 1—*Summary of antidiabetic interventions as monotherapy*

| Interventions | Expected decrease in A1C (%) | Advantages | Disadvantages |
|---|---|---|---|
| Step 1: initial | | | |
| Lifestyle to decrease weight and increase activity | 1–2 | Low cost, many benefits | Fails for most in 1st year |
| Metformin | 1.5 | Weight neutral, inexpensive | GI side effects, rare lactic acidosis |

# Failure to metformin and insulin secretagogue monotherapy: an observational cohort study

Laura Pala · Matteo Monami · Caterina Lamanna · Barbara Cresci · Claudia Colombi · Gianluca Bardini · Jolanda Sposato · Niccolò Marchionni · Carlo M. Rotella · Edoardo Mannucci

Acta Diabetogica 2009 Mar 17



# MECCANISMO D'AZIONE DELLA METFORMINA

The NEW ENGLAND JOURNAL of MEDICINE

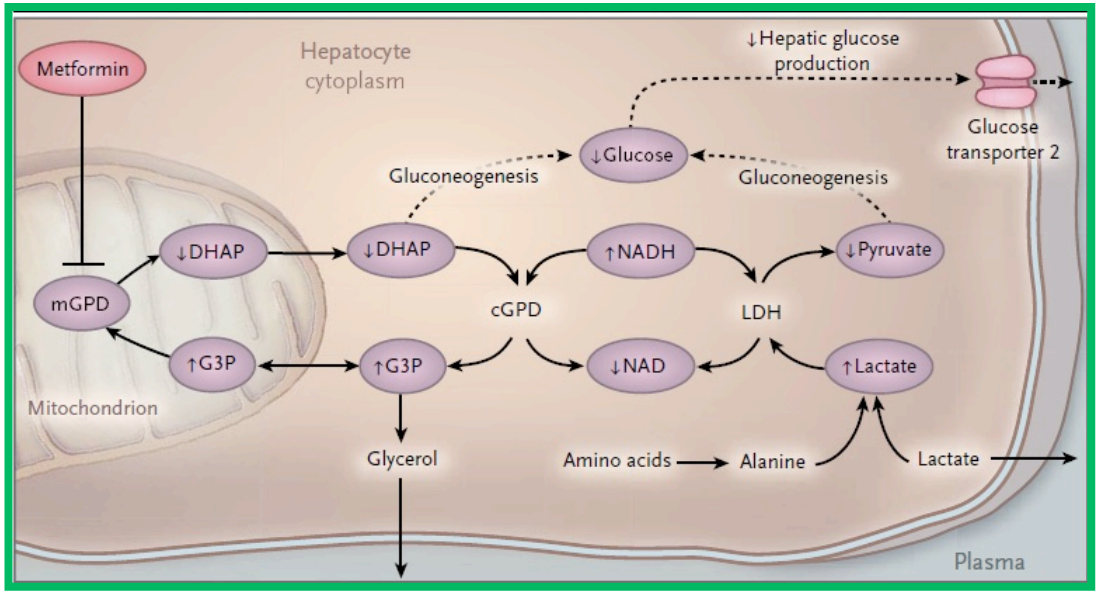
CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

# The Target of Metformin in Type 2 Diabetes

Ele Ferrannini, M.D.

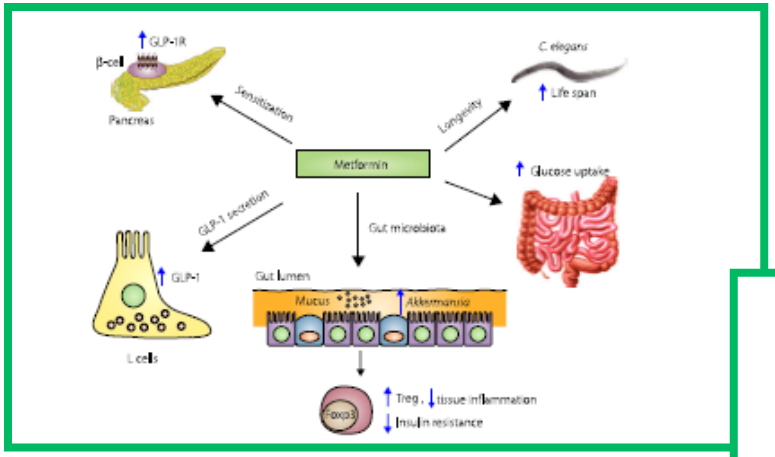
## La metformina sopprime la gluconeogenesi epatica



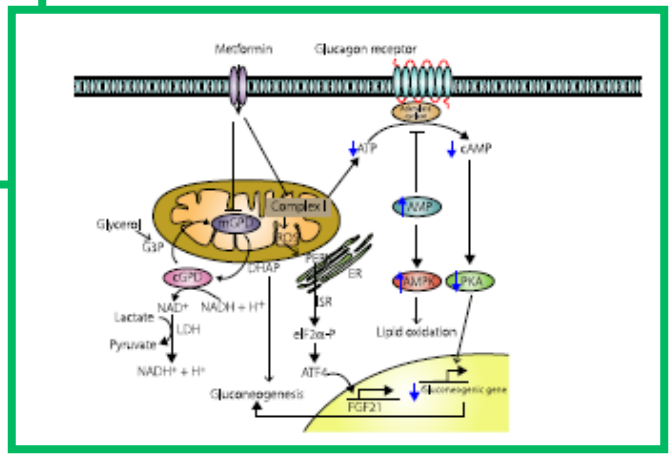
JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
REVIEW ARTICLE

# New mechanisms of metformin action: Focusing on mitochondria and the gut

Kyu Yeon Hur, Myung-Shik Lee*




La metformina stimola il rilascio di GLP-1 nelle cellule L dell'intestino e anche l'espressione dei recettori per il GLP-1 a livello pancreatico



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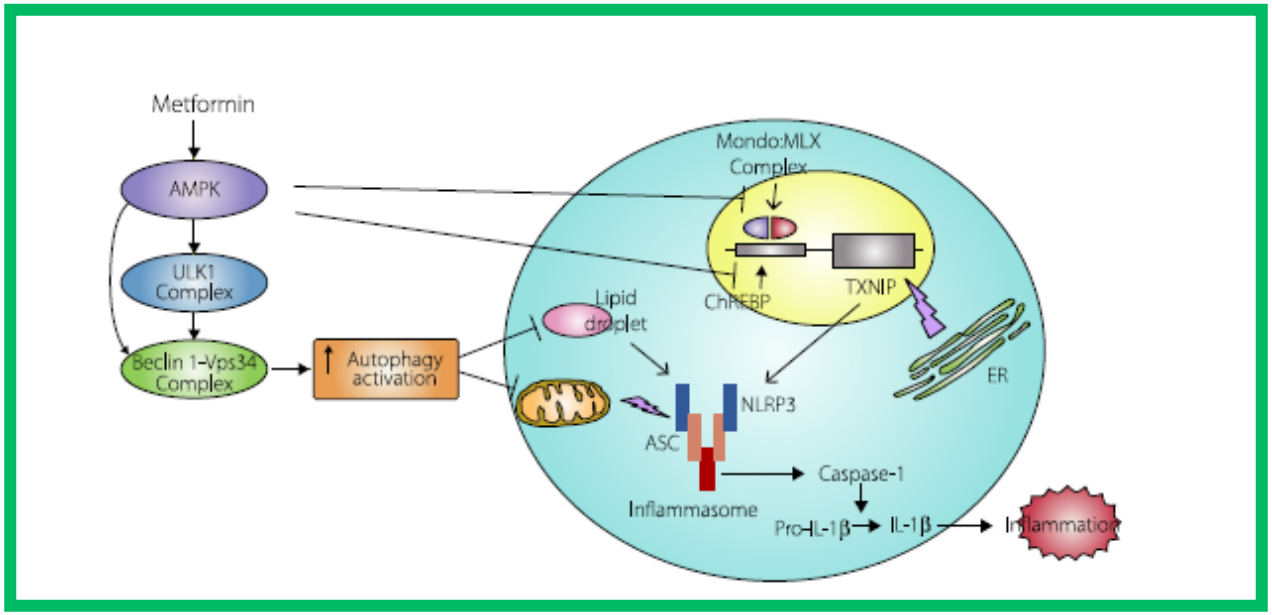
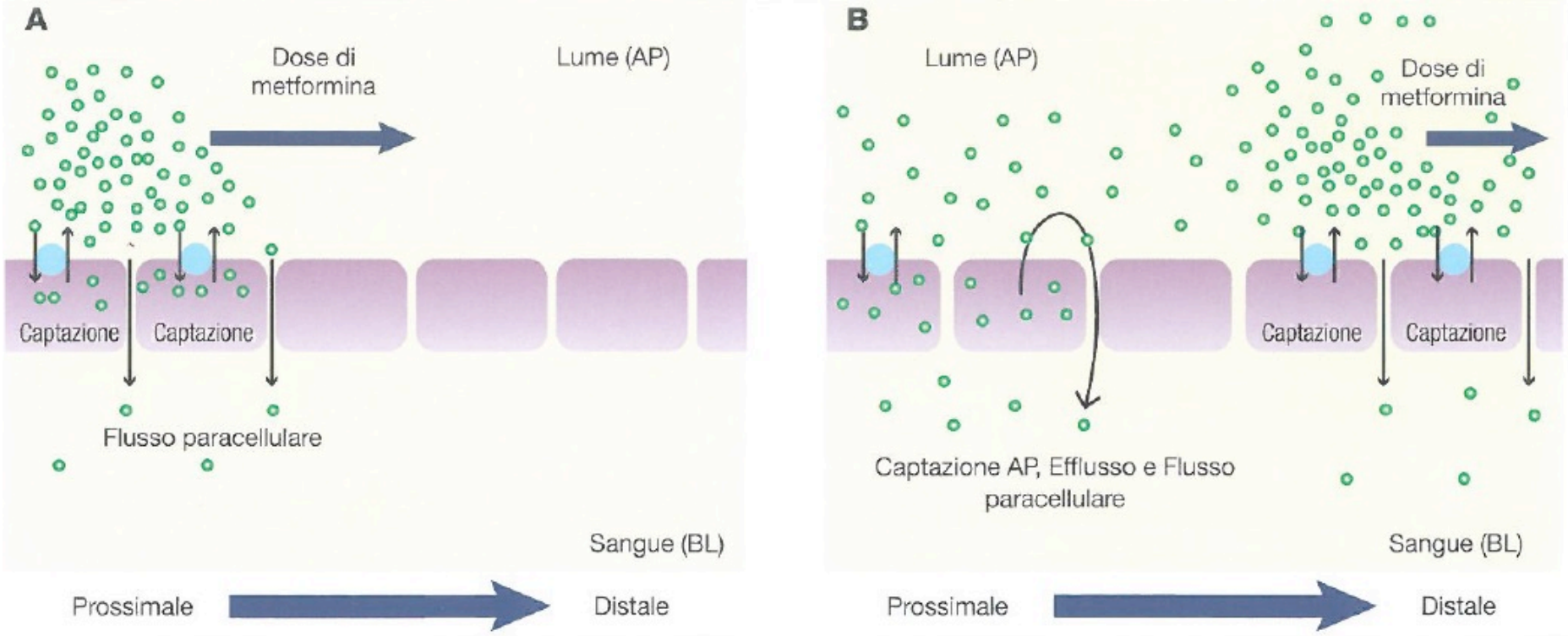
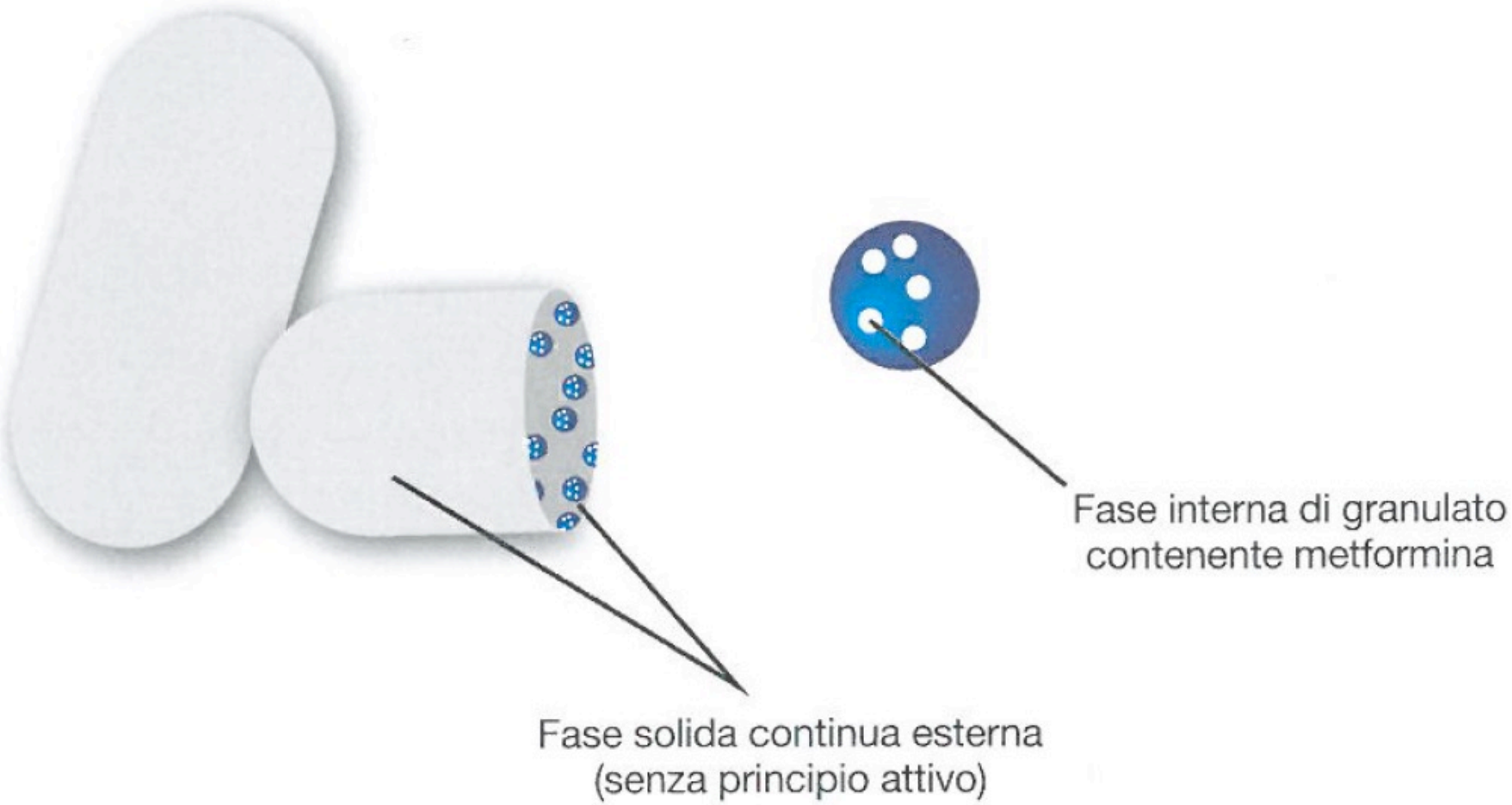
# New mechanisms of metformin action: Focusing on mitochondria and the gut

Kyu Yeon Hur, Myung-Shik Lee*



# PREPARAZIONI DI METFORMINA A RILASCIO PROLUNGATO


A
Dose di metformina
Lume (AP)
Captazione
Captazione
Flusso paracellulare
Sangue (BL)
Prossimale
Distale
B
Lume (AP)
Dose di metformina
Captazione
Captazione
Captazione AP, Efflusso e Flusso paracellulare
Sangue (BL)
Prossimale
Distale


Fase interna di granulato
contenente metformina
Fase solida continua esterna
(senza principio attivo)

J Endocrinol Invest (2014) 37:497–498
DOI 10.1007/s40618-014-0065-x

OPINION

# The "slower" the better

L. Pala · C. M. Rotella

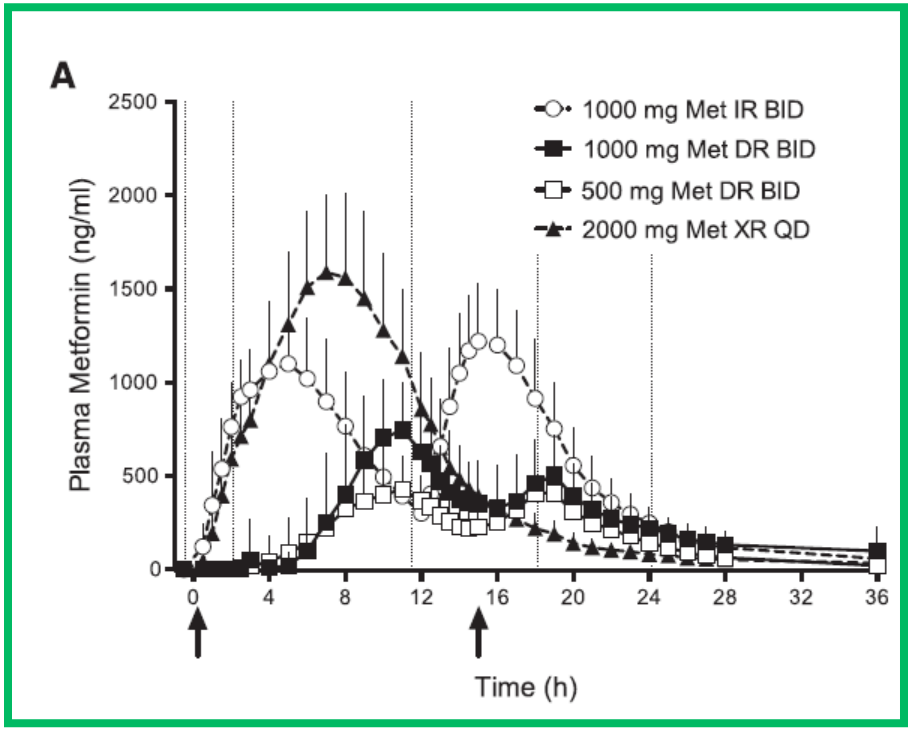
**Table 1** Comparison between metformin ER and metformin IR

| | Metformin ER | Metformin IR |
|---|---|---|
| Administration | Oral | Oral |
| Duration (hours) | 12 | 6 |
| Daily times dosing | 2 | 3 |
| Maximum plasma concentration (hours) | 7 | 3 |
| GI side effects | − | + |
| HbA1c Reduction (%) | 0.6–1 | 0.6–1 |

# The Primary Glucose-Lowering Effect of Metformin Resides in the Gut, Not the Circulation: Results From Short-term Pharmacokinetic and 12-Week Dose-Ranging Studies

John B. Buse,[1] Ralph A. DeFronzo,[2] Julio Rosenstock,[3] Terri Kim,[4] Colleen Burns,[4] Sharon Skare,[4] Alain Baron,[4] and Mark Fineman[4]

Diabetes Care 2016;39:198–205 | DOI: 10.2337/dc15-0488



**DA SCHEDA TECNICA DEL FARMACO**

(omissis) … se non si raggiunge il controllo della glicemia con *metformina* ER 2000 mg in un'unica somministrazione giornaliera, dovrebbe essere preso in considerazione il trattamento con 1000 mg due volte al giorno, assunto con il cibo.

# Effects of metformin extended release compared to immediate release formula on glycemic control and glycemic variability in patients with type 2 diabetes

**De Rosa G et al.** Drug Design, Development and Therapy 2017:11 1481–1488

**RISULTATI**: riassunti nelle tabelle e grafici sotto, a 6 mesi si è osservato

- un miglioramento maggiore per la Metformina XR rispetto al baseline e rispetto alla metformina IR per ogni aspetto del profilo glicemico, insulinemico e lipidico.
- solo la metformina XR ha mostrato una variazione in positivo delle adipocitochine.
- l'effetto sui parametri antropometrici è stato paragonabile per le due formulazioni IR e XR.
- gli effetti collaterali gastrointestinali sono stati maggiori per la IR e la compliance maggiore per XR

**CONCLUSIONI**: in terapia di 6 mesi su soggetti caucasici affetti da diabete tipo 2, la metformina XR si è mostrata più efficace della IR nel controllo glicemico, insulinemico, lipidico, e nel migliorare i livelli di alcune adipochine correlate allo stato infiammatorio e allo squilibrio metabolico.

# QUALI ALTRI FARMACI POSSONO ESSERE ASSOCIATI ALLA METFORMINA?

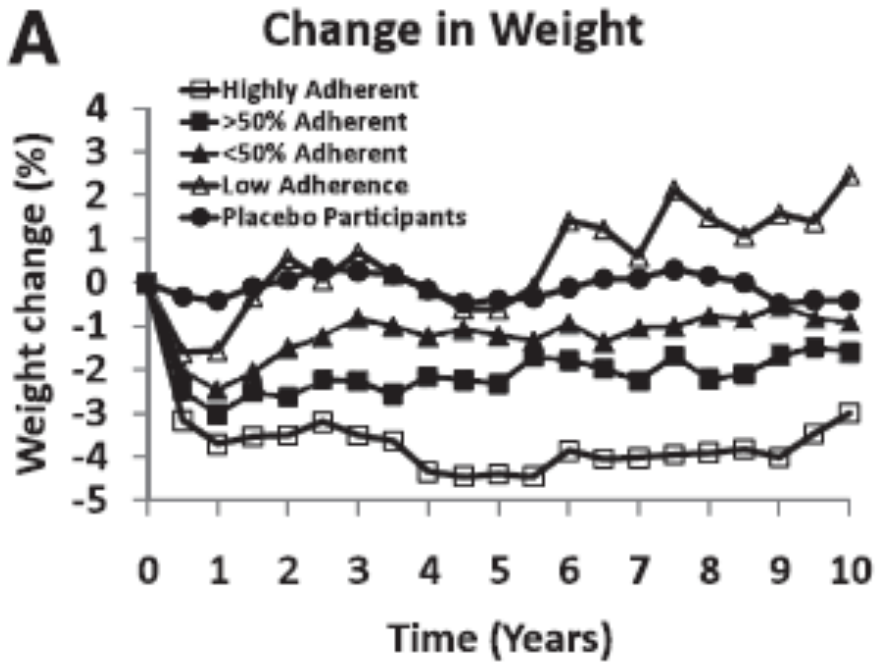
# Diabetes drugs

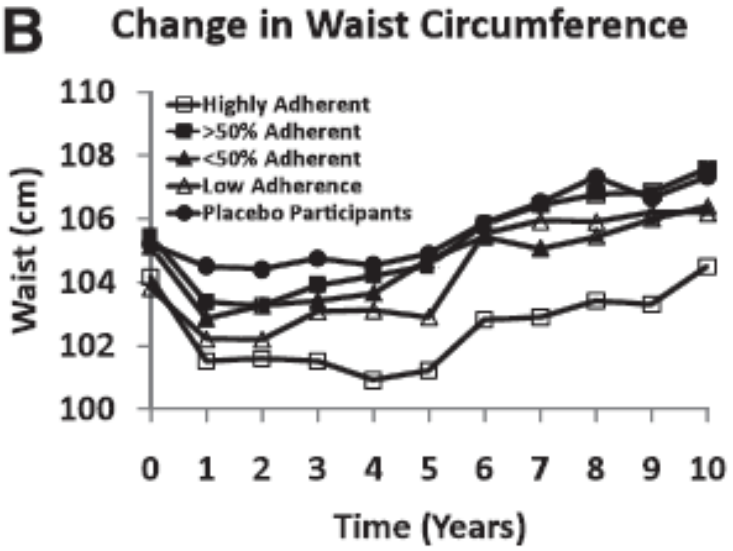
| *Not inducing hypos* | *Inducing hypos* |
| --- | --- |
| Metformin | Insulin |
| DPP4 inhibitors | Sulfonylureas |
| GLP-1 receptor agonists | Glinides |
| Thiazolidinediones | |
| AGI | |
| SGLT-2 inhibitors | |

# EFFETTI EXTRA-GLICEMICI DELLA METFORMINA

# Long-Term Safety, Tolerability, and Weight Loss Associated With Metformin in the Diabetes Prevention Program Outcomes Study

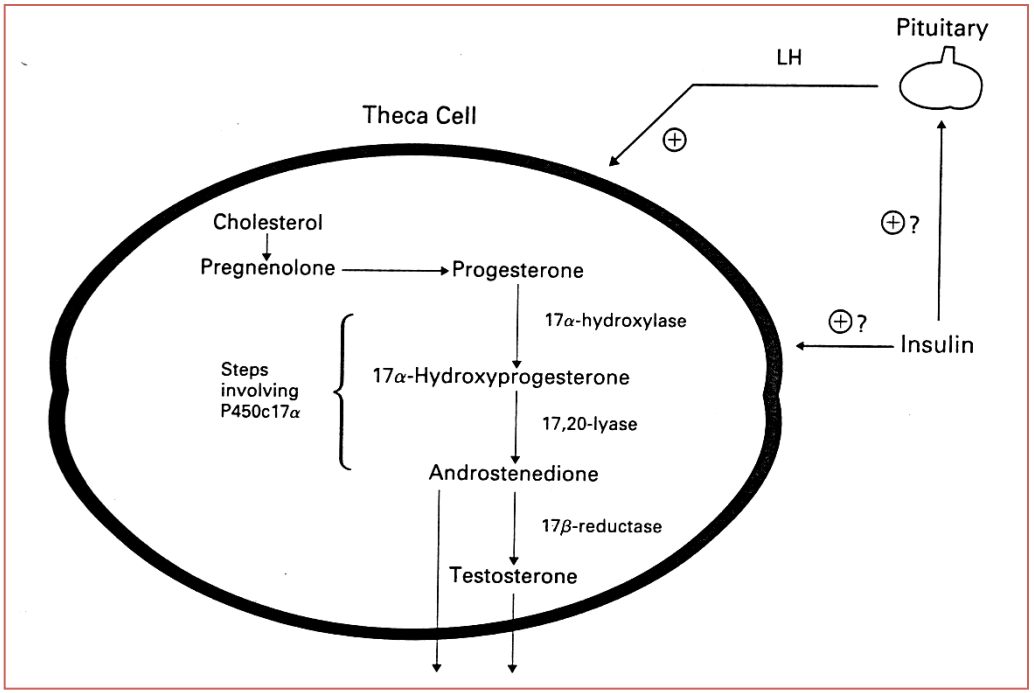
THE DIABETES PREVENTION PROGRAM RESEARCH GROUP*




*Diabetes Care* 35:731–737, 2012

# P450c17 tecale è il target di LH e insulina

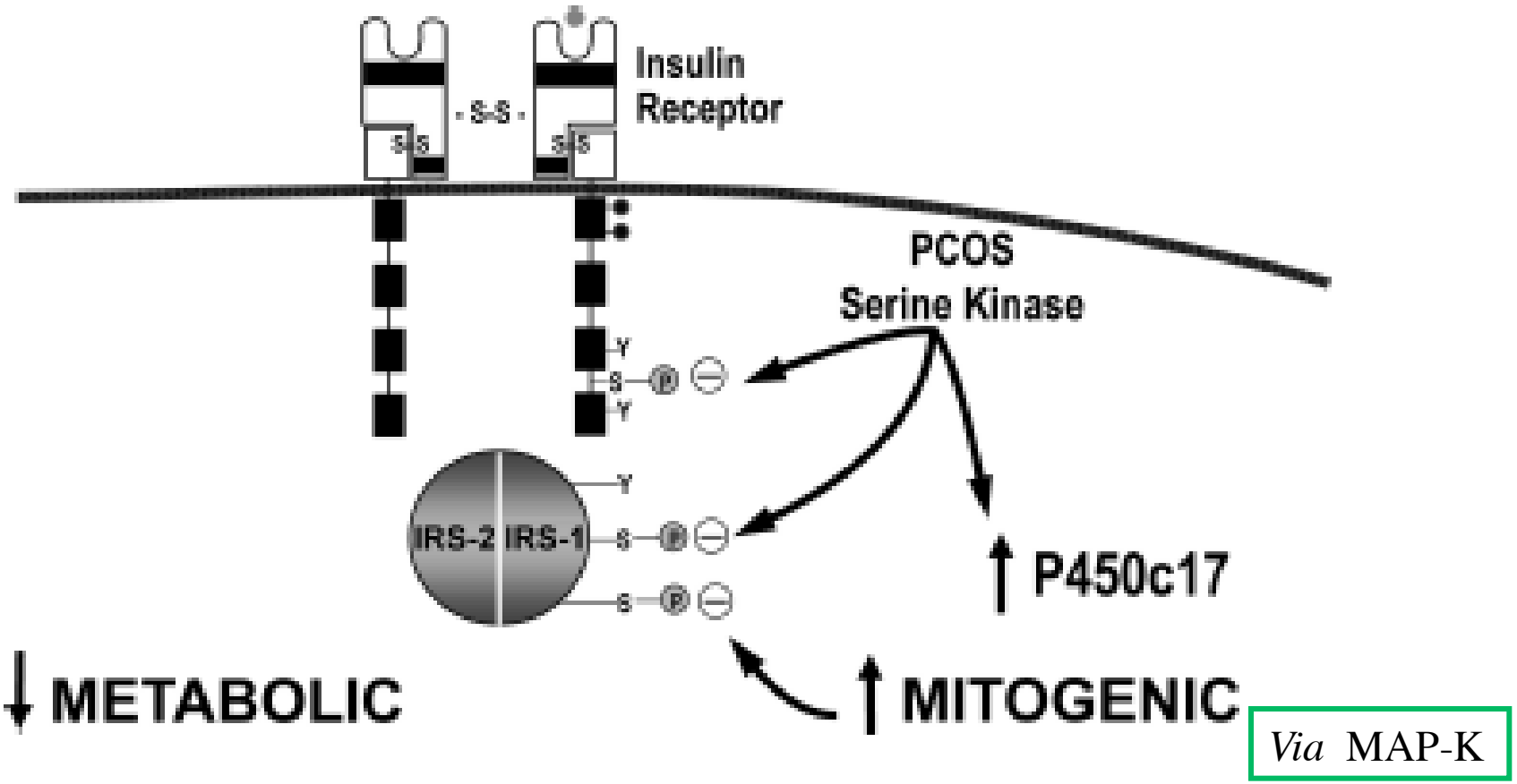



**INSULINA**

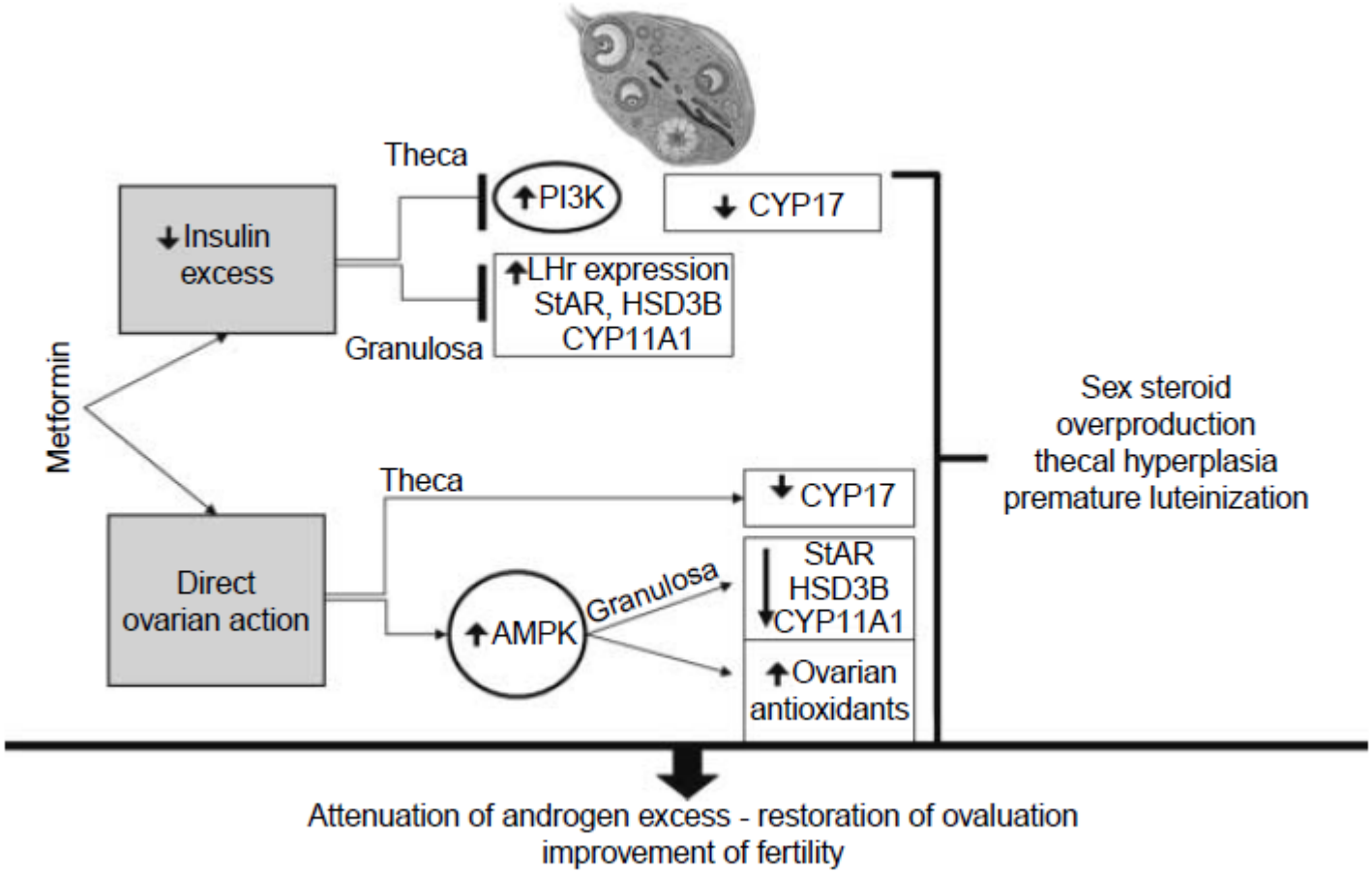
- ↑ la steroidogenesi (P450c17)
- È sinergica con LH/FSH
- ↑Stimola 17α-idrossilasi
- ↑ o ↓ aromatasi
- ↑ recettori di LH
- Promuove la crescita ovarica e la formazione di cisti
- ↑ rec. IGF-I
- ↓ recettori dell'insulina

↑ secrezione di LH
↓ produzione epatica di SHBG
↑ produzione di androgeni

# Insulina e PCOS



# Effetto di metformina su ovaio




European Journal of Endocrinology (2010) **162** 193–212

# Meta-analyses examining the effect of metformin use on cancer incidence and mortality

| Study authors (date) | Association of metformin use with overall cancer incidence, SRR (95% CI) | Association of metformin use with overall cancer mortality, SRR (95% CI) |
|---|---|---|
| DeCensi et al (2010) [18] | 0.68 (0.52, 0.88) | 0.70 (0.51, 0.96) |
| Noto et al (2012) [20] | 0.67 (0.53, 0.85) | 0.66 (0.49, 0.88) |
| Soranna et al (2012) [21] | 0.61 (0.54, 0.70) | ND |
| Stevens et al (2012) [28] | 1.02 (0.82, 1.26)[a] | ND |
| Thakkar et al (2013) [22] | 1.01 (0.81, 1.26)[a]<br>0.70 (0.67, 0.73)[b]<br>0.90 (0.84, 0.98)[c] | ND |
| Franciosi et al (2013) [19] | 0.98 (0.81, 1.19)[a]<br>0.73 (0.61, 0.88) | 0.65 (0.53, 0.80) |
| Zhang et al (2013) [25] | 0.73 (0.64, 0.83) | 0.82 (0.76, 0.89) |
| Lega et al (2014) [26] | ND | 0.74 (0.62, 0.88) |
| Zhang and Li (2014) [27] | ND | 0.70 (0.55, 0.88) |
| Gandini et al (2014) [24] | 0.69 (0.52, 0.90)<br>0.95 (0.69, 1.30)[a]<br>0.90 (0.89, 0.91)[d] | 0.66 (0.54, 0.81) |
| Wu et al (2015) [23] | 0.86 (0.83, 0.90)<br>1.05 (0.94, 1.18)[a]<br>0.88 (0.83, 0.92)[b]<br>0.71 (0.63, 0.80)[c] | 0.70 (0.53, 0.94)<br>0.91 (0.37, 2.23)[a]<br>0.66 (0.49, 0.89)[b] |

[a] RCT

[b] Cohort study

[c] Case–control study

[d] Adjusted for time bias

Diabetologia (2017) 60:1639–1647

# Meta-analyses examining the effect of metformin use on cancer site-specific mortality

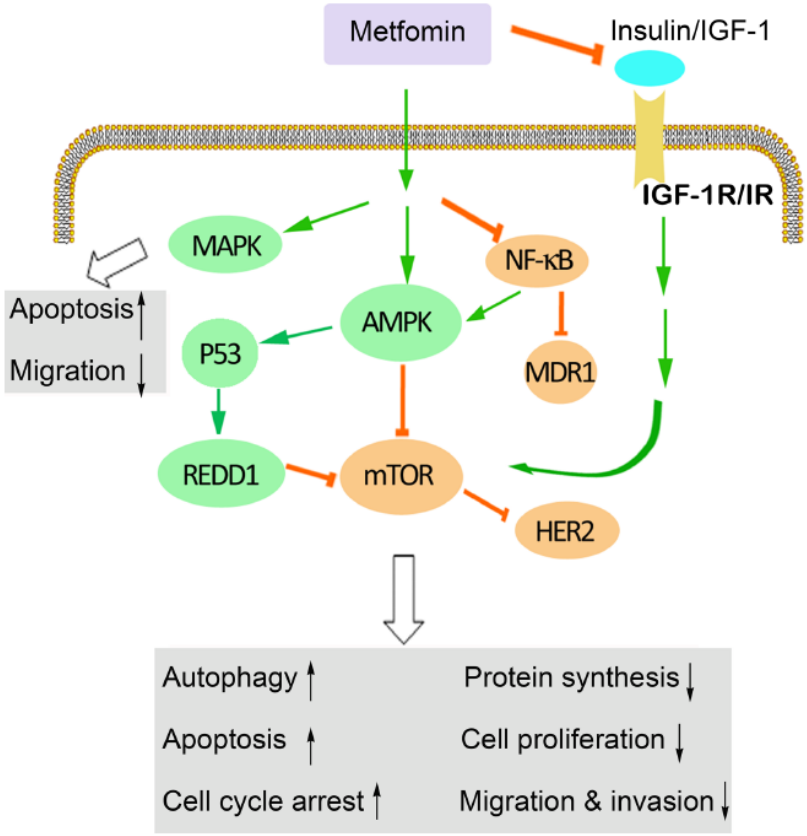
| Cancer Site | Study authors (date) | Association of metformin use with cancer site-specific mortality, HR (95% CI) | Association of metformin use with overall mortality, HR (95% CI) |
|---|---|---|---|
| Breast | Yang et al (2015) [35] | ND | 0.70 (0.51, 0.96) |
| Colon | Lega et al (2014) [26] | 0.65 (0.56, 0.76) | ND |
| | Zhang and Li (2014) [27] | ND | 0.70 (0.59, 0.84) |
| | Coyle et al (2016) [39] | 0.58 (0.39, 0.86) | 0.69 (0.58, 0.83) |
| Endometrial | Perez-Lopez et al (2017) [36] | ND | 0.64 (0.45, 0.89) |
| Liver | Ma et al (2016) [37] | ND | 0.59 (0.42, 0.83) |
| Lung | Wan et al (2016) [38] | 0.65 (0.52, 0.83) | 0.78 (0.64, 0.93) |
| | Tian et al (2016) [42] | ND | 0.90 (0.84, 0.96) |
| Ovarian | Zhang and Li (2014) [27] | ND | 0.44 (0.30, 0.64) |
| Prostate | Raval et al (2015) [43] | 0.76 (0.43, 1.33) | 0.86 (0.67, 1.10) |
| | Coyle et al (2016)[a] [39] | 0.58 (0.37, 0.93) | 0.82 (0.73, 0.93) |
| | Stopsack et al (2016) [40] | 0.76 (0.44, 1.31) | 0.88 (0.86, 0.90) |
| Pancreas | Zhou et al (2017) [41] | ND | 0.84 (0.73, 0.96) |

[a] Study focused on localised, early-stage disease

ND, no data

Diabetologia (2017) 60:1639–1647

# Metformin & Cancer: mechanisms of action




Lei *et al. Chin J Cancer (2017) 36:17*

Toxicology and Applied Pharmacology 280 (2014) 138–148

Contents lists available at ScienceDirect

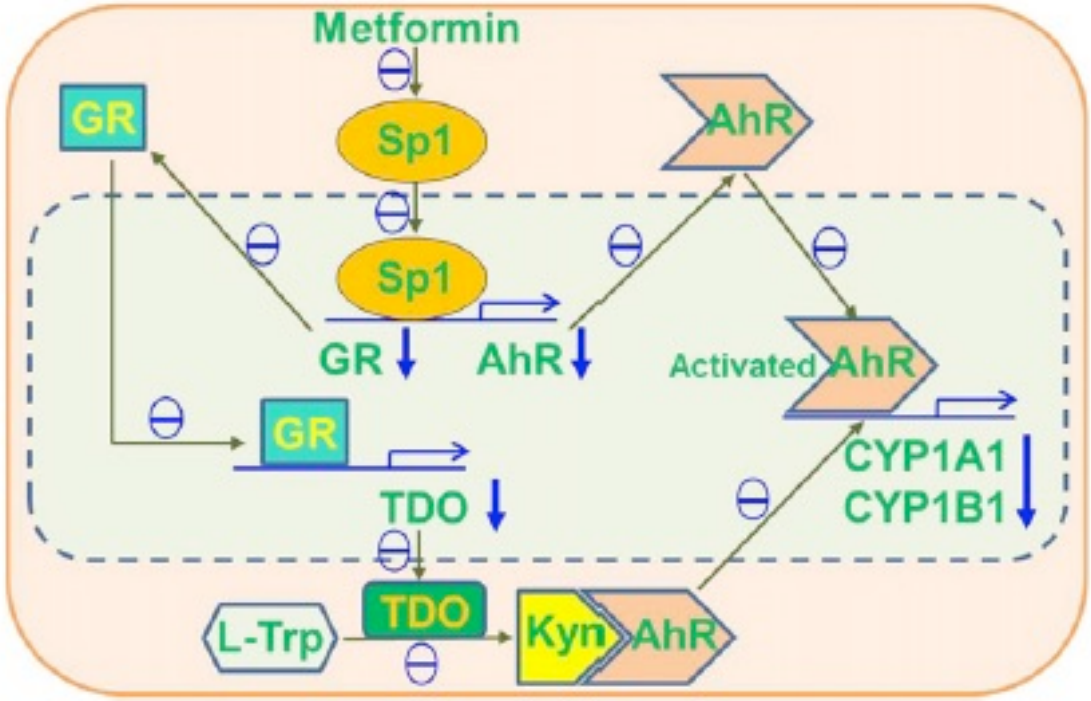
Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

# Metformin suppresses CYP1A1 and CYP1B1 expression in breast cancer cells by down-regulating aryl hydrocarbon receptor expression

Minh Truong Do [a], Hyung Gyun Kim [a], Thi Thu Phuong Tran [a], Tilak Khanal [a], Jae Ho Choi [a], Young Chul Chung [b], Tae Cheon Jeong [c,*], Hye Gwang Jeong [a,**]

[a] Department of Toxicology, College of Pharmacy, Chungnam National University, Daejeon, Republic of Korea
[b] Department of Food Science and Culinary, International University of Korea, Jinju, Republic of Korea
[c] College of Pharmacy, Yeungnam University, Gyeongsan, Republic of Korea



Grazie