Associazione Medici Endocrinologi

ITALIAN CHAPTER

2nd AME Diabetes Update

Diabete mellito e danno macrovascolare: gestione clinica

Bologna, 10 - 11 febbraio 2017

Novotel Bologna Fiera

VIII SESSIONE

Focus terapeutici nel Diabete Mellito

Metformina e rischio di acidosi lattica: fra Scilla e Cariddi

Silvio Settembrini

Servizio di Endocrinologia Diabetologia e Malattie Metaboliche - DS 26

Unita' di Nefro - Diabetologia - UOC di Nefrologia e Dialisi

Ospedale dei Pellegrini - Napoli

ASL Napoli 1

Cochrane Database Syst Rev 2010:CD002967

Risk of Fatal and Nonfatal Lactic Acidosis With Metformin Use in Type 2 Diabetes Mellitus: Systematic Review and Meta-analysis

Salpeter SR, Greyber E, Pasternak GA, Salpeter EE

There is no evidence to date that metformin therapy is associated with an increased risk of lactic acidosis or with increased levels of lactate compared with other antihyperglycemic treatments if the drugs are prescribed under study conditions, taking into account contraindications.

METFORMINA E ACIDOSI LATTICA

L'incidenza di acidosi lattica
in pazienti diabetici non trattati con metformina
è risultata pari a 0,07 casi/1000 pazienti per anno
(limitandosi ai soli casi confermati)
ed a 0,16 casi/1000 pazienti per anno
(includendo anche i casi sospetti ma non confermati)

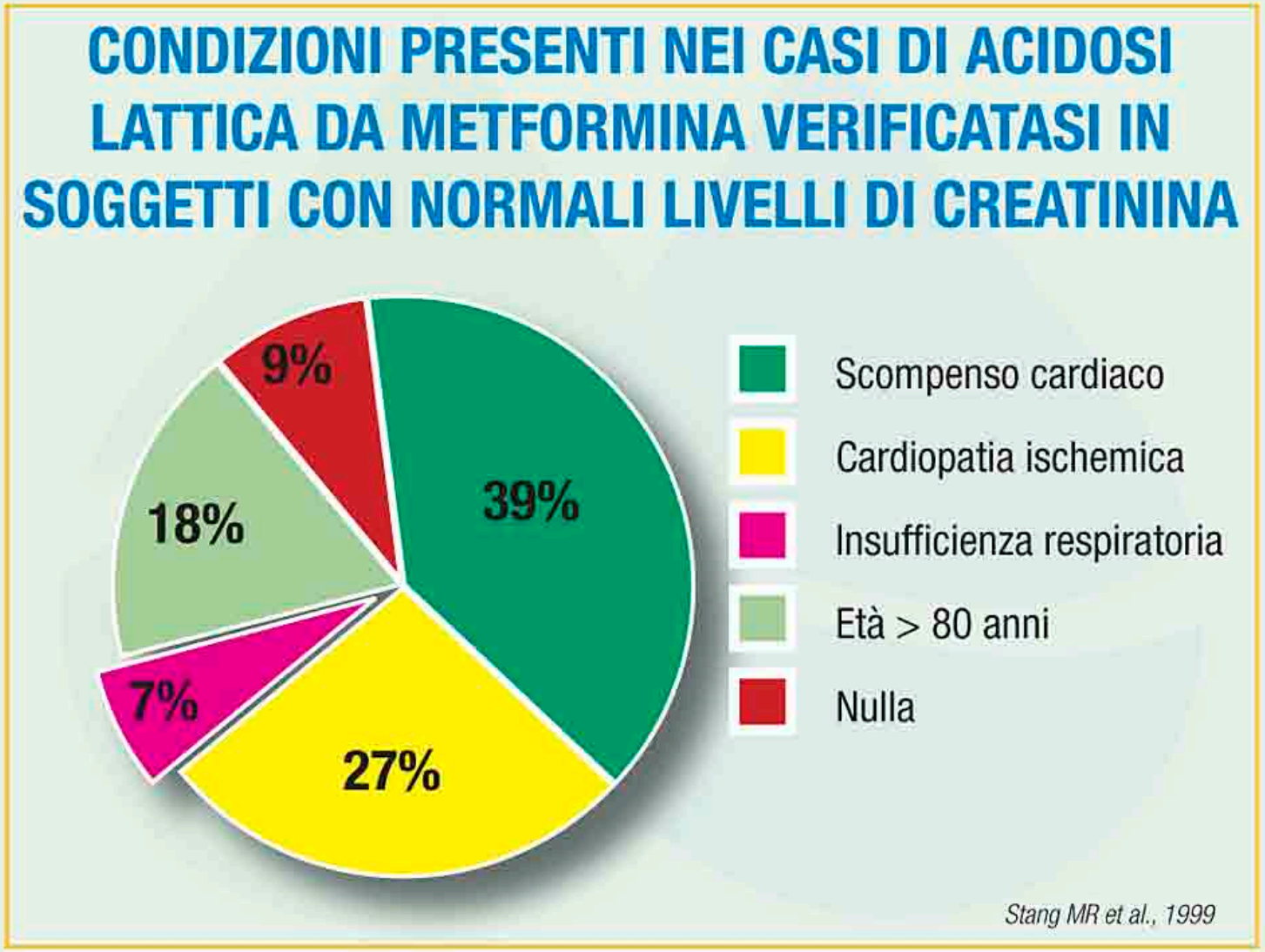
La conclusione è che:

"Nei pazienti con diabete mellito di tipo 2
non trattati con metformina
l'acidosi lattica si verifica con un'incidenza
simile a quella riportata nei soggetti
che assumono metformina"

Holstein et al., 1999

Holstein A, Nahrwold D, Hinze S, Egberts EH. Contra-indications to metformin therapy are largely disregarded. *Diabet Med* 1999;16:692-

Studio osservazionale di coorte, condotto su oltre 41000 pazienti per anno in differenti aree geografiche, dimostra che l'incidenza di acidosi lattica nei diabetici di tipo 2 non trattati con metformina risulta simile a quella riportata nei diabetici trattati con la biguanide .
È noto che il diabete di per sè tende ad aumentare i livelli di acido lattico in circolo. Pertanto, questi dati confermano l'ipotesi secondo cui "l'acidosi lattica associata alla metformina non è necessariamente dovuta all'accumulo di metformina"



Uno studio di Stang ha evidenziato che in un numero consistente di casi (cioè in oltre i 2/3 dei pazienti trattati con metformina) la decisione di iniziare il trattamento non ha tenuto conto della presenza di eventuali controindicazioni . Nonostante ciò, la frequenza di acidosi lattica è risultata bassissima, appena di 0,05–0,09 casi per 1000 pazienti/anno, dimostrando che la metformina è un farmaco decisamente sicuro. Peraltro anche in un piccolo gruppo di pazienti assolutamente privi di controindicazioni si è comunque verificata un'acidosi lattica, dimostrando la relativa indipendenza del fenomeno dall'impiego .

ADERENZA ALLE CONTROINDICAZIONI ALL'USO DI METFORMINA

Autori/ Durata	Pazienti (n)	Tutte le contro-indicazioni-rischi (%)	Insufficienza renale (%)	Epatopatia (%)	Scompenso cardiaco (%)	CHD compreso IMA (%)	Casi di acidosi lattica (n)
Sulkin et al. 3 mesi	89	54	2	2	2	22	0
Holstein et al. 3.5 anni	308	74	19	1,3	25	51	0
Emslie-Smith et al. 3 anni	1847	24,5	4,8	2,8	25,2	3,5	1
Horlen et al. 9 mesi	100	22	5	Non stabilita	14	Non stabilito	0
Calabrese et al. 6 mesi	204	62	12	Non stabilita	Non stabilito	Non stabilito	0
Kennedy e Herman	4838	Non stabiliti	4,5	Non stabilita	Non stabilito	Non stabilito	Non stabiliti
Rakovac et al. 5 anni	4401	18,9	3,1	Non stabilita	13,6	Non stabilito	Non stabiliti

Holstein A. et al., 2005

Current contraindications to metformin use

Contraindications

- Renal dysfunction
- Congestive cardiac failure needing drug treatment
- Hypersensitivity to metformin
- Acute or chronic metabolic acidosis
- Impaired hepatic function

Precautions

- Age >80 years until renal dysfunction ruled out
- Acute myocardial infarction
- Radiological studies involving iodinated contrast
- Surgical procedures
- Alcohol intake

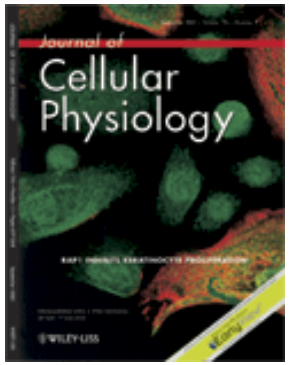
These contraindications/precautions have been increasingly challenged by recent evidence, although this evidence is mostly from observational studies

Journal of Cellular Physiology

REVIEW ARTICLE

Journal of Cellular Physiology

Nephroprotective Effects of Metformin in Diabetic Nephropathy



SREENITHYA RAVINDRAN, VINITHA KURUVILLA, KERRY WILBUR, AND SHANKAR MUNUSAMY*

College of Pharmacy, Qatar University, Doha, Qatar

Metformin, a well-known anti-diabetic agent, is very effective in lowering blood glucose in patients with type 2 diabetes with minimal side-effects. Metformin is also being recommended in the treatment of obesity and polycystic ovary syndrome. Metformin elicits its therapeutic effects mainly via activation of AMP-activated kinase (AMPK) pathway. Renal cells under hyperglycemic or proteinuric conditions exhibit inactivation of cell defense mechanisms such as AMPK and autophagy, and activation of pathologic pathways such as mammalian target of rapamycin (mTOR), endoplasmic reticulum (ER) stress, epithelial-to-mesenchymal transition (EMT), oxidative stress, and hypoxia. As these pathologic pathways are intertwined with AMPK signaling, the potential benefits of metformin therapy in patients with type 2 diabetes would extend beyond its anti-hyperglycemic effects. However, since metformin is eliminated unchanged through the kidneys and some studies have shown the incidence of lactic acidosis with its use during severe renal dysfunction, the use of metformin was contraindicated in patients with renal disease until recently. With more studies indicating the relatively low incidence of lactic acidosis and revealing the additional benefits with metformin therapy, the US FDA has now approved metformin to be administered in patients with established renal disease based on their renal function. The purpose of this review is to highlight the various mechanisms by which metformin protects renal cells that have lost its functionality in a diabetic or non-diabetic setting and to enlighten the advantages and therapeutic potential of metformin as a nephroprotectant for patients with diabetic nephropathy and other non-diabetic forms of chronic kidney disease.

J. Cell. Physiol. 232: 731–742, 2017.

J. Cell. Physiol. 232: 731–742, 2017

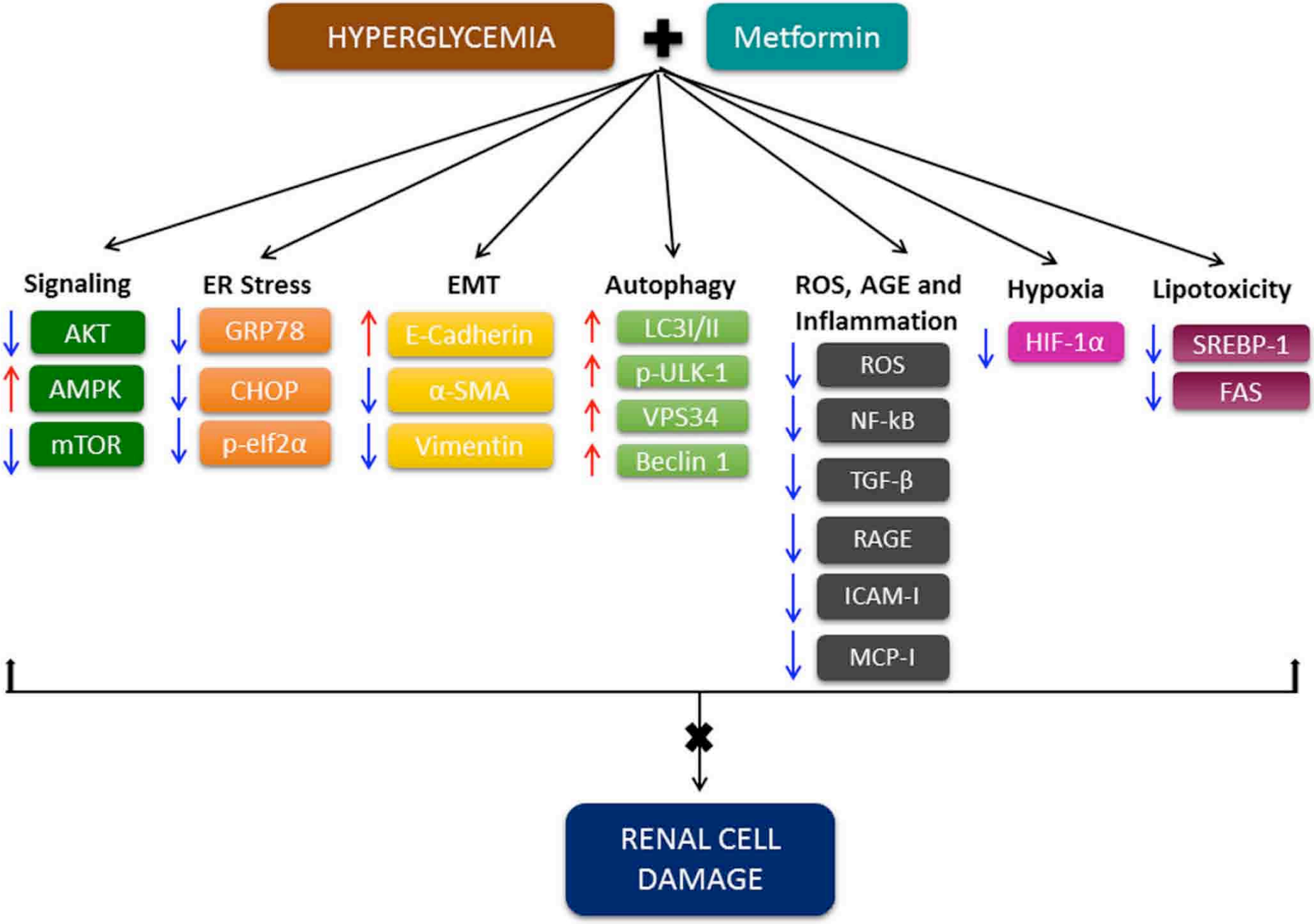


Fig. 9. Summary of the effects of metformin on various signaling pathways in diabetic nephropathy. Metformin protects renal cells under hyperglycemic and hypoxic conditions through mechanisms dependent and independent of phosphorylation of AMPK. Upward and downward arrows indicate stimulation and inhibition of the parameter respectively by metformin.

Metformin Reduces Risk of Death

Metformin Reduces Risk of Death

- A systematic review of 17 observational studies found that metformin use is associated with reduced all-cause mortality in patients with T2DM with chronic kidney disease (CKD), congestive heart failure (CHF), or chronic liver disease (CLD) with hepatic impairment, and with fewer heart failure readmissions in patients with CKD or CHF.

Metformin Reduces Risk of Death

- A meta-analysis of five studies that examined all-cause mortality in 33,442 subjects showed a 22% reduction in relative risk of dying with metformin use than without.

Annals of Internal Medicine

REVIEW

Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease

A Systematic Review

Matthew J. Crowley, MD, MHS; Clarissa J. Diamantidis, MD, MHS; Jennifer R. McDuffie, PhD; C. Blake Cameron, MD, MBI; John W. Stanifer, MD, MSc; Clare K. Mock, MD; Xianwei Wang, MD; Shuang Tang, PhD; Avishek Nagi, MS; Andrzej S. Kosinski, PhD; and John W. Williams Jr., MD, MHS

Background: Recent changes to the U.S. Food and Drug Administration boxed warning for metformin will increase its use in persons with historical contraindications or precautions. Prescribers must understand the clinical outcomes of metformin use in these populations.

Purpose: To synthesize data addressing outcomes of metformin use in populations with type 2 diabetes and moderate to severe chronic kidney disease (CKD), congestive heart failure (CHF), or chronic liver disease (CLD) with hepatic impairment.

Data Sources: MEDLINE (via PubMed) from January 1994 to September 2016, and Cochrane Library, EMBASE, and International Pharmaceutical Abstracts from January 1994 to November 2015.

Study Selection: English-language studies that: 1) examined adults with type 2 diabetes and CKD (with estimated glomerular filtration rate less than 60 mL/min/1.73 m^2), CHF, or CLD with hepatic impairment; 2) compared diabetes regimens that included metformin with those that did not; and 3) reported all-cause mortality, major adverse cardiovascular events, and other outcomes of interest.

Data Extraction: 2 reviewers abstracted data and independently rated study quality and strength of evidence.

Data Synthesis: On the basis of quantitative and qualitative syntheses involving 17 observational studies, metformin use is associated with reduced all-cause mortality in patients with CKD, CHF, or CLD with hepatic impairment, and with fewer heart failure readmissions in patients with CKD or CHF.

Limitations: Strength of evidence was low, and data on multiple outcomes of interest were sparse. Available studies were observational and varied in follow-up duration.

Conclusion: Metformin use in patients with moderate CKD, CHF, or CLD with hepatic impairment is associated with improvements in key clinical outcomes. Our findings support the recent changes in metformin labeling.

Primary Funding Source: U.S. Department of Veterans Affairs. (PROSPERO: CRD42016027708)

Ann Intern Med. doi:10.7326/M16-1901 www.annals.org

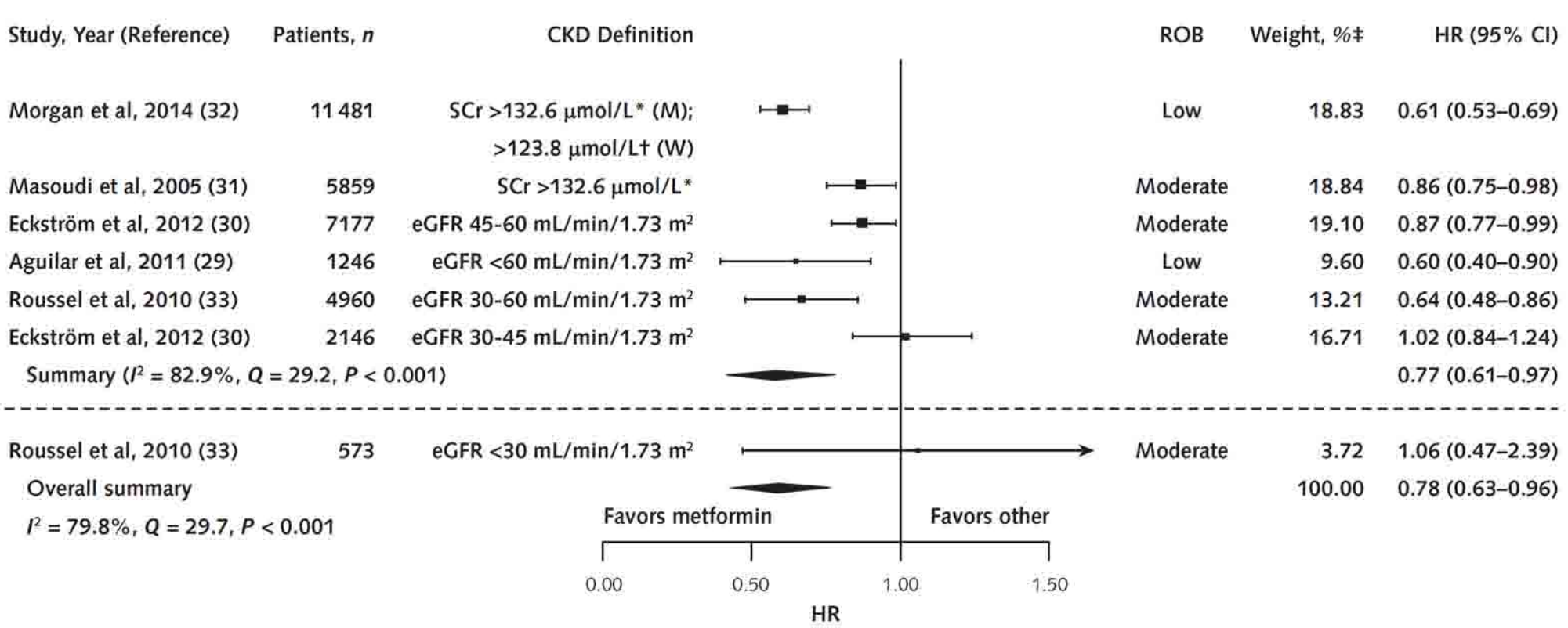
For author affiliations, see end of text.

This article was published at www.annals.org on 3 January 2017.

Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease

A Systematic Review

Figure 2. Meta-analysis of all-cause mortality among patients with moderate to severe CKD receiving treatment regimens including metformin versus those receiving regimens without metformin.

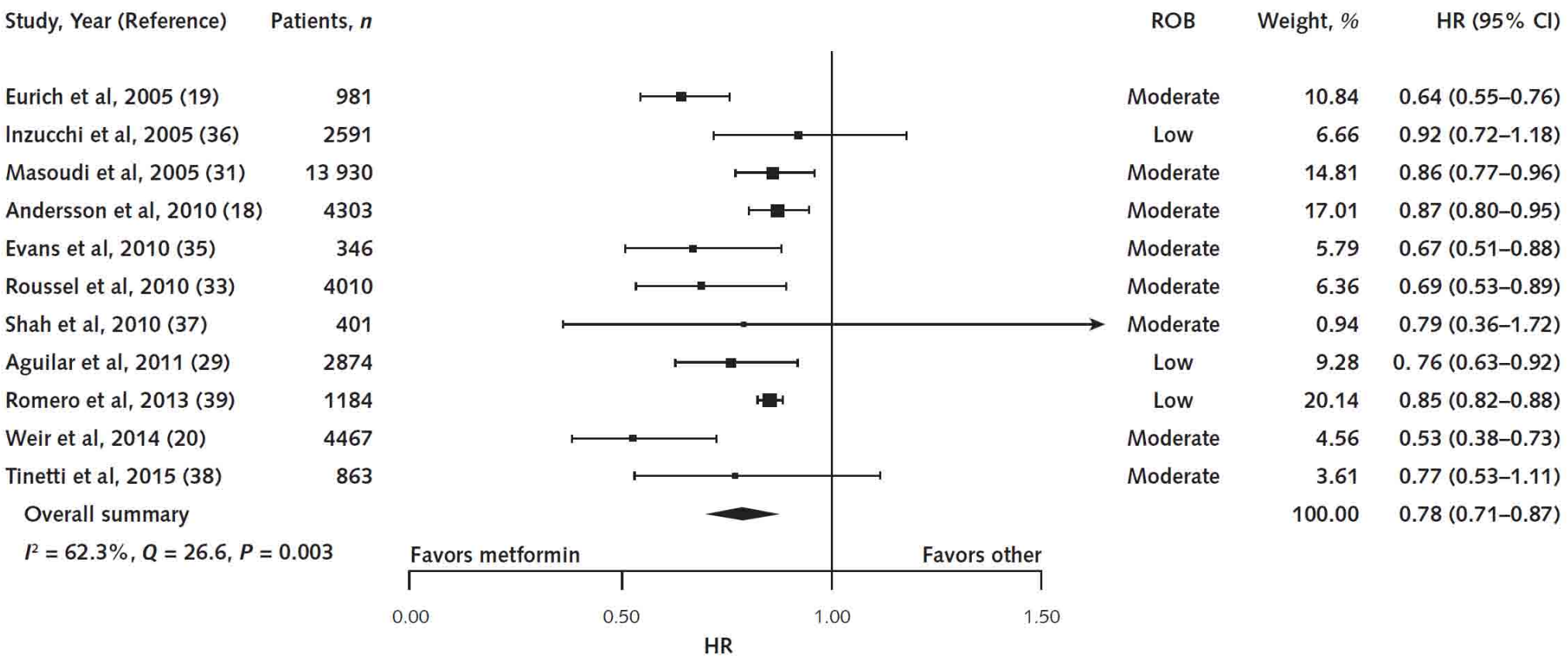


Annals of Internal Medicine REVIEW

Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease

A Systematic Review

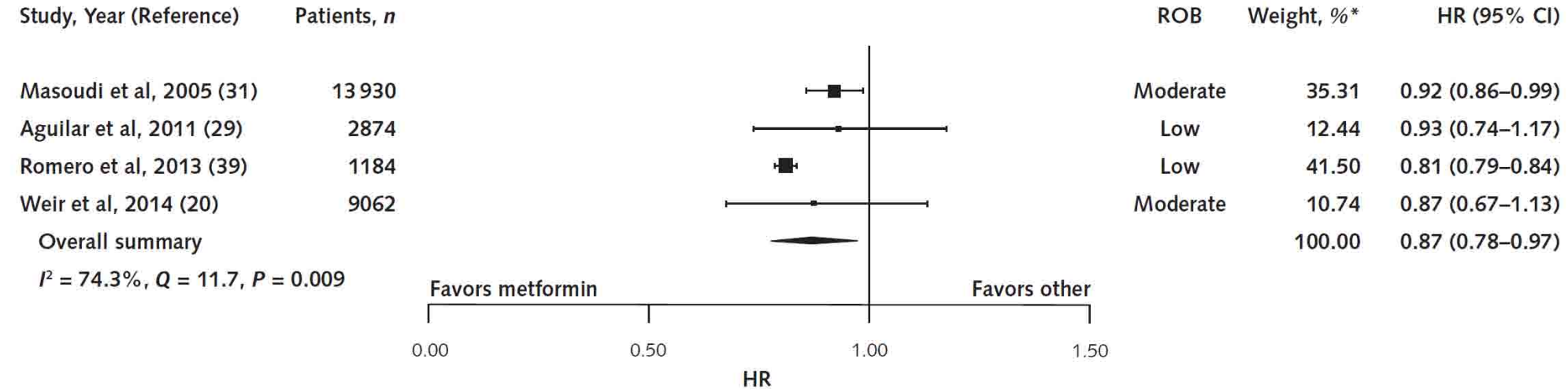
Figure 3. Meta-analysis of all-cause mortality among patients with CHF receiving treatment regimens including metformin versus those receiving regimens without metformin.



Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease

A Systematic Review

Figure 4. Meta-analysis of CHF readmission among patients with CHF receiving treatment regimens including metformin versus those receiving regimens without metformin.

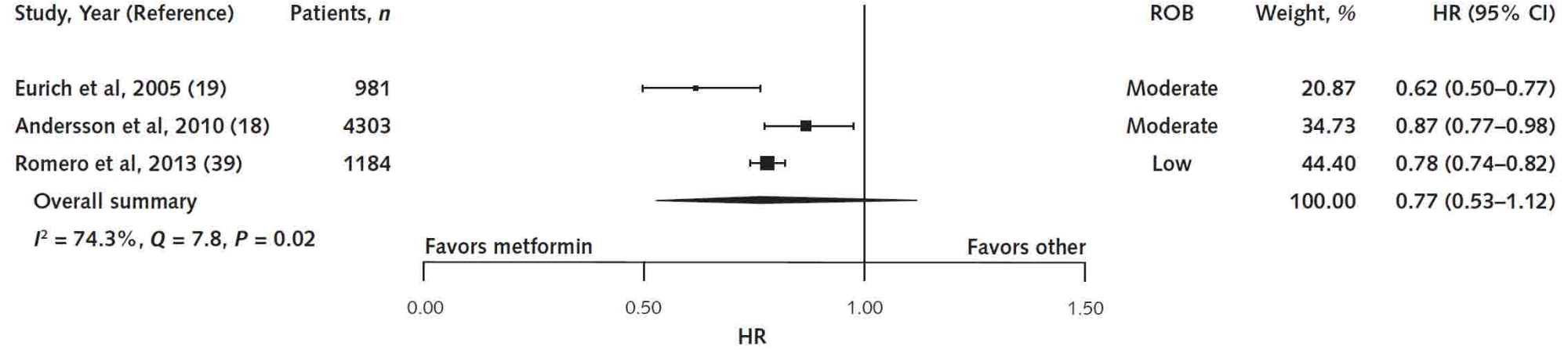


Studies are listed chronologically. CHF = congestive heart failure; HR = hazard ratio; ROB = risk of bias.
* Numbers do not total 100% because of rounding.

Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease

A Systematic Review

Figure 5. Meta-analysis of cardiovascular mortality among patients with CHF receiving treatment regimens including metformin versus those receiving regimens not including metformin.

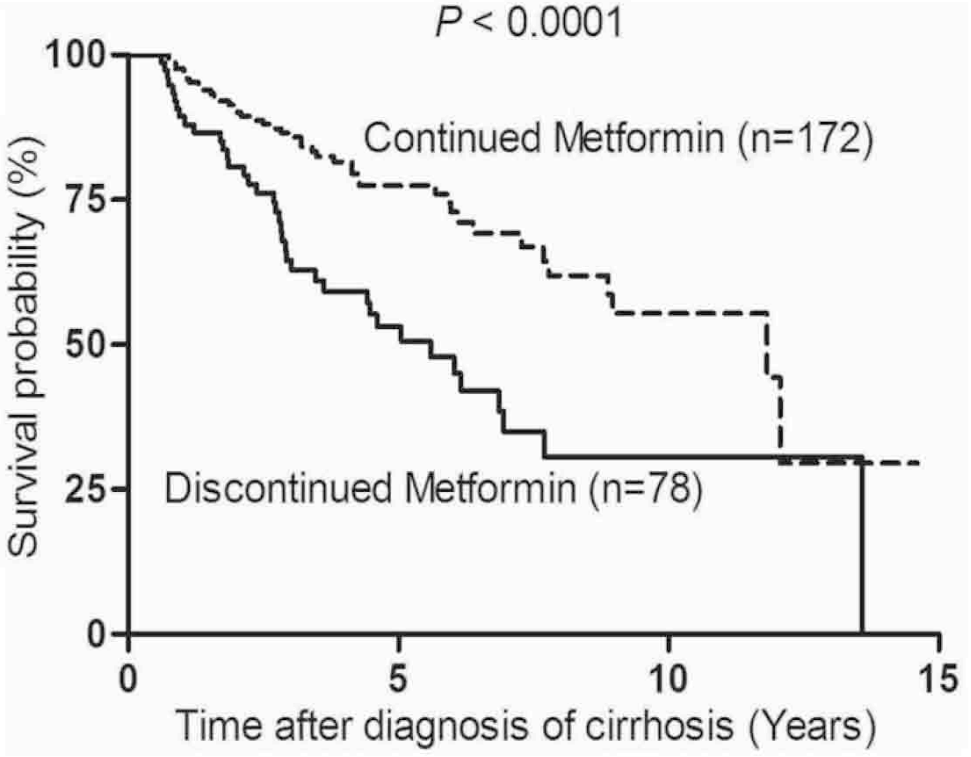


Studies are listed chronologically. CHF = congestive heart failure; HR = hazard ratio; ROB = risk of bias.

Continuation of metformin use after a diagnosis of cirrhosis significantly improved survival of patients with diabetes

Xiaodan Zhang[1], William S. Harmsen[2], Teresa A. Mettler[1], W. Ray Kim[1], Rosebud O.

[1]Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester,



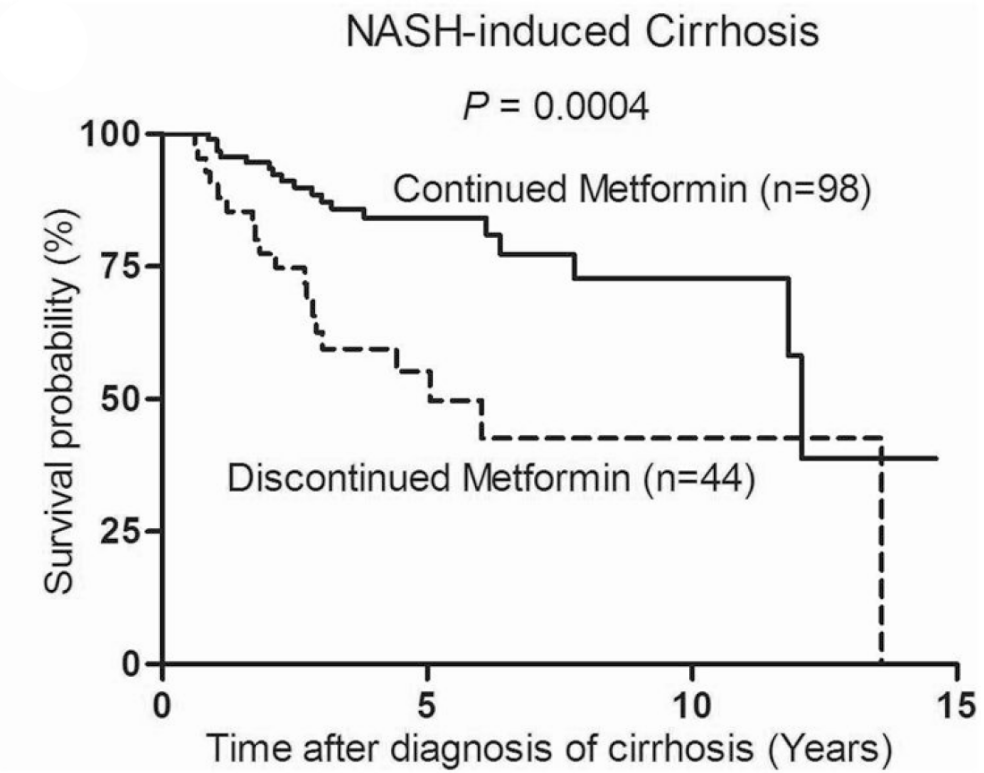


Figure 1. Survival of 250 diabetic patients who continued metformin vs. those who discontinued metformin after cirrhosis diagnosis

Survival of 142 patients with NASH related cirrhosis

Hepatology. 2014 December ; 60(6): 2008–2016.

Storia della Metformina

La *Galega officinalis,* ricca di guanidina, è usata come fitoterapico nell'Europa medievale.

1918 - Vengono descritte le proprietà ipoglicemizzanti della guanidina.

1929 – Per la prima volta vengono riportati gli effetti sulla glicemia delle biguanidi sintetiche.

1957 – Viene descritto il primo impiego clinico di metformina, fenformina e buformina.

ANNI '70 - Fenformina e buformina vengono ritirate dal commercio per il rischio di acidosi lattica.

1995 - Meformina ottiene l'autorizzazione alla commercializzazione negli USA .

Le attuali linee guida indicano la priorità di metformina rispetto a tutte le altre opzioni per il trattamento del T2DM

Storia della Metformina

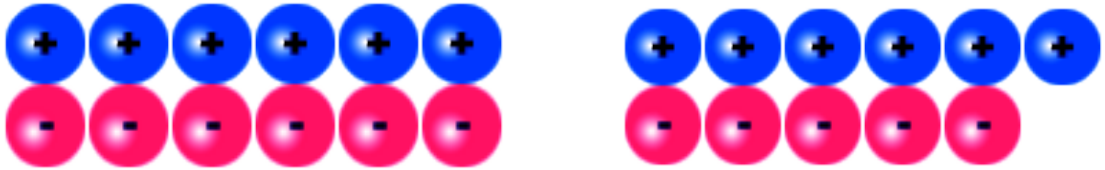
Table 1 | Summary of pharmacological differences between metformin and phenformin

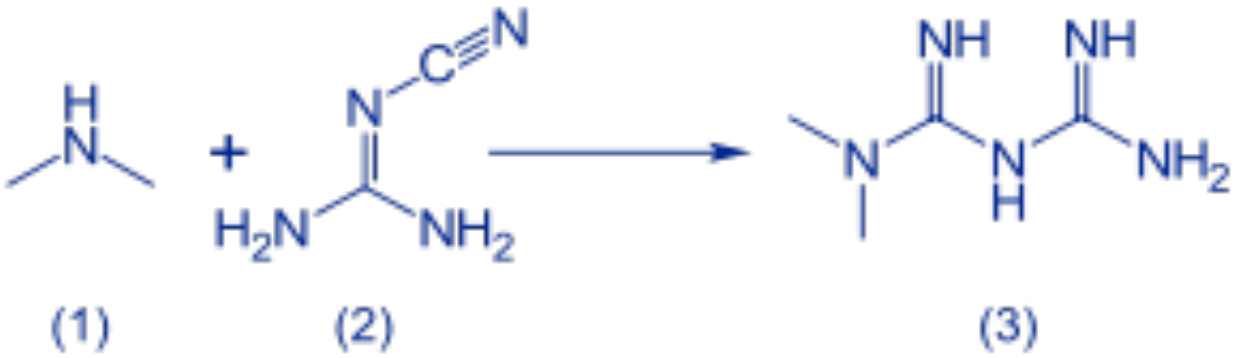
Property	Metformin	Phenformin
Adherence to mitochondrial membrane[w2 w3]	Poor	Strong
Inhibition of electron transport chain[w2 w3]	Absent	Present
Inhibition of glucose oxidation[w3]	Absent	Present
Interference with lactate turnover[w3]	Absent	Present
Metabolism[w3]	Not metabolised/ excreted unchanged	Inactive hydroxylated derivative

These differences might explain the lower incidence of lactic acidosis with metformin.

Catione e' uno ione carico positivamente

(attrae cariche + e respinge cariche -)





dimethylamine and 2-cyanoguanidine

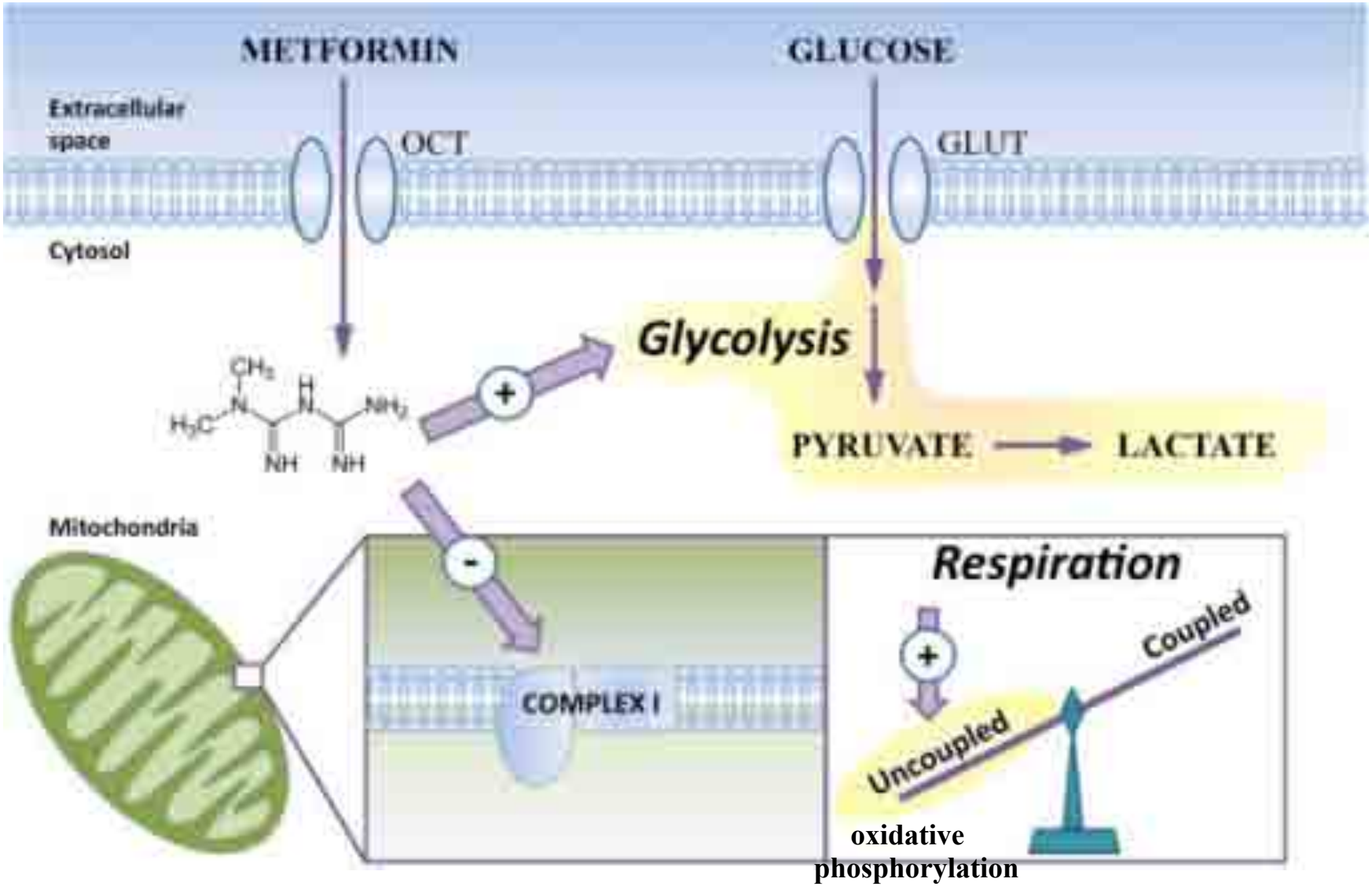
Metformin is an organic cation and is positively charged at physiological pH that renders it hydrophilic, resulting in limited passive diffusion .

Metformin's mechanism of action :

1) Decreased hepatic and intestinal gluconeogenesis

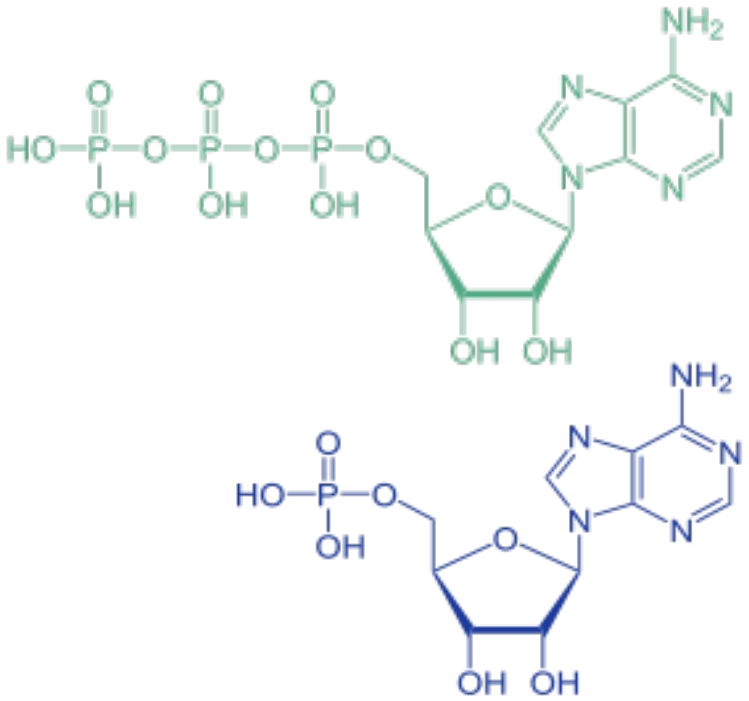
2) Enhanced muscle – adipose glucose utilization,

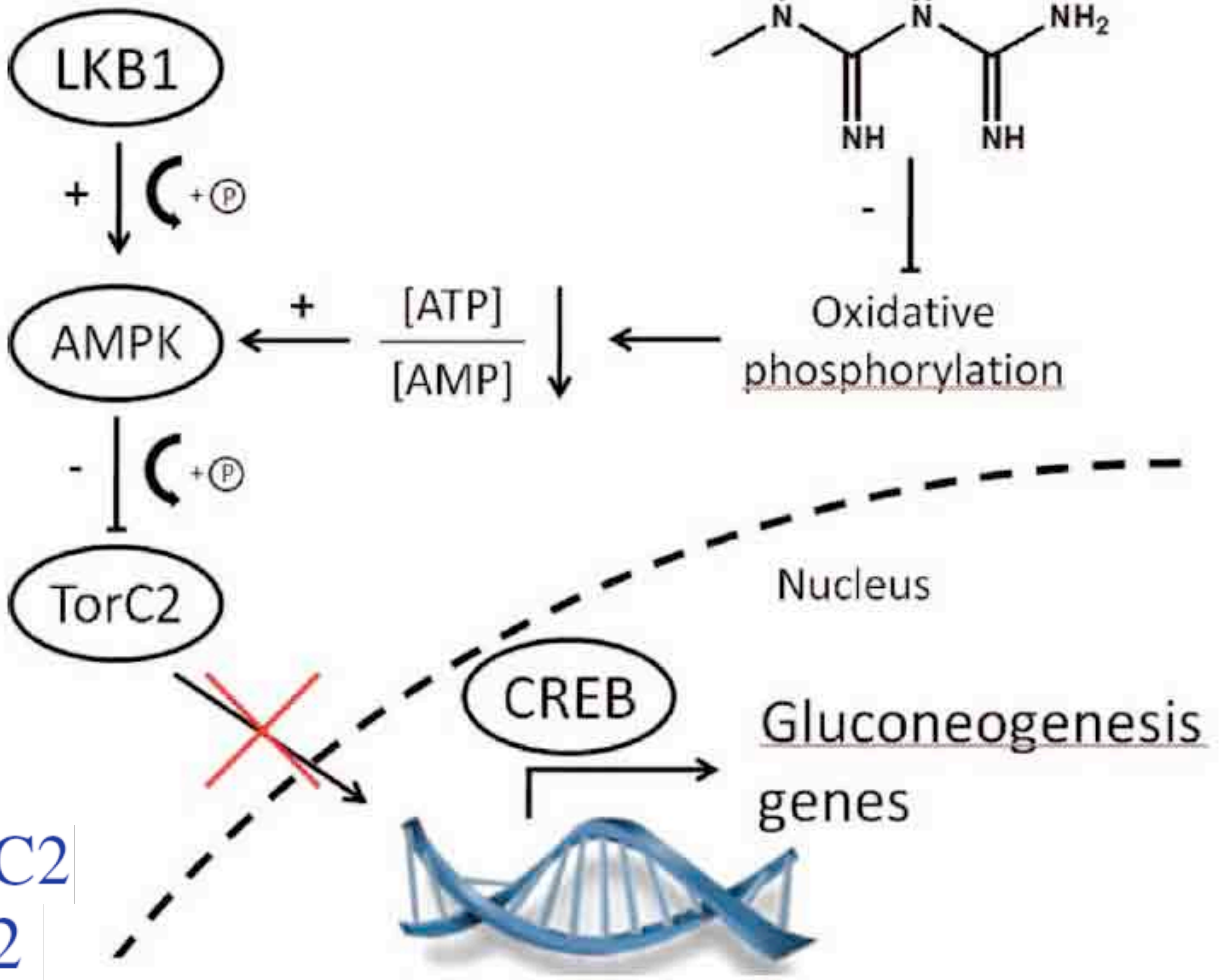
3) Modulation of mitochondrial oxidation of F.A.



Metformin directly acts on mitochondria and shifts the balance between coupling and uncoupling reactions. Metformin is transported into cells through the OCT family of transporters, where it acts on mitochondria to inhibit complex I-dependent respiration and increase the proportion of uncoupled respiration. Cells respond by increasing glycolysis, ultimately leading to increased lactate production. As a result, mitochondrial metabolism becomes energetically inefficient, and cells compensate for this limitation in ATP production by increasing aerobic glycolysis .

kinase and tumor suppressor LKB1

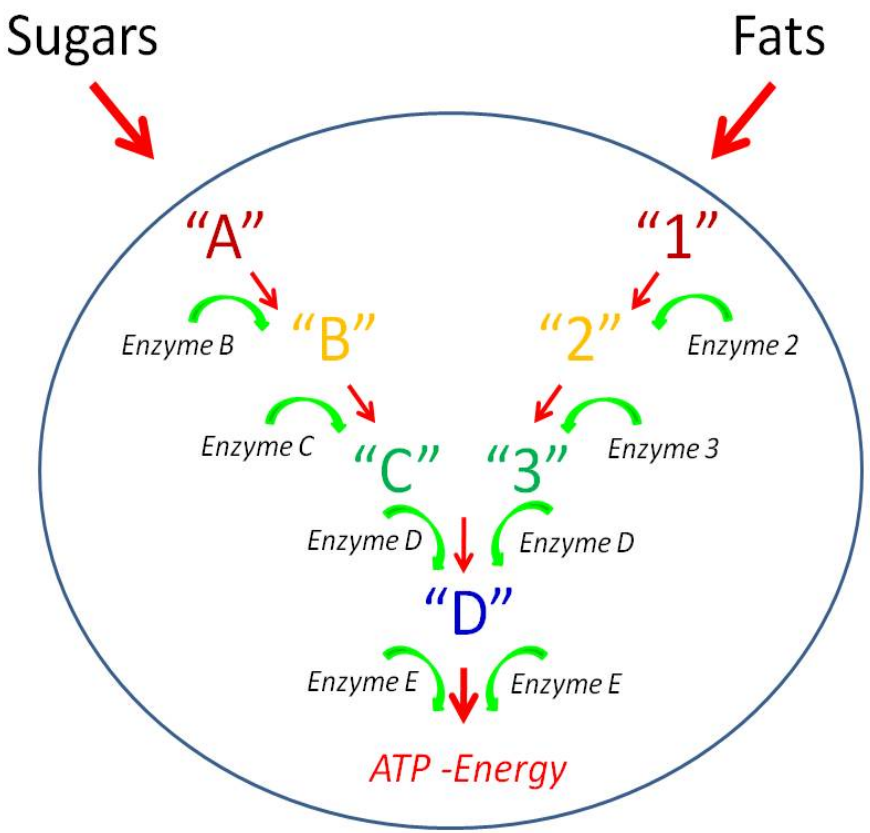


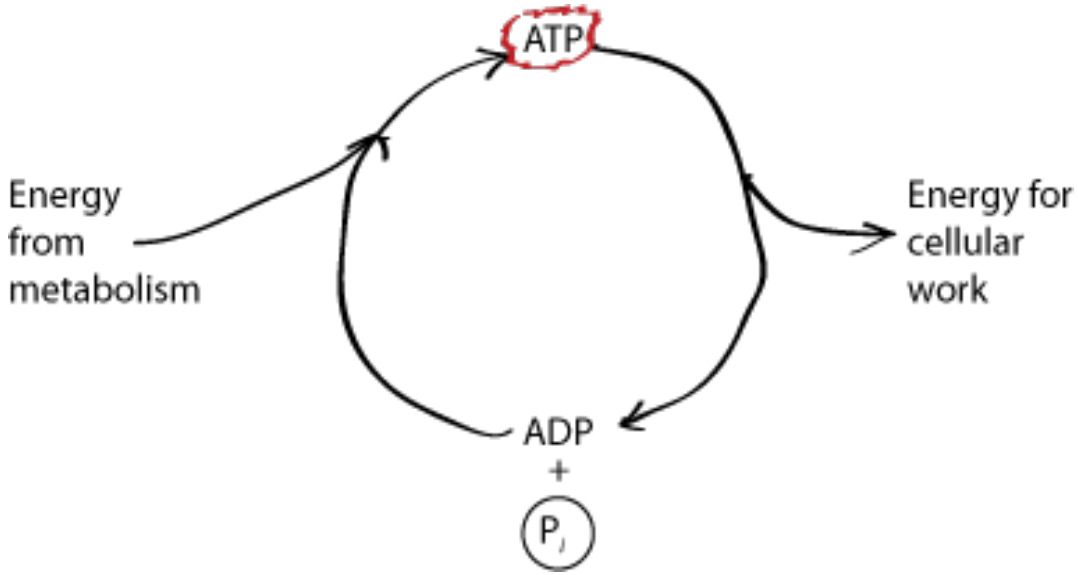


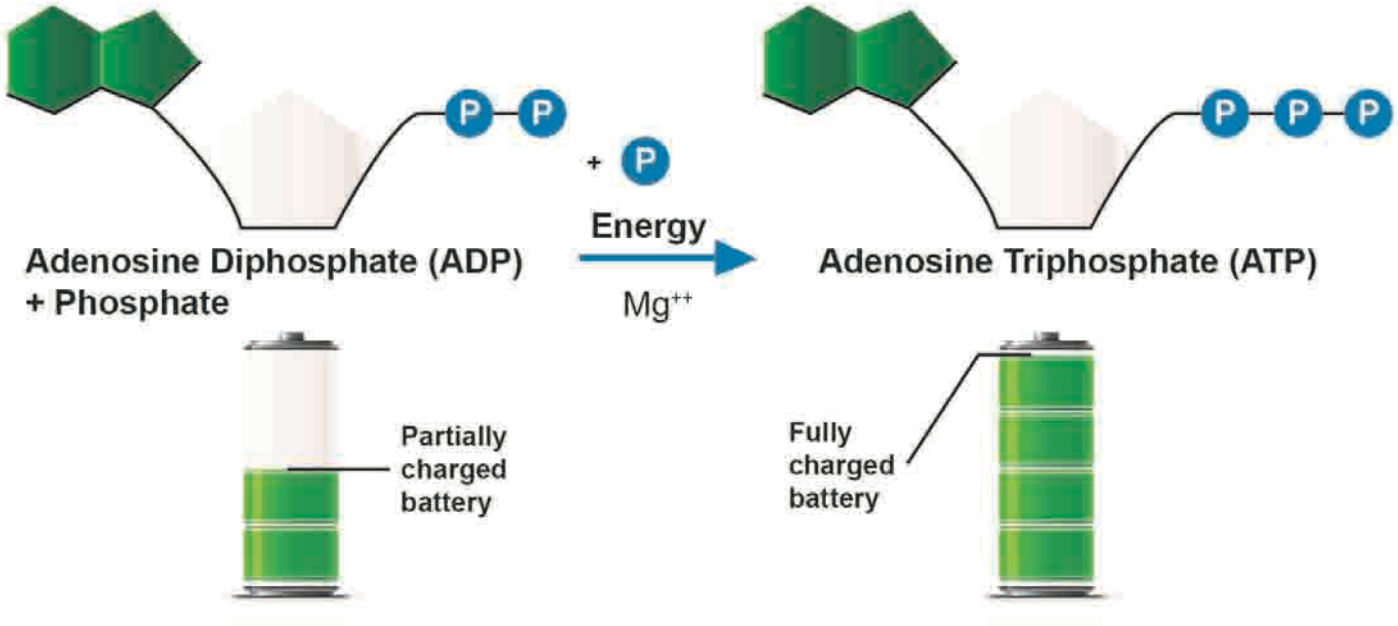
transcriptional activator TorC2

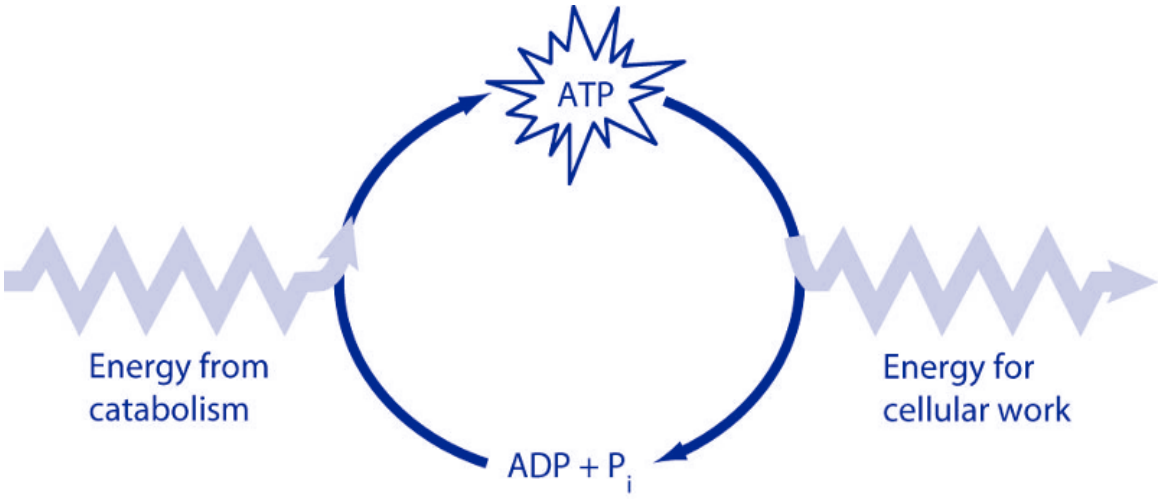
CREB coactivator TORC2

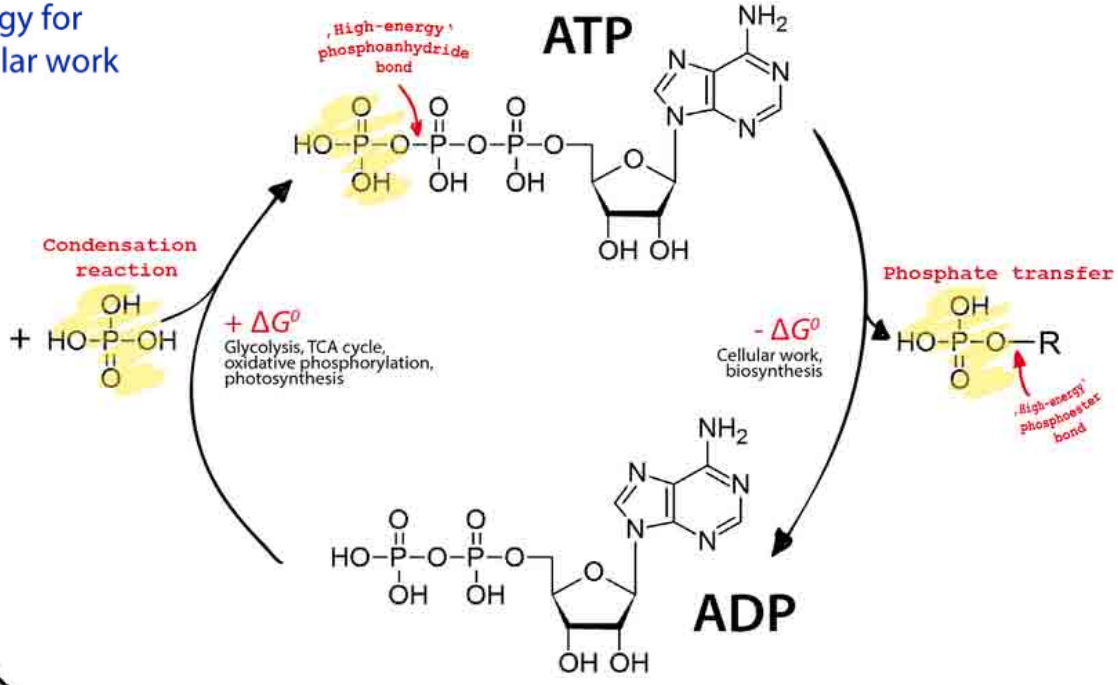
AMP-activated protein kinase (AMPK) is an energy sensor and master regulator of metabolism. AMPK functions as a fuel gauge monitoring systemic and cellular energy status. Activation of AMPK occurs when the intracellular AMP/ATP ratio increases and leads to a metabolic switch from anabolism to catabolism. Cytosolic ATP/ADP ratio is a key feature that determines if cell metabolism is predominantly oxidative or glycolytic. High cytosolic ATP/ADP generated by oxidative phosphorylation inhibits glycolysis .

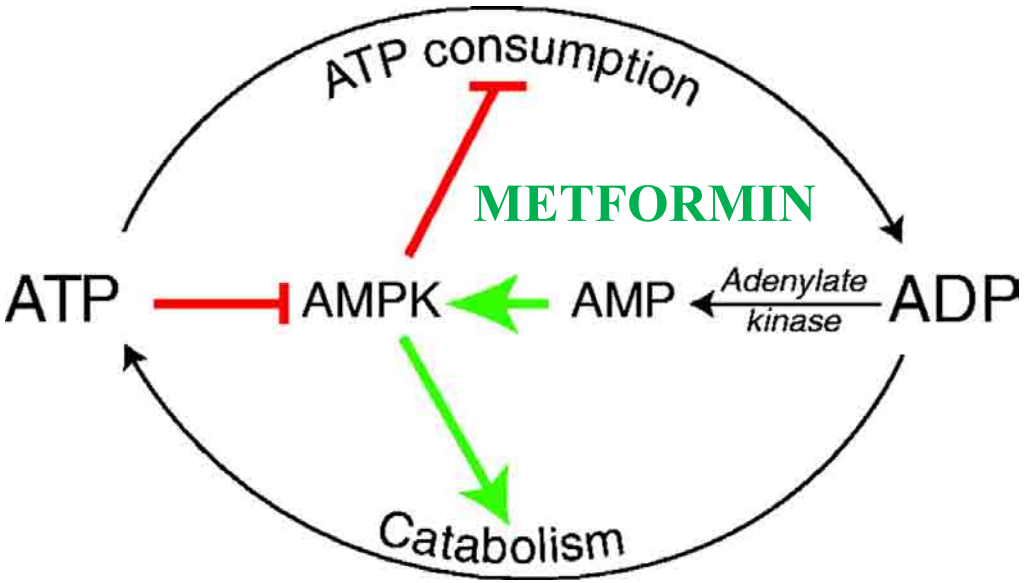

Sugars
Fats
"A"
"1"
Enzyme B
"B"
"2"
Enzyme 2
Enzyme C
"C"
"3"
Enzyme 3
Enzyme D
Enzyme D
"D"
Enzyme E
Enzyme E
ATP -Energy


ATP
Energy from metabolism
Energy for cellular work
ADP
+
P_i

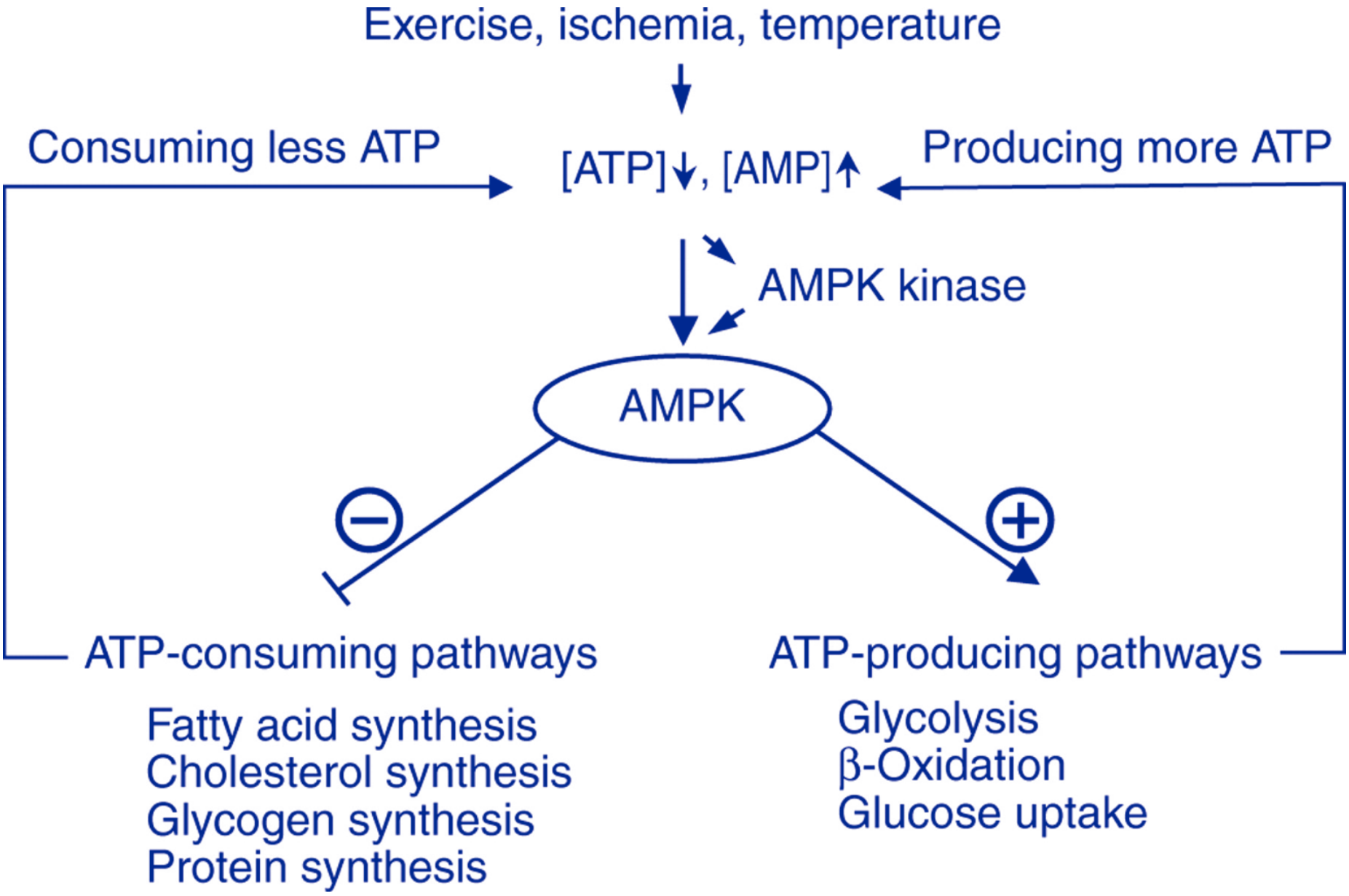

P
P
+ P
Energy
Mg^{++}
P
P
P
Adenosine Diphosphate (ADP)
+ Phosphate
Adenosine Triphosphate (ATP)
Partially charged battery
Fully charged battery

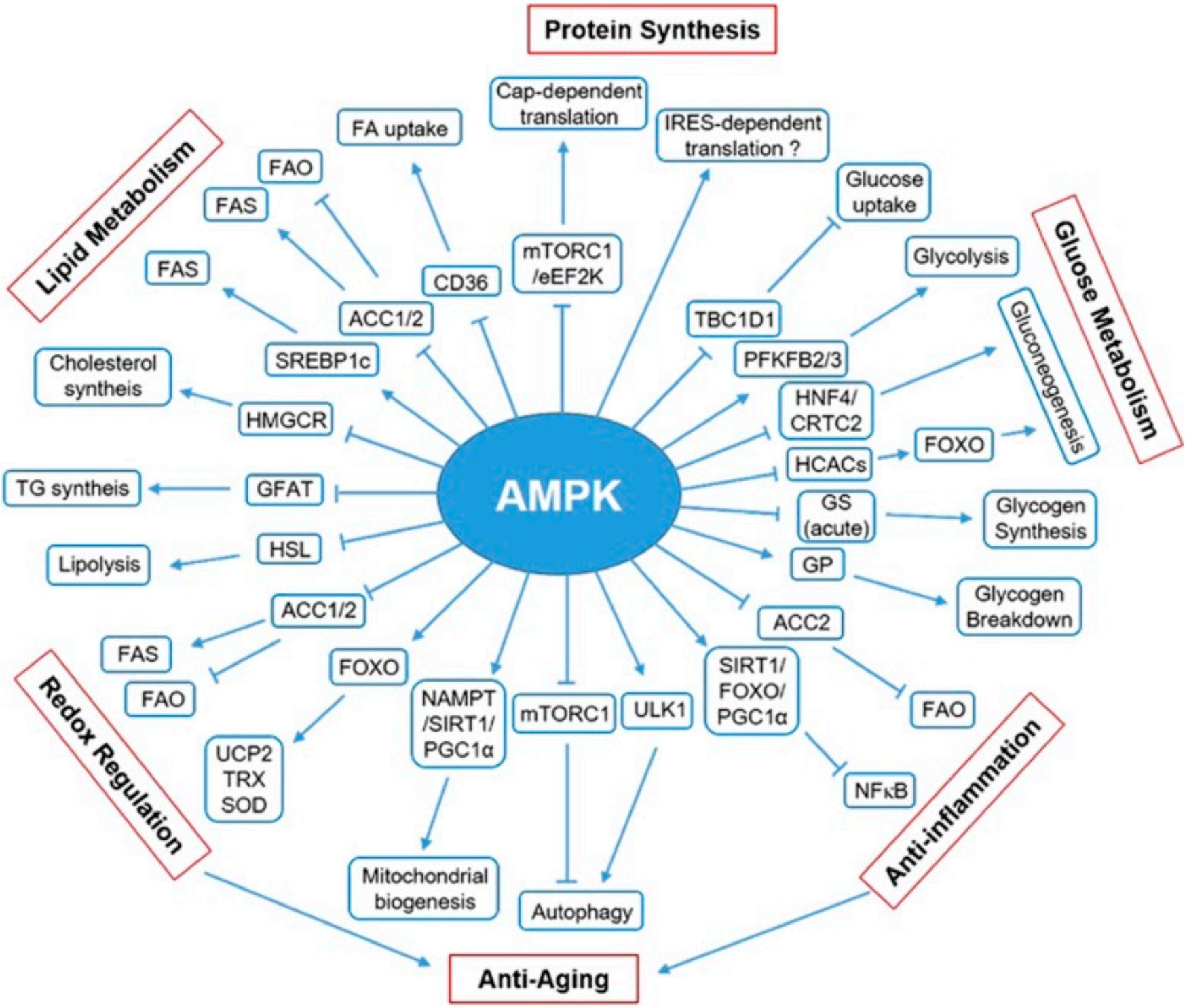

ATP
Energy from catabolism
Energy for cellular work
ADP + P i


'High-energy' phosphoanhydride bond
ATP
Condensation reaction
+ HO–P–OH
+ ΔG⁰
Glycolysis, TCA cycle, oxidative phosphorylation, photosynthesis
- ΔG⁰
Cellular work, biosynthesis
Phosphate transfer
HO–P–O–R
'High-energy' phosphoester bond
ADP

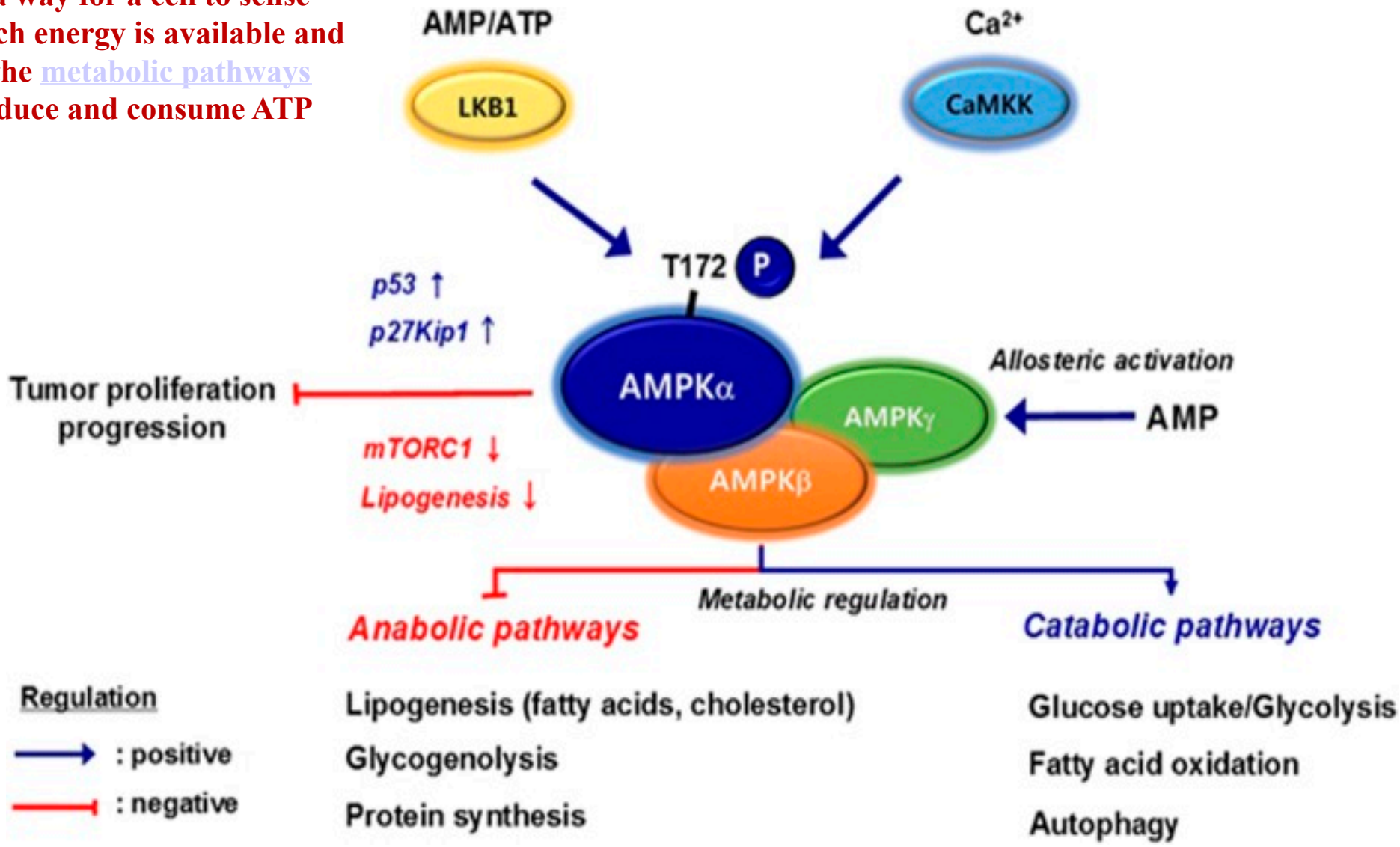

ATP consumption
METFORMIN
ATP
AMPK
AMP
Adenylate kinase
ADP
Catabolism

METFORMIN


Exercise, ischemia, temperature
Consuming less ATP
[ATP]↓, [AMP]↑
Producing more ATP
AMPK kinase
AMPK
ATP-consuming pathways
Fatty acid synthesis
Cholesterol synthesis
Glycogen synthesis
Protein synthesis
ATP-producing pathways
Glycolysis
β-Oxidation
Glucose uptake


Protein Synthesis
Cap-dependent translation
IRES-dependent translation ?
FA uptake
Lipid Metabolism
FAO
FAS
FAS
CD36
mTORC1 /eEF2K
Glucose uptake
Glycolysis
Gluose Metabolism
ACC1/2
TBC1D1
Gluconeogenesis
SREBP1c
PFKFB2/3
Cholesterol syntheis
HNF4/ CRTC2
HMGCR
FOXO
HCACs
AMPK
TG syntheis
GFAT
GS (acute)
Glycogen Synthesis
HSL
Lipolysis
GP
Glycogen Breakdown
ACC1/2
ACC2
FAS
FOXO
SIRT1/ FOXO/ PGC1α
FAO
NAMPT /SIRT1/ PGC1α
mTORC1
ULK1
FAO
Redox Regulation
UCP2 TRX SOD
NFκB
Anti-inflammation
Mitochondrial biogenesis
Autophagy
Anti-Aging

The ratio between ATP and AMP is used as a way for a cell to sense how much energy is available and control the metabolic pathways that produce and consume ATP



High cytosolic ATP/ADP ratio inhibit glycolysis

Lower cytosolic ATP/ADP ratios enhanced glycolysis

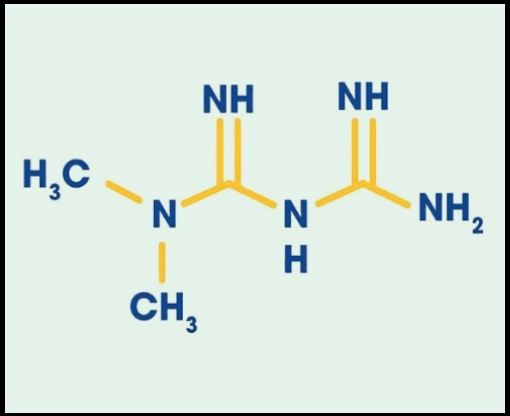
Metformin's pharmacokinetic :

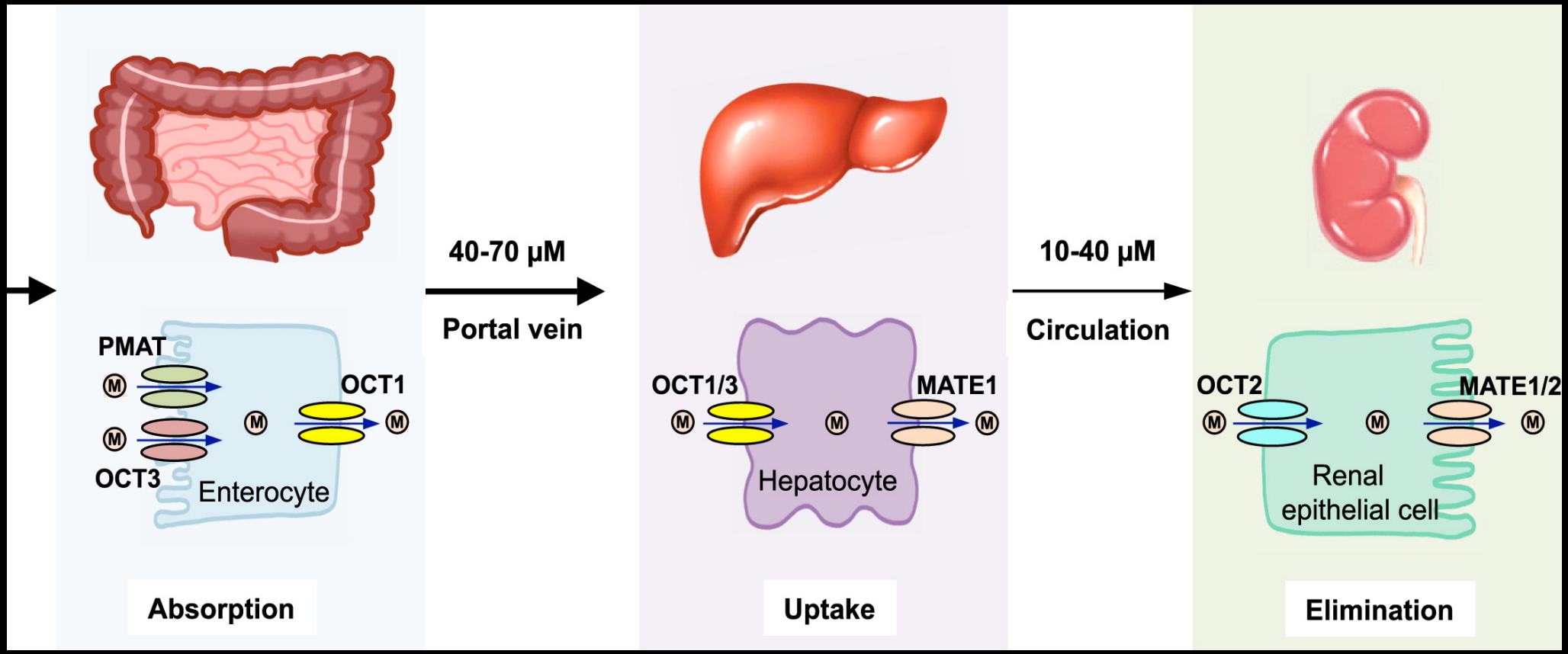
Metformin peak serum concentration approximately 2 h after ingestion. Steady-state levels are achieved within 24 to 48 h . The half-life ranges between 2.5 and 4.9 h . Metformin is excreted predominantly unchanged by the kidneys. The elimination half-life is approximately 17 h , with 90 % of the dose ingested being renally cleared within 24 h . The drug has high water solubility, minimal plasma protein binding, and a large volume of distribution, being concentrated primarily in the intestinal wall, salivary glands, kidneys, and liver .

Caratteristiche farmacocinetiche della Metformina

Dosaggio (g/die)	0,5 – 3
Biodisponibilità (%)	50 – 60
AUC (ore x mg/l)	8 – 12
C_{MAX} (mg/l)	1 – 1,5
T_{MAX} (ore)	2,5 – 3,5
$T_{1/2}$ (ore)	5 – 8
Clearance renale (1/ore)	25 – 30
Legame plasmaproteine	< 20%*

*La clearance renale è pari a 3,5 volte quella della creatinina





Transport of Metformin by :

OCT s 1 – 2 – 3 (organic cation transporters)

PMAT (plasma membrane monoamine transporter)

MATE s 1 – 2 (multidrugs and toxin extrusion antiporter)

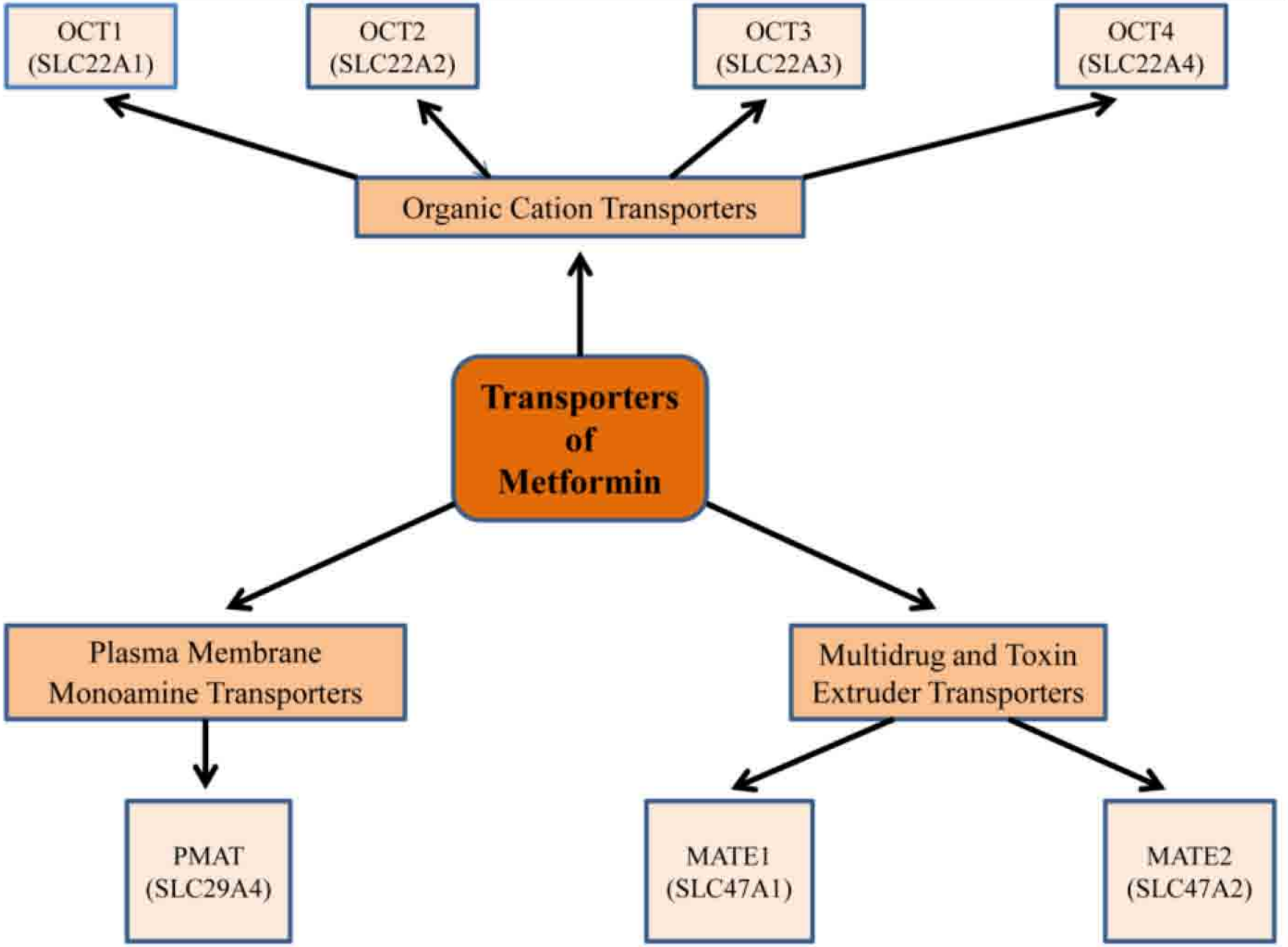
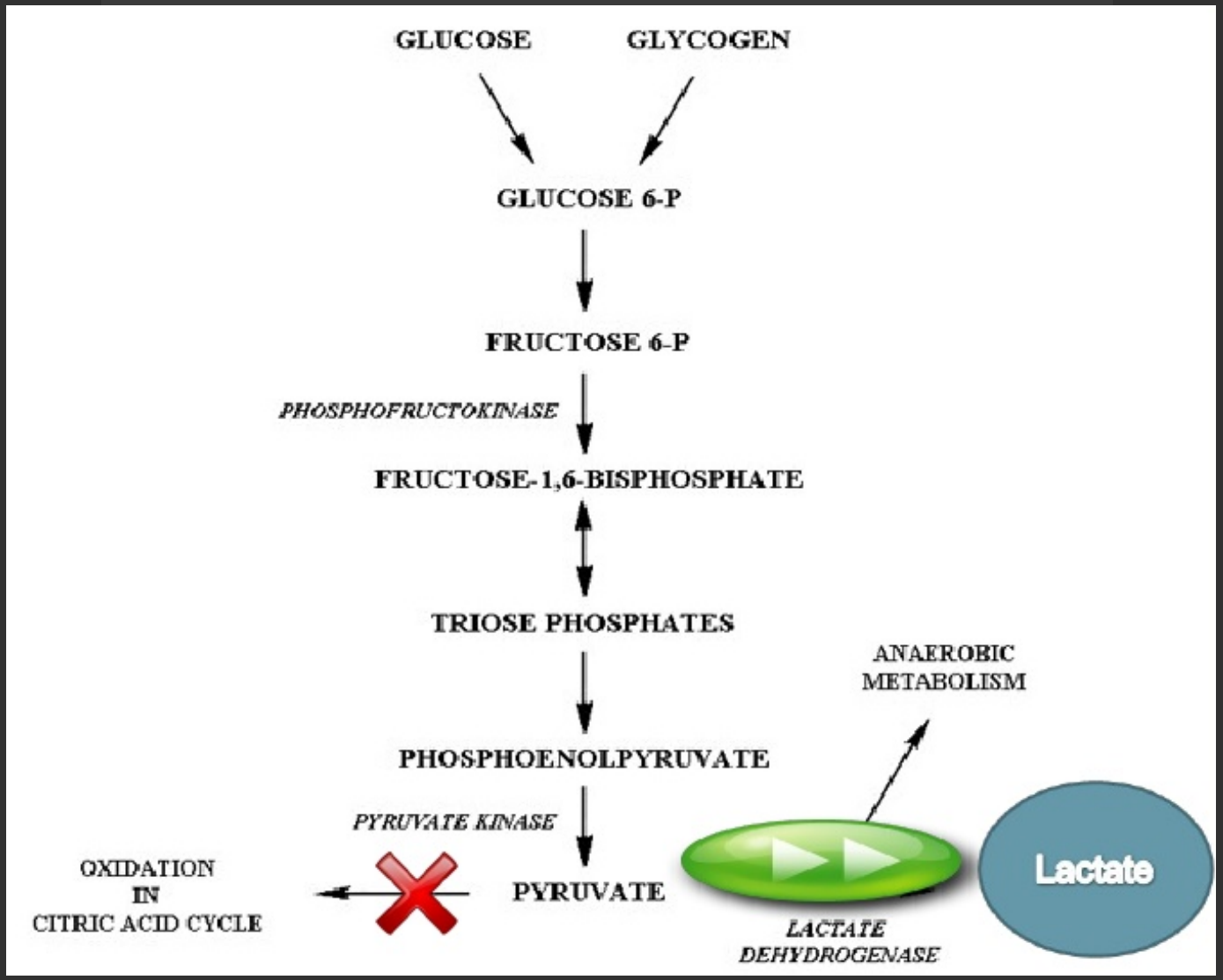


Figure 2. Metformin transporters: Isoforms and genes that demonstrate a role in metformin pharmacokinetics, pharmacogenetics, and thus have an impact on its pharmacological efficacy. Metformin is absorbed from the lumen of the gastrointestinal tract through plasma membrane monoamine transporter (PMAT). It requires the organic cation transporters (OCTs), located in the basolateral membrane of human hepatocytes, to be transported into the liver, thus decreasing hepatic glucose synthesis. The multidrug and toxin extrusion 1 and 2 (MATE1 and MATE2), located in the apical membrane of kidney proximal tubular cells, facilitate metformin excretion into urine. Genetic variation in transporter genes may alter transporter expression and functionality and thus metformin response.

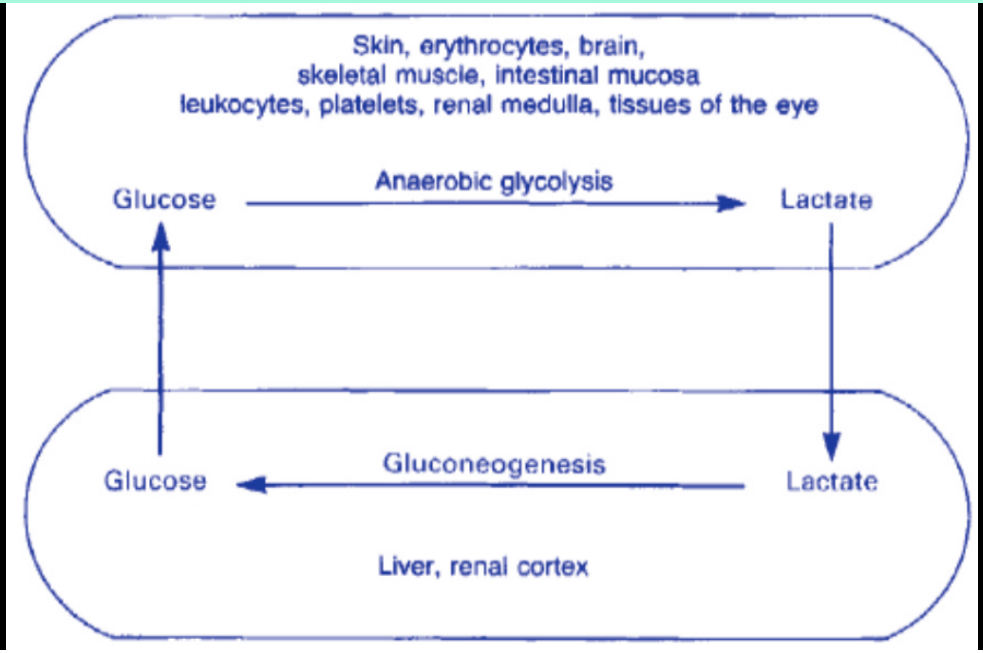
In the anaerobic state...

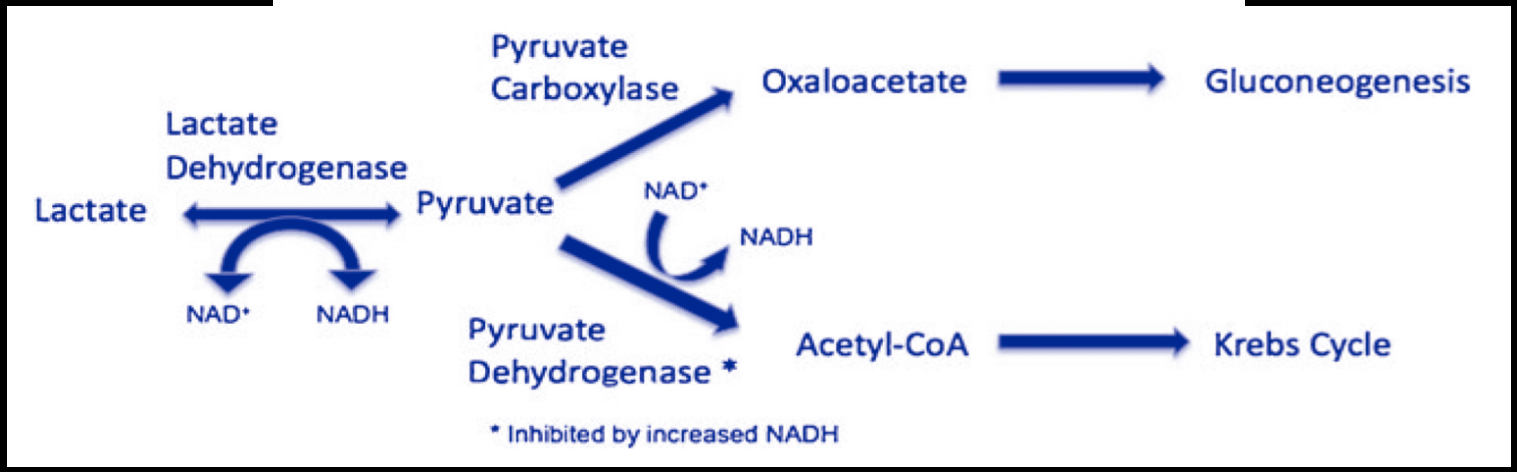


The hallmark of LA is the presence of tissue hypoxemia, which leads to enhanced anaerobic glycolysis and to increased lactic acid formation LA results from decreased availability of NAD caused by lack of oxygen.

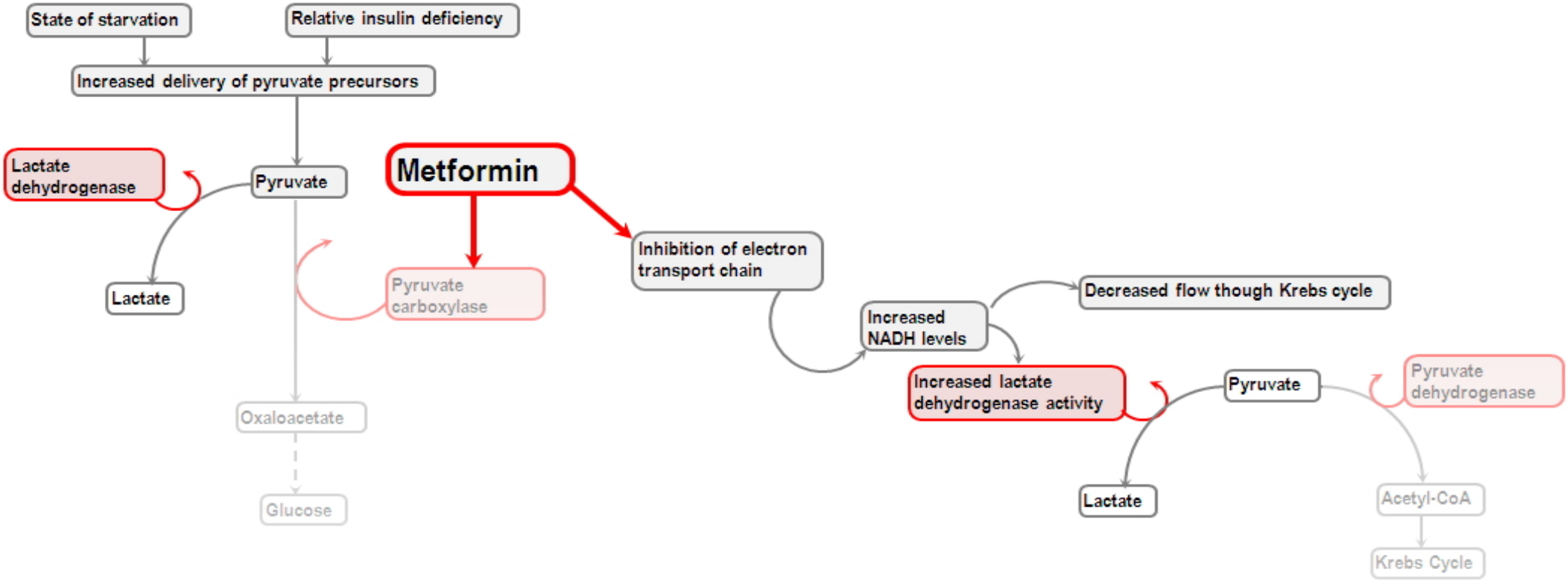
The normal blood lactic acid concentration is 1 mmol/l, and the pyruvic to lactic ratio is 10:1.

LACTATE ELIMINATION-CORI CYCLE

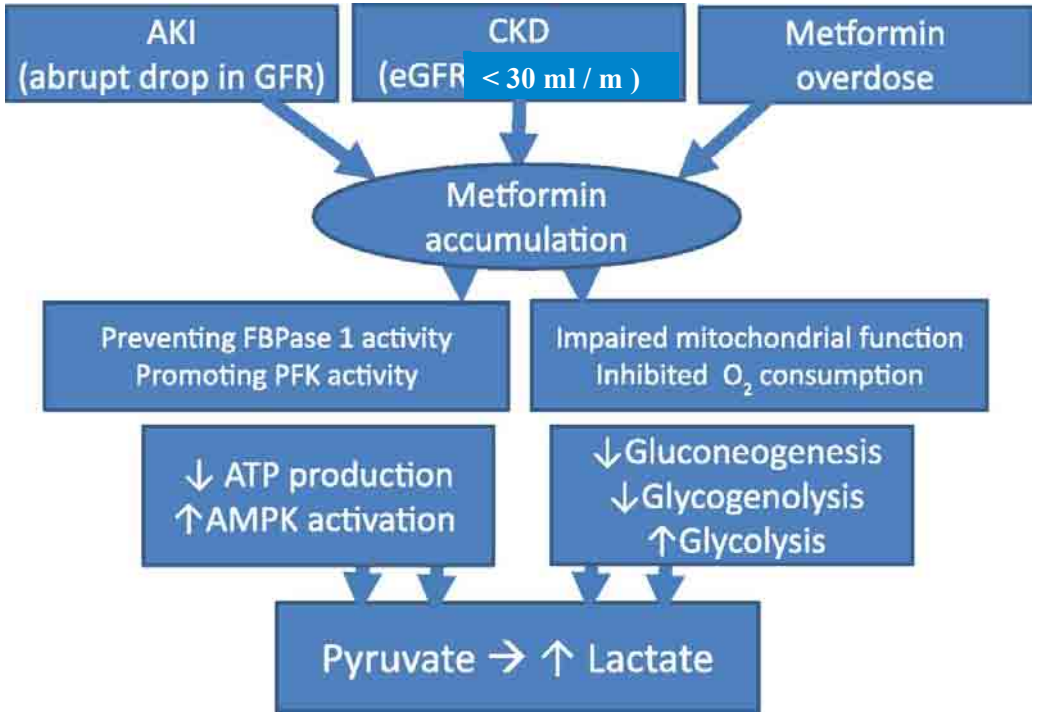


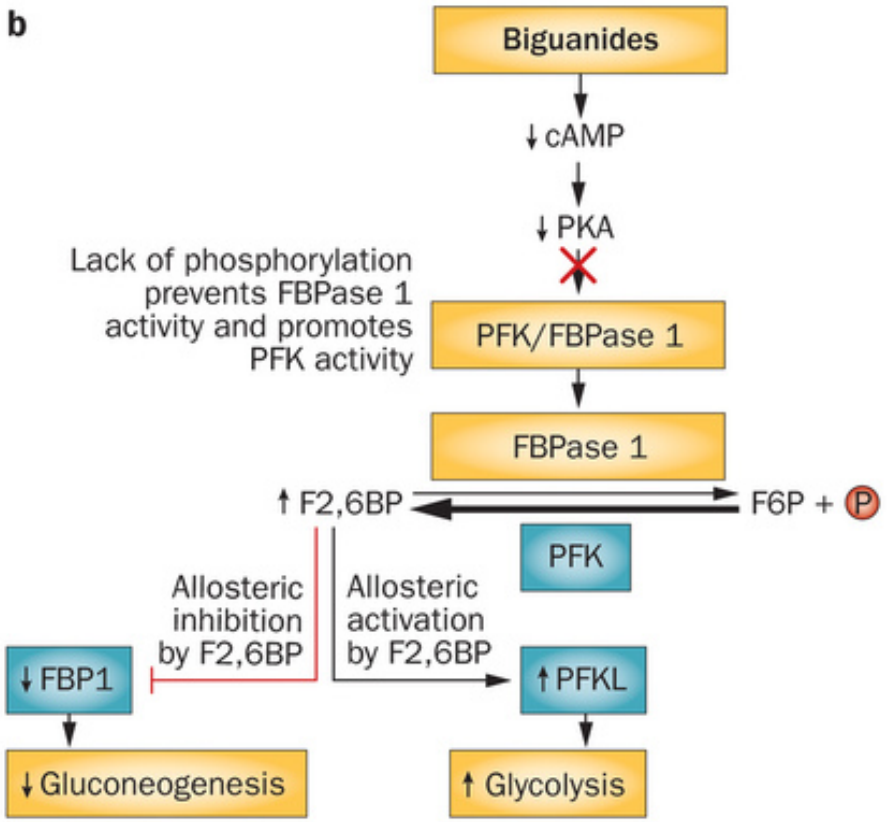


Under normal conditions, gluconeogenesis consumes pyruvate through pyruvate-carboxylase. Metformin inhibit pyruvate carboxylase, thereby causing pyruvate to accumulate . Increased amounts of pyruvate are then converted to lactate via lactate dehydrogenase. Conversely, metformin also inhibit conversion of lactate back to pyruvate for use in gluconeogenesis

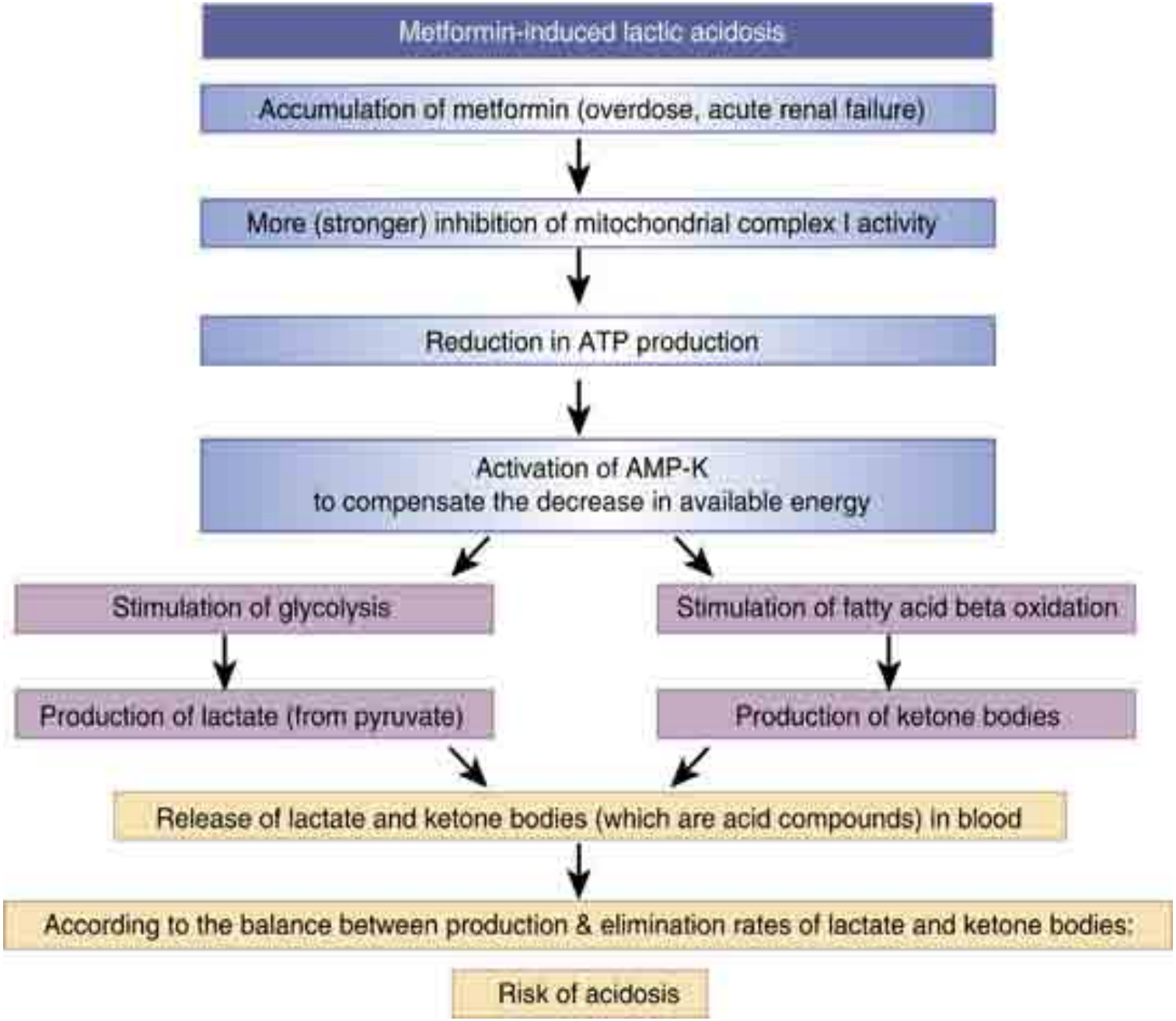

State of starvation
Relative insulin deficiency
Increased delivery of pyruvate precursors
Lactate dehydrogenase
Pyruvate
Lactate
Metformin
Pyruvate carboxylase
Oxaloacetate
Glucose
Inhibition of electron transport chain
Increased NADH levels
Decreased flow though Krebs cycle
Increased lactate dehydrogenase activity
Pyruvate
Pyruvate dehydrogenase
Lactate
Acetyl-CoA
Krebs Cycle

Mechanisms of lactic acidosis with use of metformin under renal impairment





. **The increase in PFK activity along with FBPase 1 activity inhibition suppresses gluconeogenesis and stimulates glycolysis. The subsequent decrease in hepatic energy status activates AMPK, a cellular metabolic sensor, leading to a reduction in hepatic gluconeogenesis and glycogenolysis while glycolysis is promoted and enhanced by impaired mitochondrial function with secondary inhibition of oxygen consumption, resulting in increased lactate generation and accumulation.** **FBPase 1, fructose-2,6-bisphosphatase 1 ; PFK, phosphorylated phosphofructokinase 2.**


Metformin-induced lactic acidosis
Accumulation of metformin (overdose, acute renal failure)
More (stronger) inhibition of mitochondrial complex I activity
Reduction in ATP production
Activation of AMP-K
to compensate the decrease in available energy
Stimulation of glycolysis
Stimulation of fatty acid beta oxidation
Production of lactate (from pyruvate)
Production of ketone bodies
Release of lactate and ketone bodies (which are acid compounds) in blood
According to the balance between production & elimination rates of lactate and ketone bodies:
Risk of acidosis

Lactate/pyruvate ratio

$$\text{Lactate/pyruvate} = K \times (\text{NADH/NAD}) \times H^{+}$$

- Hypoxia blocks oxidative phosphorylation
  - *prevents NADH re-oxidation to NAD*
  - *increases the NADH/NAD ratio*
  - **increases the lactate/pyruvate ratio**
  - *Normal ratio around 10:1*

Cardiogenic shock

L/P ratio 40:1
Consistent with hypoxia

Resuscitated septic shock

L/P ratio 14:1
Not consistent with hypoxia

When ↑ lactate = hypoperfusion

- Cardiogenic shock
- Haemorrhagic shock
- Septic shock *if*
  - Catecholamine resistant + depressed CI
  - Unresuscitated (see Rivers)

When ↑ lactate ≠ hypoperfusion

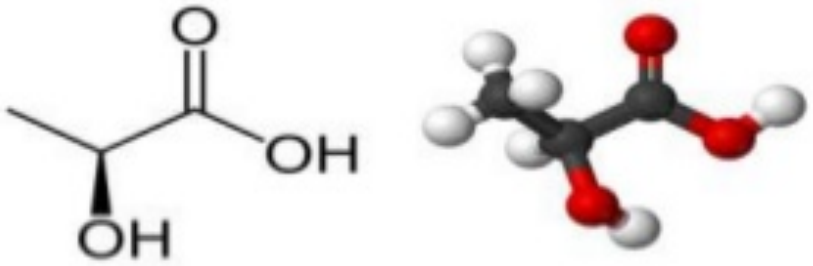
- Reduced lactate clearance
  - Conflicting data depending on technique and initial lactate
  - Possibly contributes to mild hyperlactataemia
  - Unlikely to play major role in cases where production is near normal
- Pyruvate dehydrogenase dysfunction
  - PDH shifts pyruvate to Kreb's cycle not to lactate
  - Sub-normal levels in muscle in sepsis
  - Function restored by dichloroacetate which also reduces lactate level
- Protein catabolism
  - AA's converted to pyruvate then lactate
- Inhibition of mitochondrial respiration
  - Sepsis, drugs e.g. metformin (rare), cyanide, antiretrovirals

Normal Lactate Metabolism

Daily production ~ 1400 mmol/day

Serum Level< 2 mmol/l

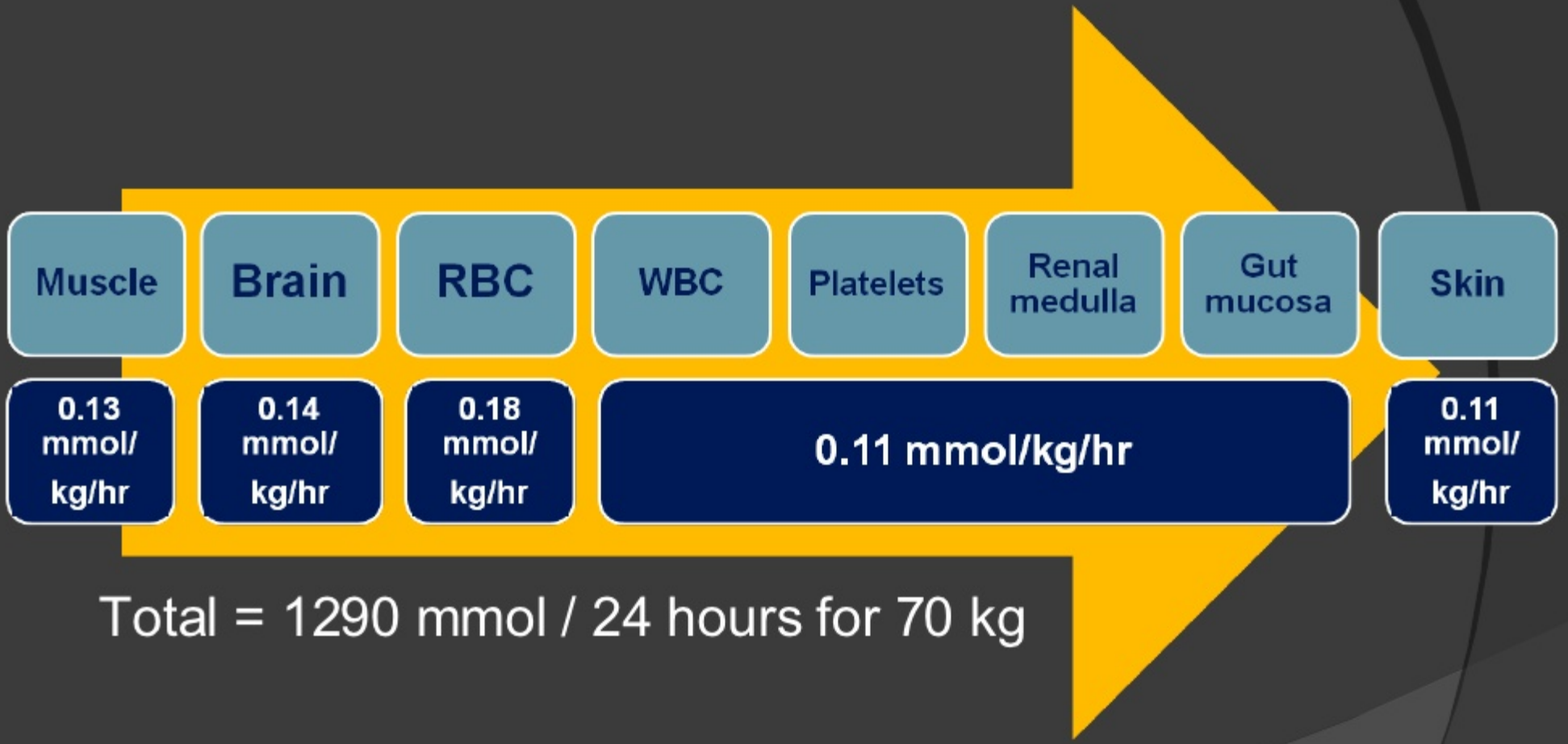
Metabolized in liver (70%) and kidney (30%) via Cori cycle



Lactate Metabolism

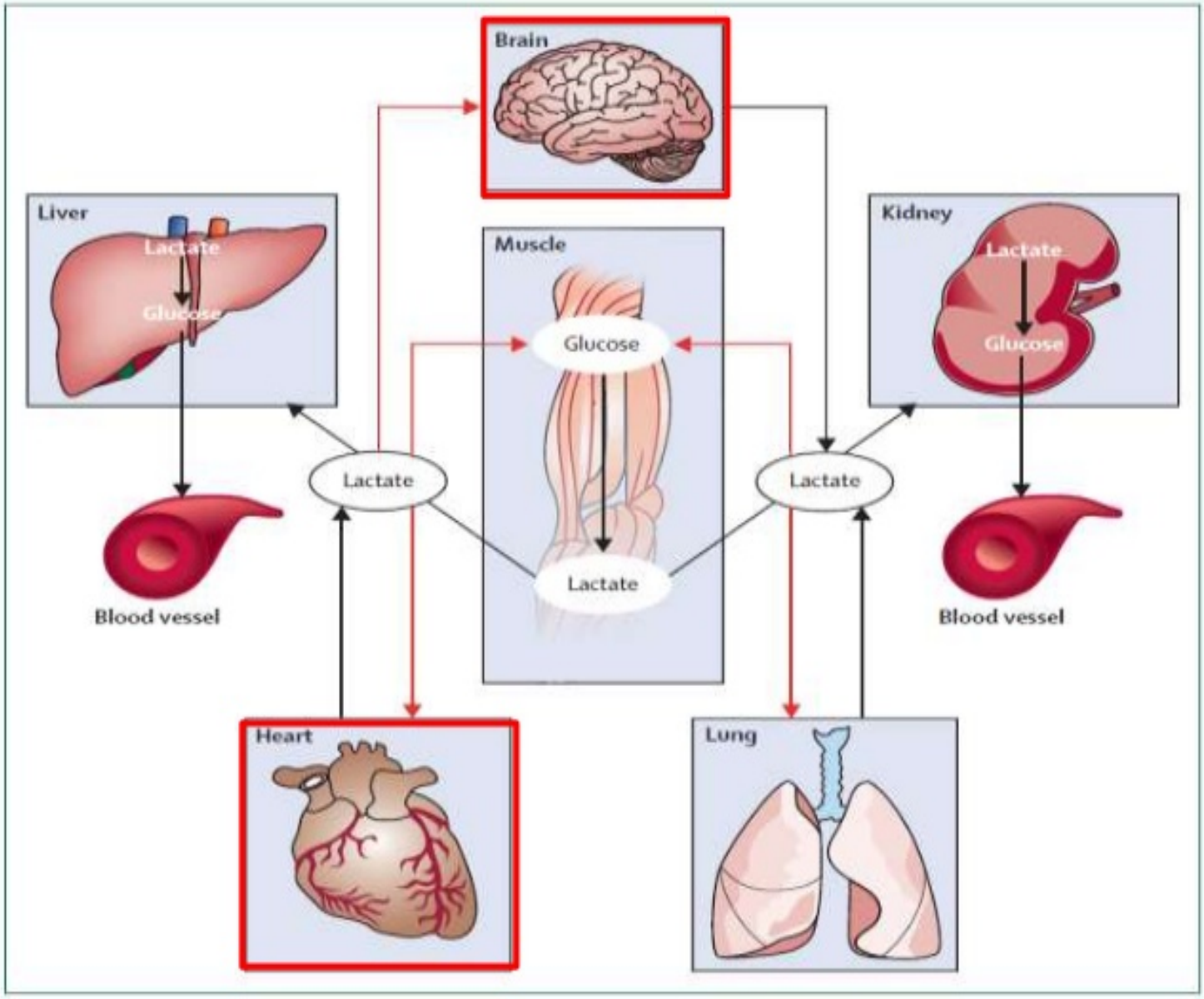
Excretion renal
threshold = 5-6 mmol/L

Basal lactate production



Total = 1290 mmol / 24 hours for 70 kg

Cell-to-cell lactate shuttle



LACTIC ACIDOSIS (LA)

DEFINITION

- Lactic acidosis is a pathological state diagnosed when the serum concentration of lactate or lactic acid is persistently 5mmol/L or greater and there is significant acidemia and serum pH< 7.35.

  (Normal lactate concentration is 2.0 mmol/L).

Classification of lactic acidosis

Type A Lactic Acidosis

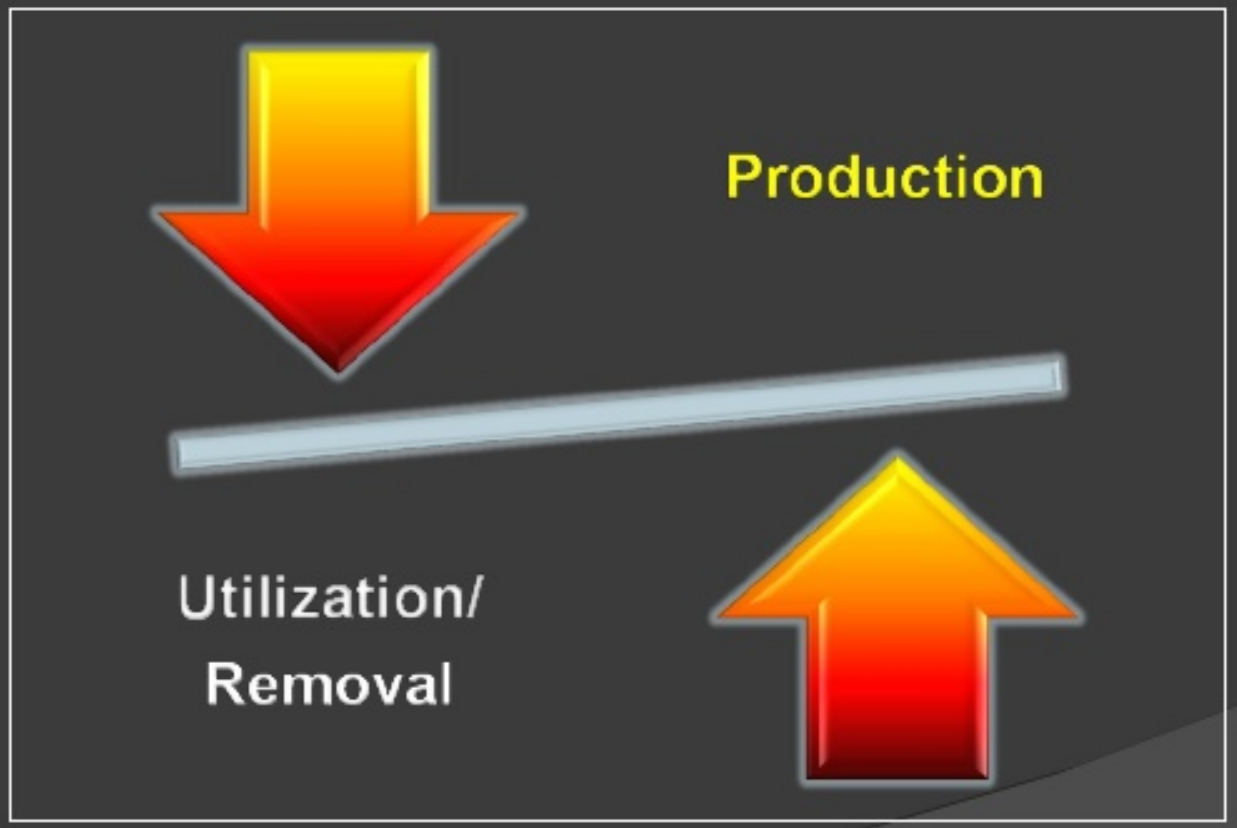
Associated with malperfusion / dysoxia

Type B Lactic Acidosis

In the absence of malperfusion / dysoxia

B1 – Disease states e.g. DKA, leukaemia, lymphoma, thiamine deficiency
B2 – Drugs e.g. metformin, cyanide, b agonists, HAART
B3 – Inborn errors of metabolism

Hyperlactataemia (> 2mmol/L)



Pathophysiological classification of lactic acidosis

HYPOXIC	NON-HYPOXIC
Ischemia	Delayed Clearance
Shock, severe anemia, cardiac arrest	Renal or hepatic dysfunction
Global Hypoxia	Pyruvate Dehydrogenase Dysfunction
Carbon monoxide poisoning	Sepsis, thiamine deficiency, catecholamine excess, alcoholic and diabetic ketoacidosis
Respiratory Failure	Uncoupling of Oxidative Phosphorylation
Severe asthma, COPD, asphyxia	Cyanide, salicylates, methanol & ethylene glycol metabolites, anti-retroviral drugs, valproic acid, biguanides, INH
Regional Hypoperfusion	Accelerated Aerobic Glycolysis
Limb or mesenteric ischemia	Increased effort, sepsis, seizures, large fructose loads, malignancies

PATHOPHYSIOLOGY OF LACTIC ACIDOSIS

Increased lactic acid generation

- Reduced oxygen delivery (hypotension, shock, hypoxemia, anemia, carbon monoxide poisoning)
- Increased tissue demand (exercise, seizures, sepsis)

PATHOPHYSIOLOGY OF LACTIC ACIDOSIS

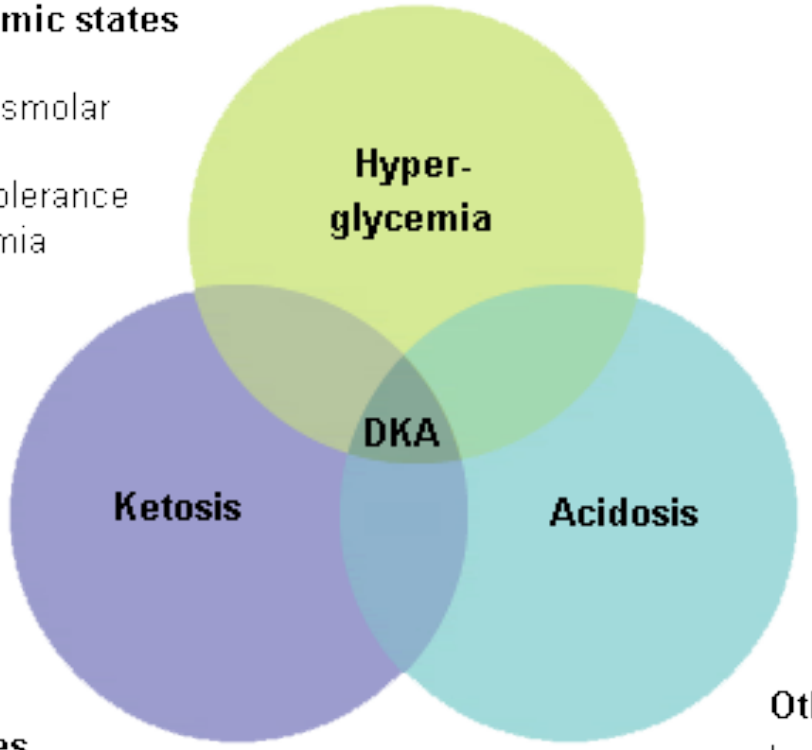
Decreased lactic acid utilization

- Liver dysfunction
- Reduced perfusion
- cellular dysfunction
- Enzymatic or cofactor deficiency: Inherited, Acquired

Combination

- Malignancy, diabetes, alcohol, other drugs

Other hyperglycemic states
Diabetes mellitus
Non-ketotic hyperosmolar coma
Impaired glucose tolerance
Stress hyperglycemia

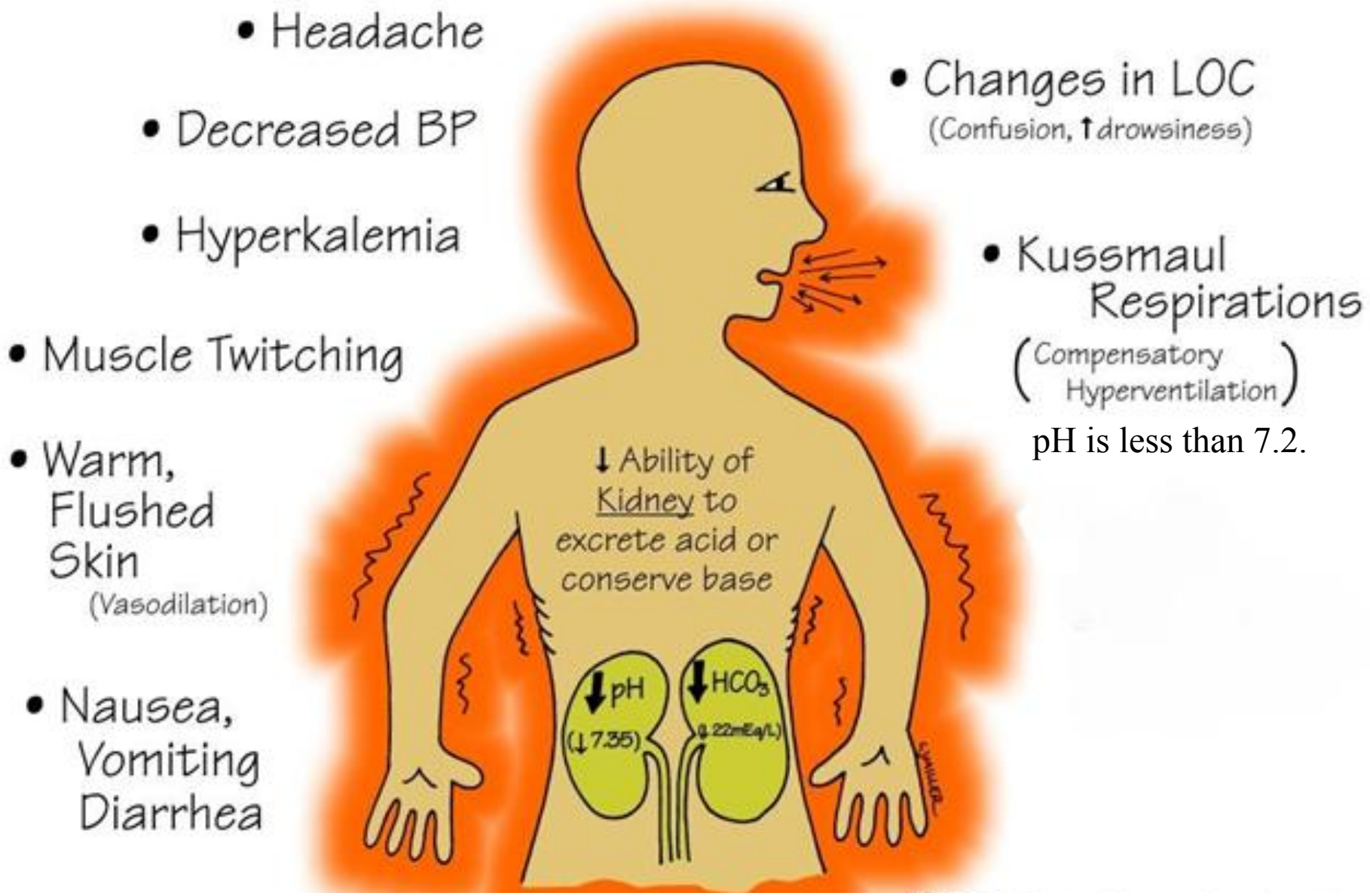


Other ketotic states
Ketotic hypoglycemia
Alcoholic ketosis
Starvation ketosis

Other metabolic acidotic states
Lactic acidosis
Hyperchloremic acidosis
Salicylism
Uremic acidosis
Drug-induced acidosis

Category	Lactate mmol/L (mg/dl)	Symptoms of Lactic Acidemia*	pH (if measured)
Low-Level Lactic Acidemia	2-5 (18-45)	Absent or Mild	≥7.30
Moderate-Level Lactic Acidemia	5-10 (45-90)	Absent or Mild	≥7.30
Severe-Level Lactic Acidemia	5-10 (45-90)	Present	≥7.30
	>10 (>90)	Absent or Present	
Lactic Acidosis	>2 (>18)	Absent or Present	<7.30

v.n. pH 7.35 - 7.45
v.n. HCO3 21–30 mEq/L



Blood glucose level is not high - Glucosuria is absent

Common Symptoms of Lactic Acidosis

- Weakness
- Fatigue
- Increased breathing rate
- Increased heart rate
- Mental status changes
- Decreased ability to recover from exercise
- Nausea and vomiting
- Abdominal pain

Common Causes

- Chronic alcohol use
- Heart failure
- Cancer
- Seizures
- Liver failure
- Prolonged lack of oxygen
- Low blood sugar
- Prolonged exercise can lead to lactic acid buildup
- Mitochondrial dysfunction
- Poor circulation
- Diabetes
- Metformin use

EFFECTS ON CELLULAR FUNCTION

- The cellular dysfunction in hyperlactatemia is complex.
- Tissue hypoxia, if present, is a major factor.
- If the cellular milieu is also severely acidic, cellular dysfunction is likely to be exacerbated.
- Decrease cardiac contractility, cardiac output, blood pressure, and tissue perfusion.
- Sensitize the myocardium to cardiac arrhythmias; and can attenuate the cardiovascular responsiveness to catecholamines.

HYPERLACTATAEMIA

- Lactate production exceeds lactate consumption.
- Addition of a number of protons equivalent to the number of excess lactate ions
- Coexisting acidemia contributes to decreased lactate removal by the liver
- Severe hypoxia and acidemia can convert the liver into a net lactate-producing organ.

Anion gap is the difference in the measured cations (positively charged ions) and the measured anions (negatively charged ions) in serum, plasma, or urine

If the gap is greater than normal, then high anion gap, lactic acidosis is diagnosed.

Normal Anion Gap (3–11 mEq/L)

BENTHAM SCIENCE

Current Drug Metabolism

Pharmacogenetic Variation and Metformin Response

Current Drug Metabolism, 14(10): 1070-1082.

Author(s): Suning Chen, Jie Zhou, Miaomiao Xi, Yanyan Jia, Yan Wong, Jinyi Zhao, Likun Ding, Jian Zhang and Aidong Wen.

Affiliation: Department of Pharmacy, Xijing Hospital, and The State Key Laboratory of Cancer Biology and The Department of Biochemistry and Molecular Biology, The Fourth Military Medical University, Xi'an, Shaanxi Province, 710032, People's Republic of China.

Abstract

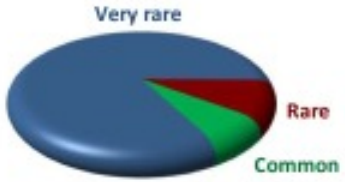
Diabetes is a major health problem worldwide, and metformin, a traditional oral anti-hyperglycemic drug, is now believed to be the most widely prescribed antidiabetic drug. Metformin acts primarily by inhibiting hepatic glucose production and improving insulin sensitivity. Metformin is absorbed predominately by the small intestine and excreted in an unaltered form in the urine. The pharmacokinetics of metformin is primarily determined by membrane transporters, including the plasma membrane monoamine transporter (PMAT), the organic cation transporters (OCTs), the multidrug and toxin extrusion (MATE) transporters, and the critical protein kinase AMPactivated protein kinase (AMPK). PMAT may play a role in the uptake of metformin from the gastrointestinal tract, while OCTs mediate the intestinal absorption, hepatic uptake, and renal excretion of metformin. MATEs are believed to contribute to the hepatic and renal excretion of the drug. The pharmacologic effects of metformin are primarily exerted in the liver, at least partly via the activation of AMPK and the subsequent inhibition of gluconeogenesis. A considerable amount of pharmacogenetic research has demonstrated that genetic variation is one of the major factors affecting metformin response. Moreover, it has become increasingly clear that membrane transporters are important determinants of the pharmacokinetics of metformin. In this review, we will discuss the genetic variants of major transporters that purportedly determine the pharmacokinetics of metformin in terms of drug bioavailability, distribution, and excretion, such as PMAT, OCTs, and MATEs. Understanding how genetic variation affects metformin response will help promote more effective use of the drug for the treatment of type 2 diabetes (T2D).

Keywords: AMPK, MATE, metformin, OCT, pharmacogenetic, SNP, T2D.

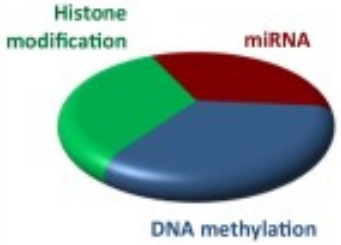
Sources of interindividual variability in drug response

Non-genetic factors

Genetic variation

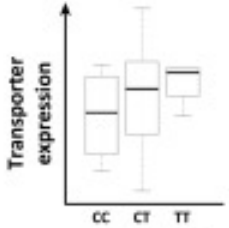


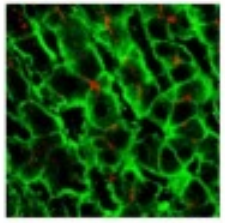
Epigenetics



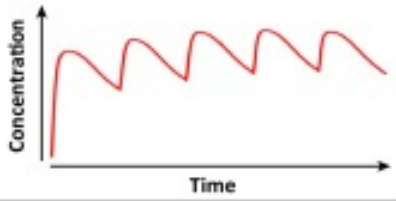
Regulation

Transporter function and expression





Pharmacokinetics



Drug response

- Drug efficacy
- Drug resistance
- Drug toxicity

Effect of Genetic Variation in the Organic Cation Transporter 1, OCT1, on Metformin Pharmacokinetics

Y Shu[1,5], **C Brown**[1], **RA Castro**[1], **RJ Shi**[1], **ET Lin**[1], **RP Owen**[1], **SA Sheardown**[2], **L Yue**[3], **EG Burchard**[1], **CM Brett**[4], and **KM Giacomini**[1]

[1] Department of Biopharmaceutical Sciences, University of California San Francisco, San Francisco, California, USA

[2] GlaxoSmithKline, New Frontiers Science Park, Harlow, UK

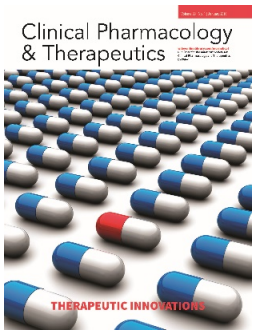
[3] GlaxoSmithKline, Collegeville, Pennsylvania, USA

[4] Department of Anesthesiology, University of California San Francisco, San Francisco, California, USA

Abstract

The goal of this study was to determine the effects of genetic variation in the organic cation transporter 1, OCT1, on the pharmacokinetics of the antidiabetic drug, metformin. Twenty healthy volunteers with known OCT1 genotype agreed to participate in the study. Each subject received two oral doses of metformin followed by collection of blood and urine samples. OCT1 genotypes had a significant ($P<0.05$) effect on metformin pharmacokinetics, with a higher area under the plasma concentration–time curve (AUC), higher maximal plasma concentration (C_{max}), and lower oral volume of distribution (V/F) in the individuals carrying a reduced function OCT1 allele (R61C, G401S, 420del, or G465R). The effect of OCT1 on metformin pharmacokinetics in mice was less than in humans possibly reflecting species differences in hepatic expression level of the transporter. Our studies suggest that OCT1 genotype is a determinant of metformin pharmacokinetics.

Clin Pharmacol Ther. 2008 February ; 83(2): 273–280



Effect of Genetic Variation in the Organic Cation Transporter 1, OCT1, on Metformin Pharmacokinetics

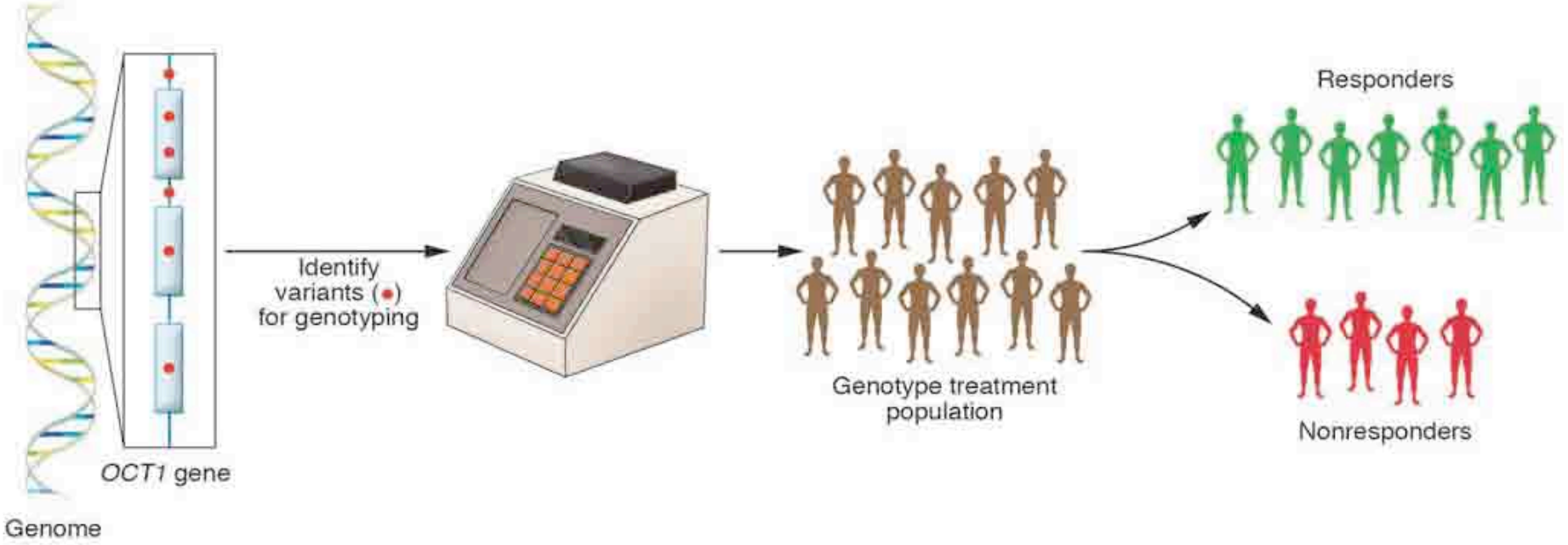
Y Shu[1,5], **C Brown**[1], **RA Castro**[1], **RJ Shi**[1], **ET Lin**[1], **RP Owen**[1], **SA Sheardown**[2], **L Yue**[3], **EG Burchard**[1], **CM Brett**[4], and **KM Giacomini**[1]

[1] Department of Biopharmaceutical Sciences, University of California San Francisco, San Francisco, California, USA

[2] GlaxoSmithKline, New Frontiers Science Park, Harlow, UK

[3] GlaxoSmithKline, Collegeville, Pennsylvania, USA

[4] Department of Anesthesiology, University of California San Francisco, San Francisco, California, USA



Clin Pharmacol Ther. 2008 February ; 83(2): 273–280

Effect of Genetic Variation in the Organic Cation Transporter 1, OCT1, on Metformin Pharmacokinetics

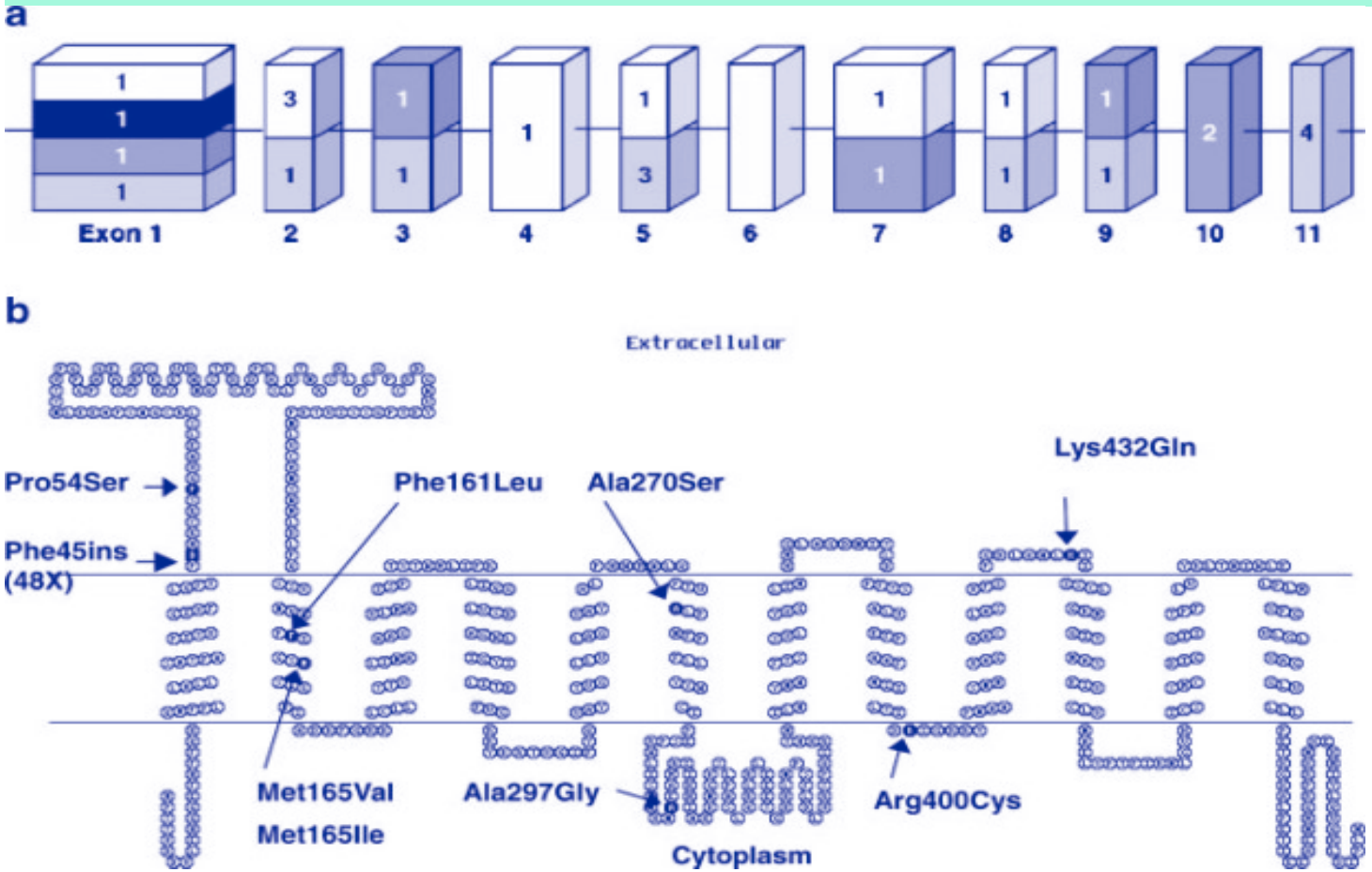
Y Shu[1,5], **C Brown**[1], **RA Castro**[1], **RJ Shi**[1], **ET Lin**[1], **RP Owen**[1], **SA Sheardown**[2], **L Yue**[3], **EG Burchard**[1], **CM Brett**[4], and **KM Giacomini**[1]

[1] Department of Biopharmaceutical Sciences, University of California San Francisco, San Francisco, California, USA

[2] GlaxoSmithKline, New Frontiers Science Park, Harlow, UK

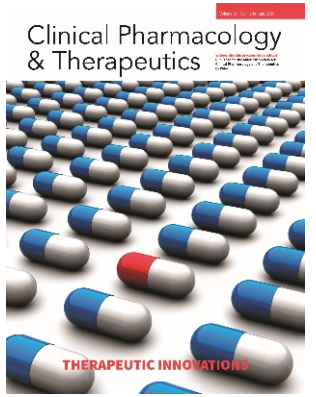
[3] GlaxoSmithKline, Collegeville, Pennsylvania, USA

[4] Department of Anesthesiology, University of California San Francisco, San Francisco, California, USA



Clin Pharmacol Ther. 2008 February ; 83(2): 273–280

Clin Pharmacol Ther. 2008 February ; 83(2): 273–280



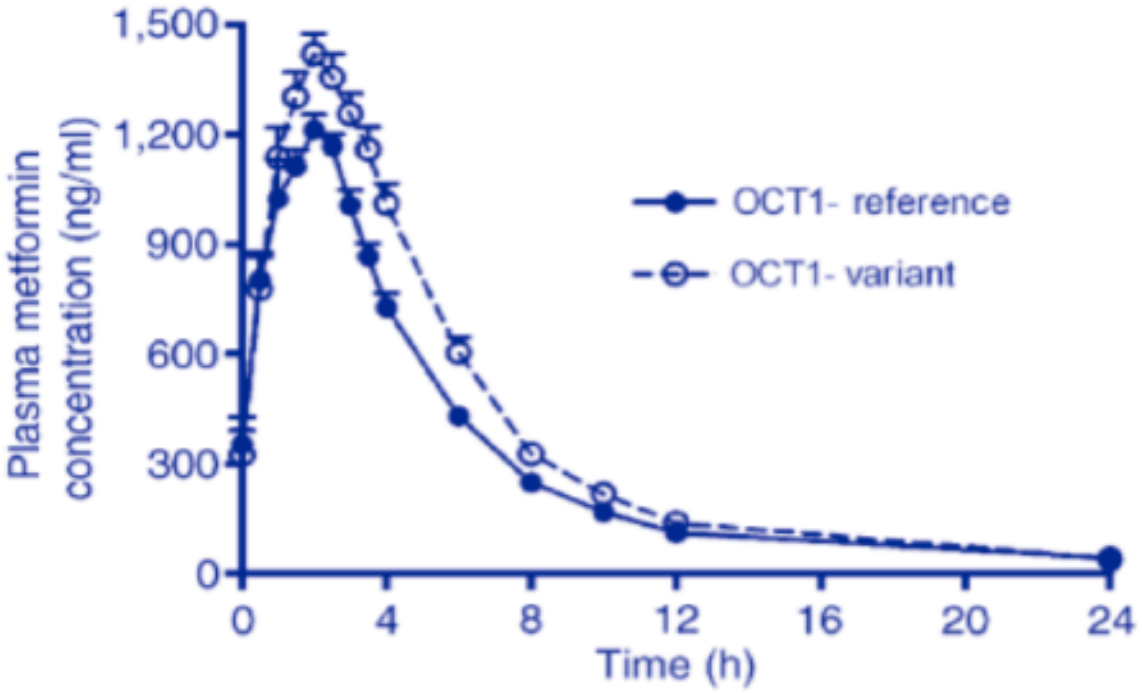


Figure 1.

The plasma concentration-time curves of metformin after oral administration in healthy individuals who carry an OCT1-variant allele (n=12) and those who carry only OCT1-reference alleles (n=8). The individuals were given two doses of metformin. The first dose of 850mg was given at 1800hours on study day 1 and the second dose of 1,000mg at 0600hours on study day 2. Blood samples for the pharmacokinetic analysis were drawn up to 24h after the second dose. The plasma metformin concentration-time curves after the second dose are shown. Data represent mean±SE.

The AAPS Journal (© 2013)
DOI: 10.1208/s12248-013-9465-7

Springer | The AAPS Journal | The AAPS Journal

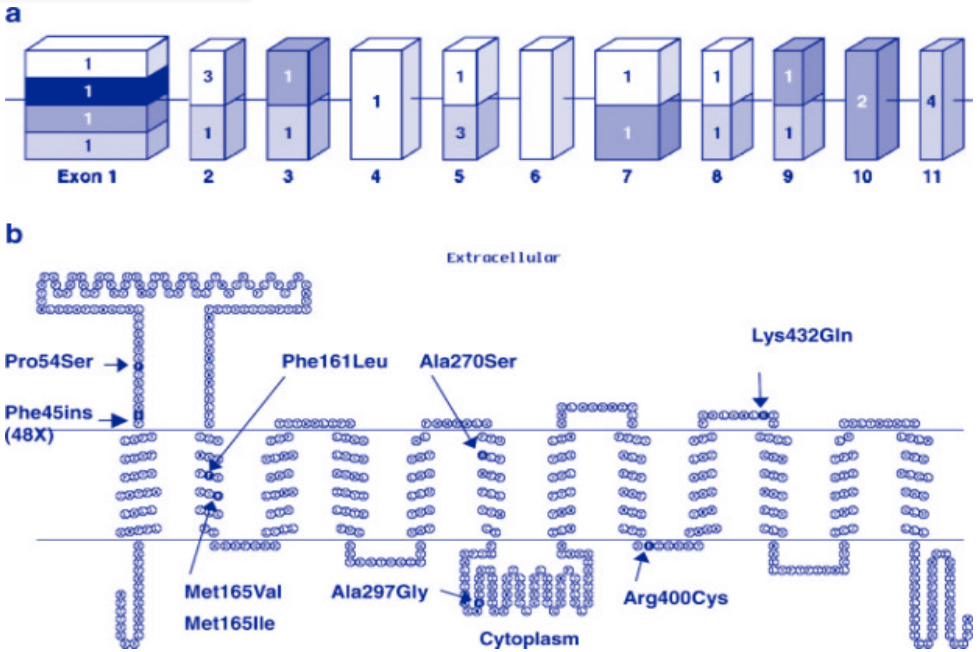
Review Article
Theme: Kidney Transporters: Importance in Clearance, Disease, and Drug-Drug Interactions
Guest Editors: Marilyn Morris and Colin Brown

Organic Cation Transporter OCTs (SLC22) and MATEs (SLC47) in the Human Kidney

Table II

Comparison of Affinity for Human MATE1, MATE2-K, and OCT2 of Organic Cations and Various Drugs

Compound	Affinity (Ki) for transporters (μM)			Plasma concentration (μM)
	MATE1	MATE2-K	OCT2	
Organic cation				
TEA	380 (km)[a]	760 (km)[a]	48–270	
MPP	100 (km)[a]	110 (km)[a]	19–78	
Guanidine	2,100	4,200	3,030	
Antidiabetic drug				
Metformin	667	6,516	339–1,700	4.1
Phenformin	16 (IC_{50})[b]	73 (IC_{50})[b]	65	Not used



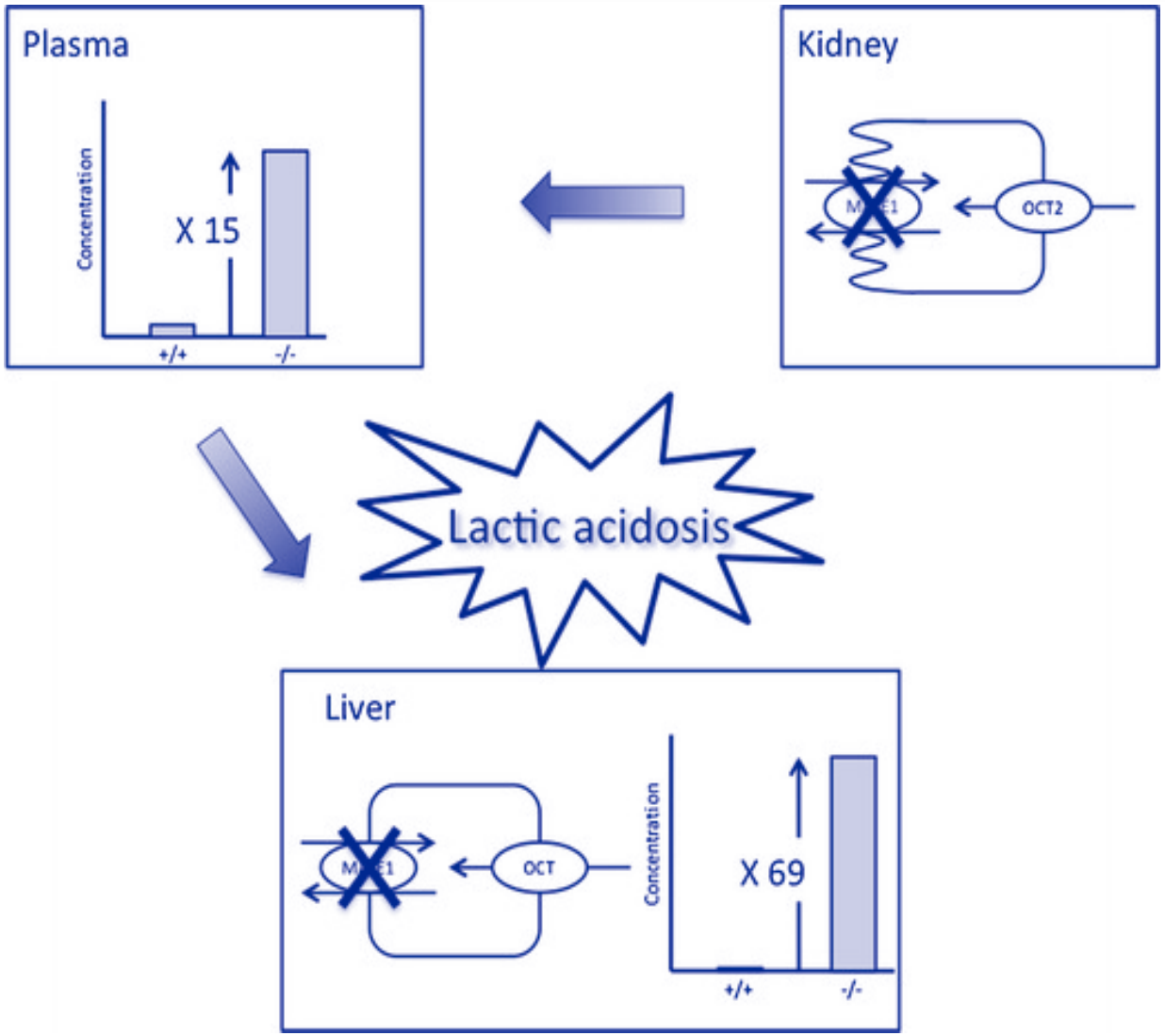
The AAPS Journal (© 2013)
DOI: 10.1208/s12248-013-9465-7

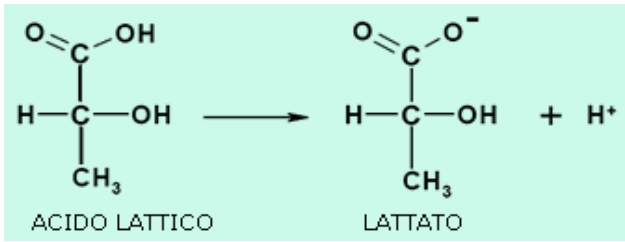
Springer | The AAPS Journal | The AAPS Journal

Review Article

Theme: Kidney Transporters: Importance in Clearance, Disease, and Drug-Drug Interactions
Guest Editors: Marilyn Morris and Colin Brown

Organic Cation Transporter OCTs (SLC22) and MATEs (SLC47) in the Human Kidney





The influence of dysfunctional MATE1 on pharmacokinetics and toxicodynamics of metformin. Plasma concentrations of metformin are increased in Slc47a1 knockout mice, compared with their wild-type counterparts. This increased concentration is due to the loss of urinary and biliary efflux of metformin. Therefore, impaired functioning of MATEs synergistically increases metformin accumulation in the liver and blood lactate levels resulting in the development of lactic acidosis

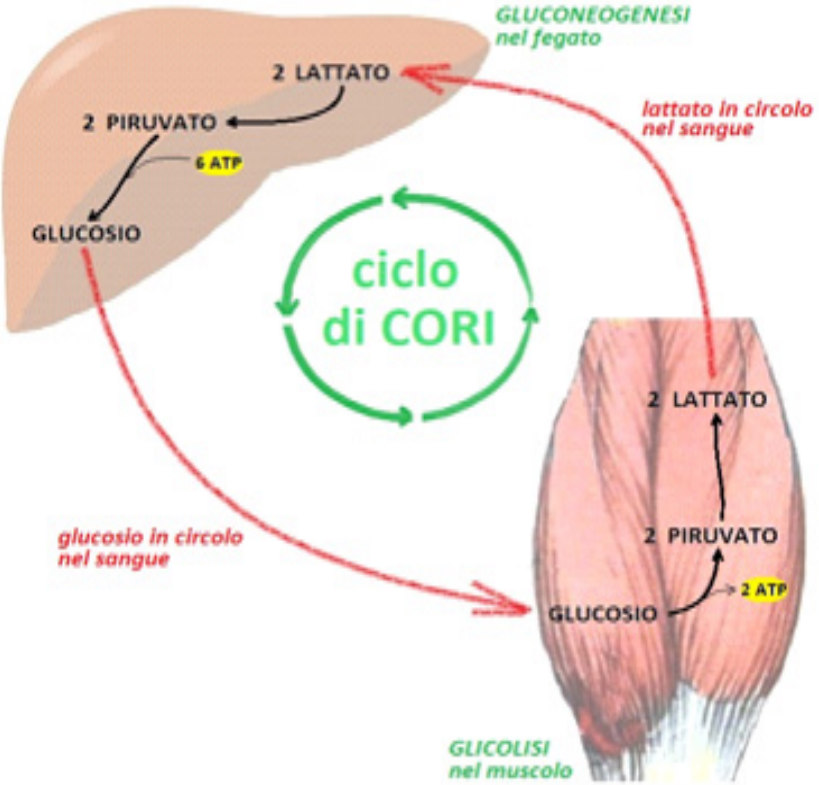
The AAPS Journal (© 2013)
DOI: 10.1208/s12248-013-9465-7

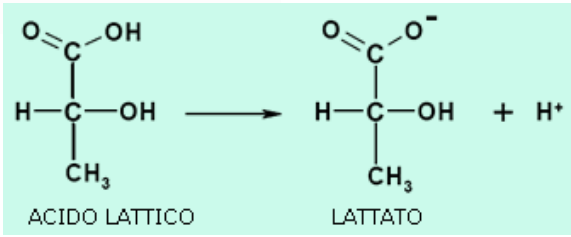
Springer | The AAPS Journal | The AAPS Journal

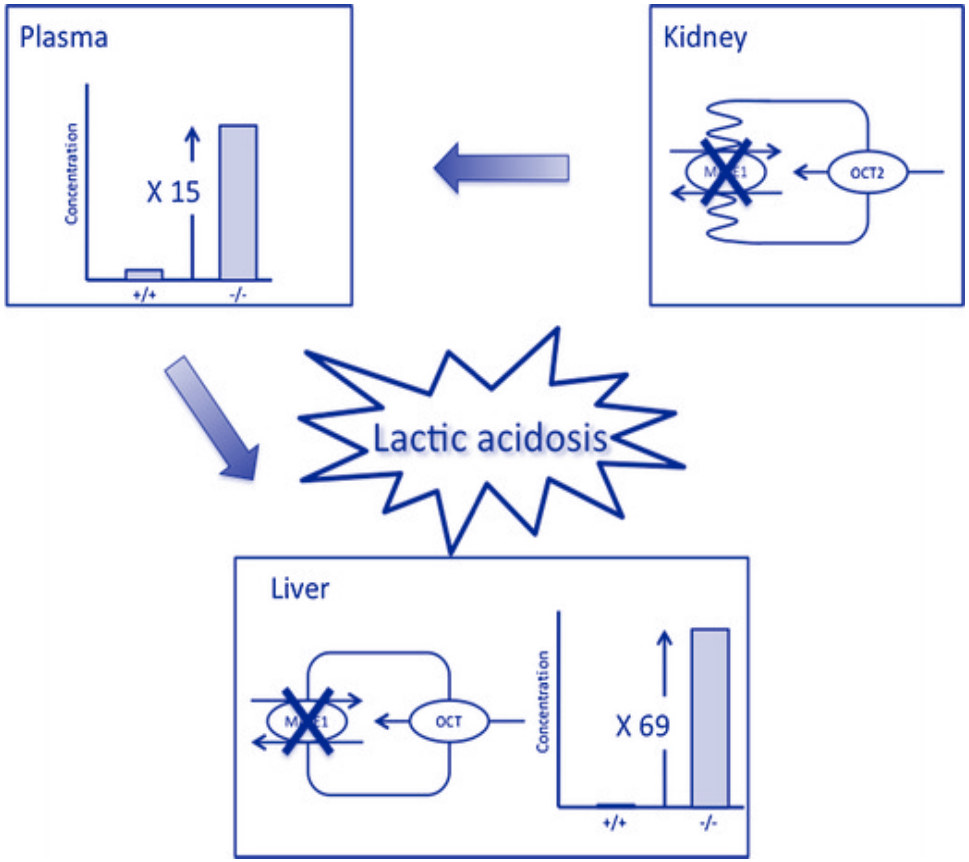
Review Article

Theme: Kidney Transporters: Importance in Clearance, Disease, and Drug-Drug Interactions
Guest Editors: Marilyn Morris and Colin Brown

Organic Cation Transporter OCTs (SLC22) and MATEs (SLC47) in the Human Kidney







Treatment of lactic acidosis

1. Treatment underlying disease

2. Sodium bicarbonate: may worsen oxygen delivery, increase lactate production (especially when hypoxia=>induce glycolysis), decrease portal vein flow

- **The surviving sepsis campaign recommended** hold sodium bicarbonate unless profound lactic acidosis and acidemia (arterial pH less than 7.1 and serum bicarbonate 6 meq/L or less).

3. Hemodialysis / CRRT

Hemodialysis

- Dialysis may be a useful mode of therapy when severe lactic acidosis exists in conjunction with renal failure or congestive heart failure.
- Dialysis would allow bicarbonate infusion without precipitating or worsening fluid overload. Therefore, dialysis would correct acidosis by restoring the buffer pool.

Guo PY, Storsley LJ, Finkle SN. Severe lactic acidosis treated with prolonged hemodialysis: recovery after massive overdoses of metformin. *Semin Dial*. 2006;19(1):80-3.

Table 1: Optimal physicochemical properties for extracorporeal removal of drugs.

	Hemodialysis	Hemofiltration	Hemoperfusion
Molecular weight	<500 Da	<40 KDa	<40 KDa
Protein binding	Low (<80%)	Low	Low or high
Volume of distribution	<1 L/Kg	<1 L/Kg	<1 L/Kg
Solubility	Water	Water	Water or lipid
Endogenous clearance	<4 mL/Kg/min	<4 mL/Kg/min	<4 mL/Kg/min

Table 3: Summary of pharmacological and clearance properties of some pharmacological substances*.

Substance	Molecular weight (daltons)	Protein binding (%)	Volume of distribution (L/kg)	Metabolism and excretion (%)	Clearance without hemodialysis (mL/min)	Clearance with hemodialysis (mL/min)
Metformin	~129	Minimal	~1.1	>90 renal	~7	Up to 170

The pharmacokinetics of metformin are generally favorable for hemodialysis and extracorporeal elimination such as a low molecular weight and minimal protein binding except with high volume of distribution . The low molecular weight, negligible plasma protein binding, and rapid transport of drug from cells to serum allow for drug removal by hemodialysis despite a relatively large VD (Volume Distribution).

Table 1: Optimal physicochemical properties for extracorporeal removal of drugs.

	Hemodialysis	Hemofiltration	Hemoperfusion
Molecular weight	<500 Da	<40 KDa	<40 KDa
Protein binding	Low (<80%)	Low	Low or high
Volume of distribution	<1 L/Kg	<1 L/Kg	<1 L/Kg
Solubility	Water	Water	Water or lipid
Endogenous clearance	<4 mL/Kg/min	<4 mL/Kg/min	<4 mL/Kg/min

Table 3: Summary of pharmacological and clearance properties of some pharmacological substances*.

Substance	Molecular weight (daltons)	Protein binding (%)	Volume of distribution (L/kg)	Metabolism and excretion (%)	Clearance without hemodialysis (mL/min)	Clearance with hemodialysis (mL/min)
Metformin	~129	Minimal	~1.1	>90 renal	~7	Up to 170

Hemodialysis should be strongly considered in patients with advanced renal failure, decompensated congestive heart failure, severe metabolic acidosis (pH < 7.1), and hemodynamic and clinical decline despite supportive care .

Table 2 Indications for HD/CVVH [33]

Indications for HD/CVVH
Significant comorbidities
Critically ill
pH<7.1
Failure of supportive care
Renal insufficiency
Fluid overload state

33. Nguyen H (2011) Metformin intoxication requiring dialysis. Hemodial Int 15:S68–S71

N.B. : valutare l'*anion gap* (v.n. 10-18 mmol l^{-1}) e ripristinare il valore di concentrazione plasmatica della Metformina < 2 mg l^{-1} .

- Using **dialysis** to provide bicarbonate can prevent a decrease in ionized calcium, prevent volume overload and hyperosmolality (potential complications of bicarbonate infusion), and remove substances associated with lactic acidosis, such as **metformin.**
- **Continuous dialysis** is often favored over intermittent dialysis because it delivers bicarbonate at a **lower rate** and is associated with fewer adverse events in patients with hemodynamic instability.

Indications for HD/CVVH

Significant comorbidities

Critically ill

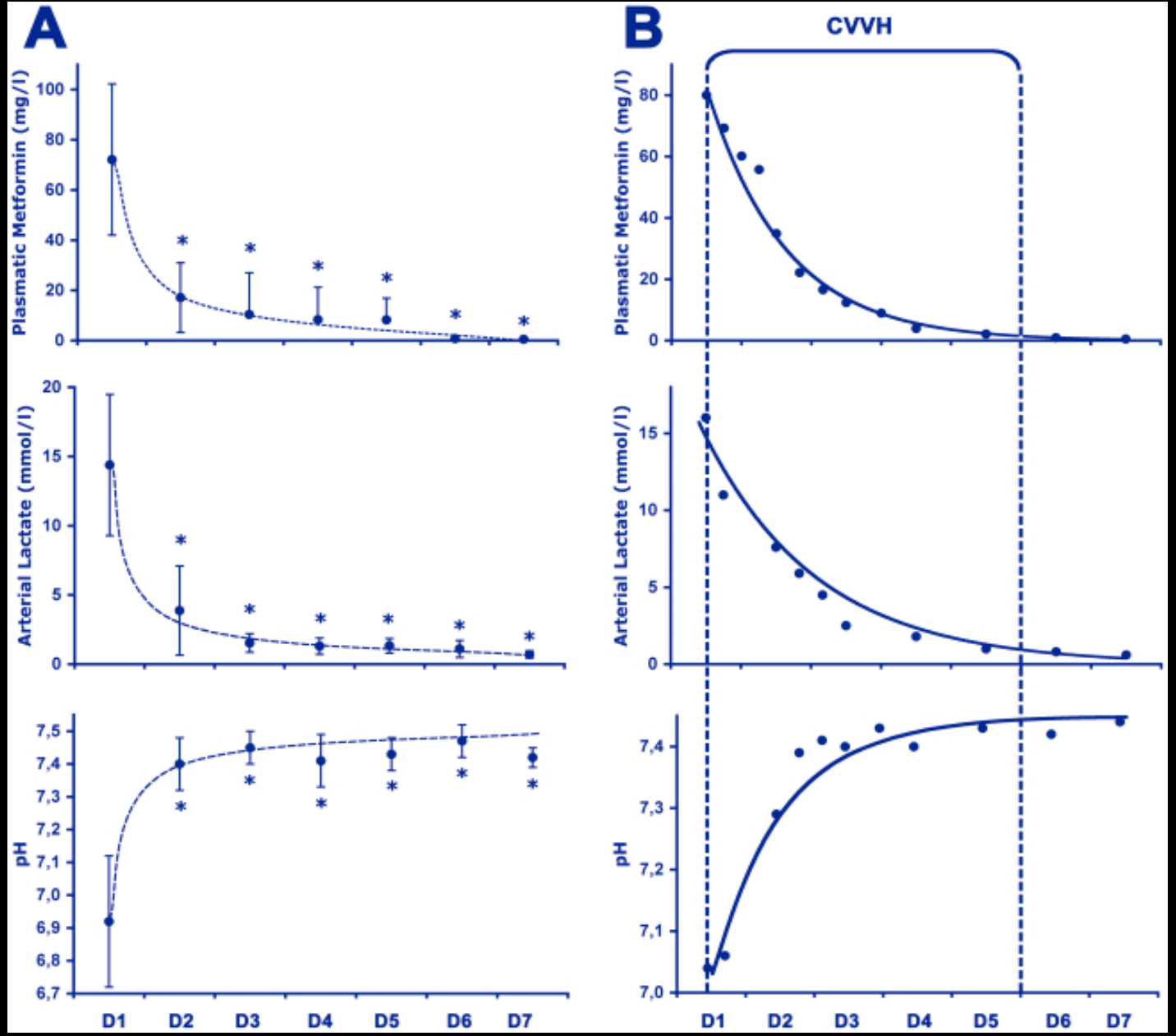
pH<7.1

Failure of supportive care

Renal insufficiency

Fluid overload state

Nguyen H (2011) Metformin intoxication requiring dialysis. Hemodial Int 15:S68–S71



Acidosis, lactate and metformin levels under continuous renal replacement

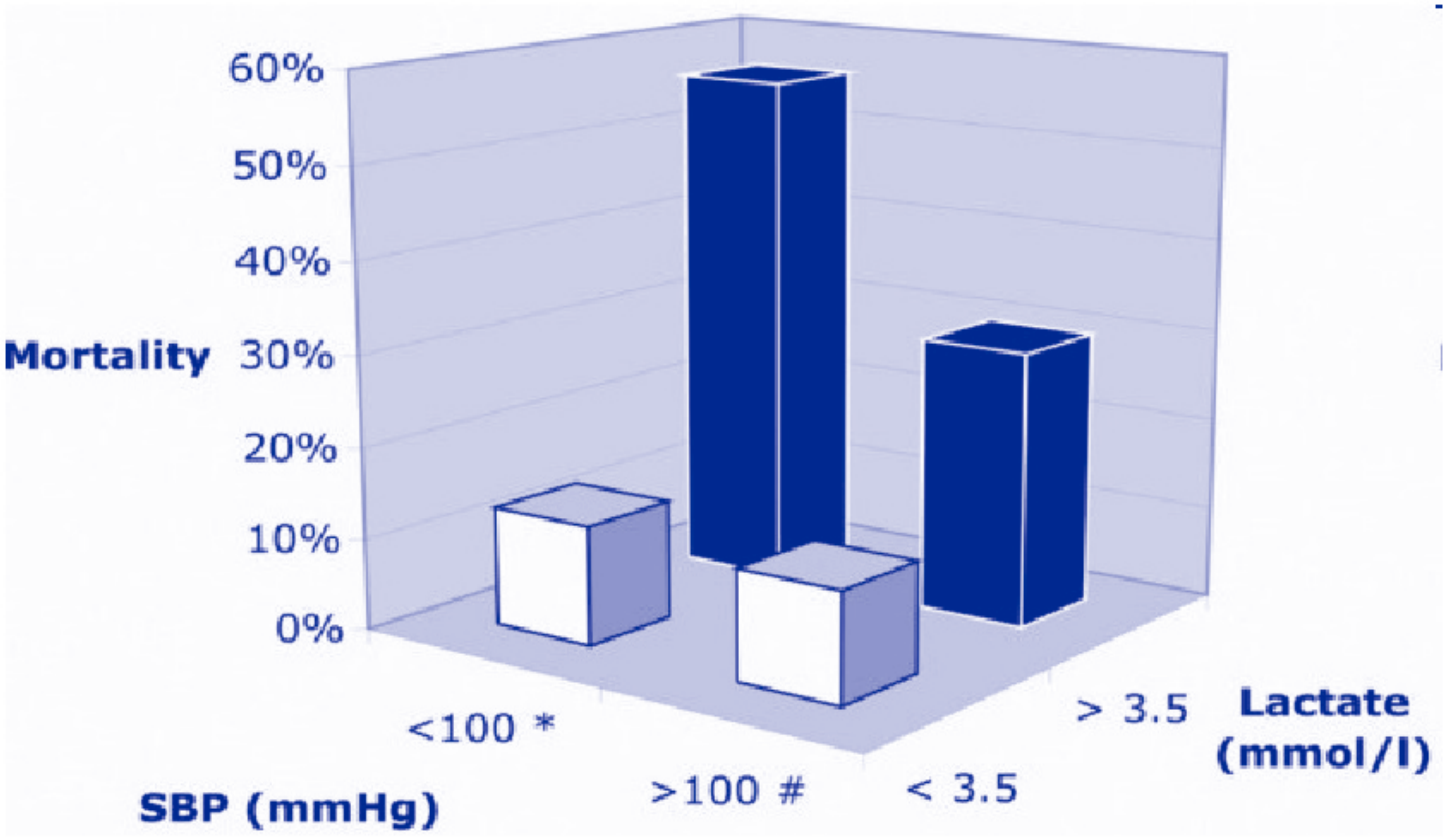
Panel A: Data from all patients, expressed as mean ± SD, showing that metabolic acidosis, as well as the excessive dose of metformin observed at admission (day 1, D1), were dramatically reduced from day 2 (D2). * $p<0.01$ versus D1. Panel B: Typical evolution in case patient 1 of both metformin plasma concentrations and metabolic disorders, which were controlled within 2 days of initiating continuous venovenous hemofiltration (CVVH), i.e. without dialysate.

Table 3 Acid-base parameters postdialysis

	N	Mean	Standard deviation
HCO3 after dialysis (mEq/L)	8	19.2	4.1
Lactic acid postdialysis (mmol/L)	9	6.1	4.9
pH postdialysis	8	7.4	0.06
Metformin level postdialysis (μg/mL)	8	8.9	5.7
Percentage of metformin removal	8	60.1	24.9

All pre/post values have $P < 0.05$.

Pre-Hospital Lactate and Mortality



Critical Care 2008, **12**:R160

Prognostic value

- Source doesn't matter
- High lactate still a marker of severe physiological stress and risk of death
- High lactate often not hypoxia related but represents metabolic changes of severe stress

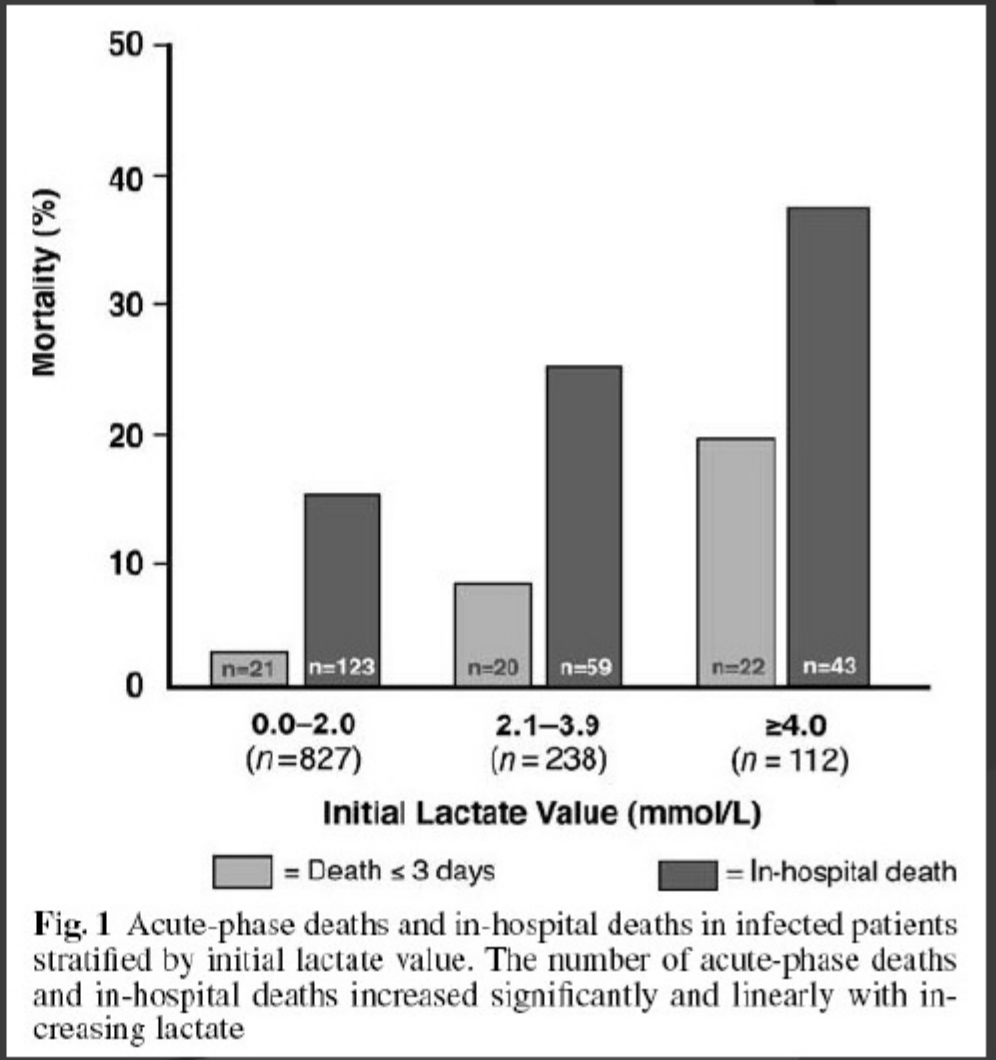


Fig. 1 Acute-phase deaths and in-hospital deaths in infected patients stratified by initial lactate value. The number of acute-phase deaths and in-hospital deaths increased significantly and linearly with increasing lactate

Metformin in Patients With Type 2 Diabetes and Kidney Disease

A Systematic Review

Silvio E. Inzucchi, MD[1]; Kasia J. Lipska, MD, MHS[1]; Helen Mayo, MLS[2]; Clifford J. Bailey, PhD[3]; Darren K. McGuire, MD, MHSc[4]

[+] Author Affiliations

JAMA. 2014;312(24):2668-2675. doi:10.1001/jama.2014.15298.

JAMA® The Journal of the American Medical Association

JAMA The Journal of the American Medical Association

Approach to Metformin Prescribing in the Setting of CKD[a]

CKD Stage	eGFR, mL/min per 1.73 m^2	Maximal Total Daily Dose, mg	Other Recommendations
1	≥90	2550	
2	60 -<90	2550	
3A	45 -<60	2000	Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function
3B	30 -<45	1000	Do not initiate therapy at this stage but drug may be continued Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function
4	15 -<30	Do not use	
5	<15	Do not use	

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

[a] This strategy has not been evaluated or validated in a clinical trial; there are no data to support its efficacy, safety, or potential to improve clinical outcomes.

METFORMINA E RISCHIO DI ACIDOSI LATTICA

- **Insufficienza renale cronica**
  - **Se eGFR (MDRD) > 60 ml/min: dose piena**
  - **Se eGFR (MDRD) = 30-60 ml/min: max 1500 mg/die**
  - **Se eGFR (MDRD) < 30 ml/min: sospendere**
- **Insufficienza respiratoria grave**
- **Scompenso cardiaco classe III-IV NYHA**
- **Insufficienza epatica grave**

Table 5. Precautions with metformin

Check at least annually

Renal function*

Caution

Introduction of drugs affecting renal function
e.g. antihypertensives, diuretics, NSAIDs
Temporary discontinuation
e.g. surgery, IV contrast media, pregnancy

Possible dose adjustment

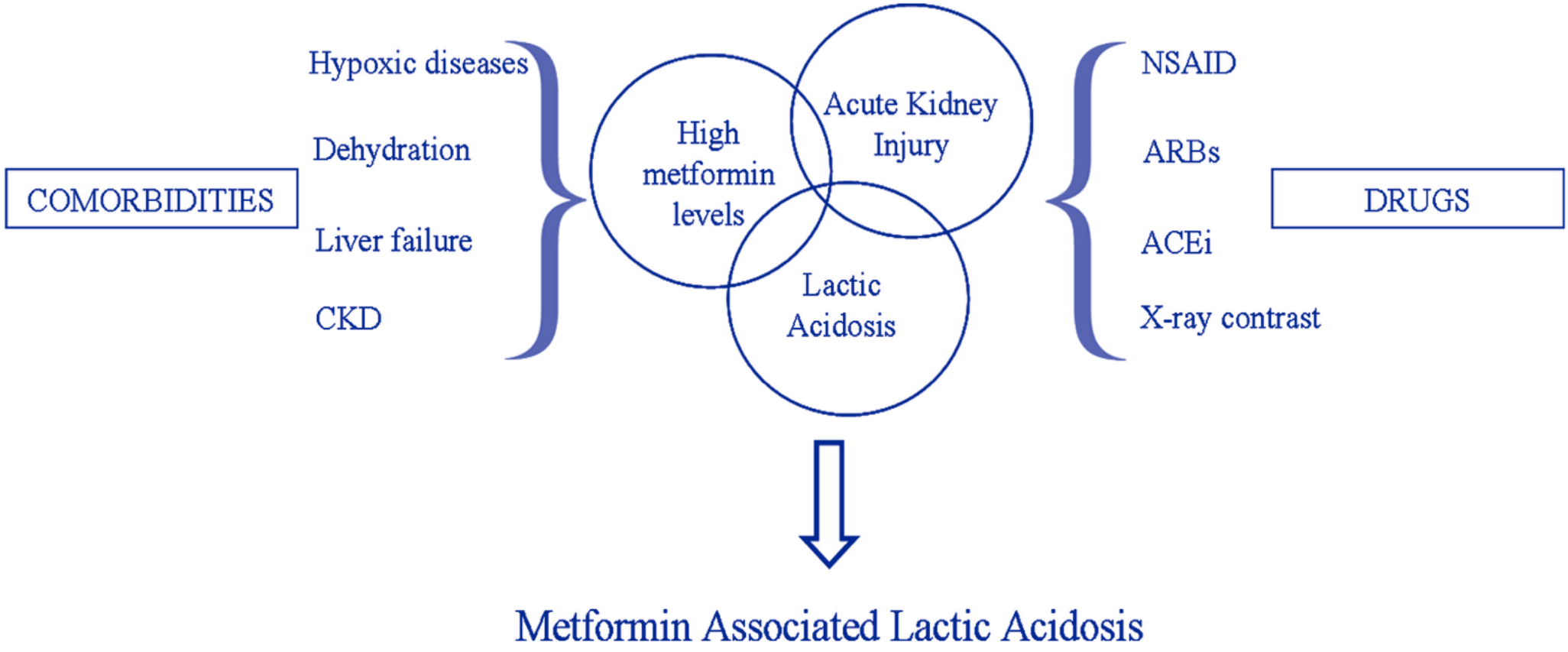
Introduction of other antidiabetic agents
Use of other agents that can alter glycaemic control
e.g. glucocorticoids, beta-2 agonists, diuretics, ACE-inhibitors

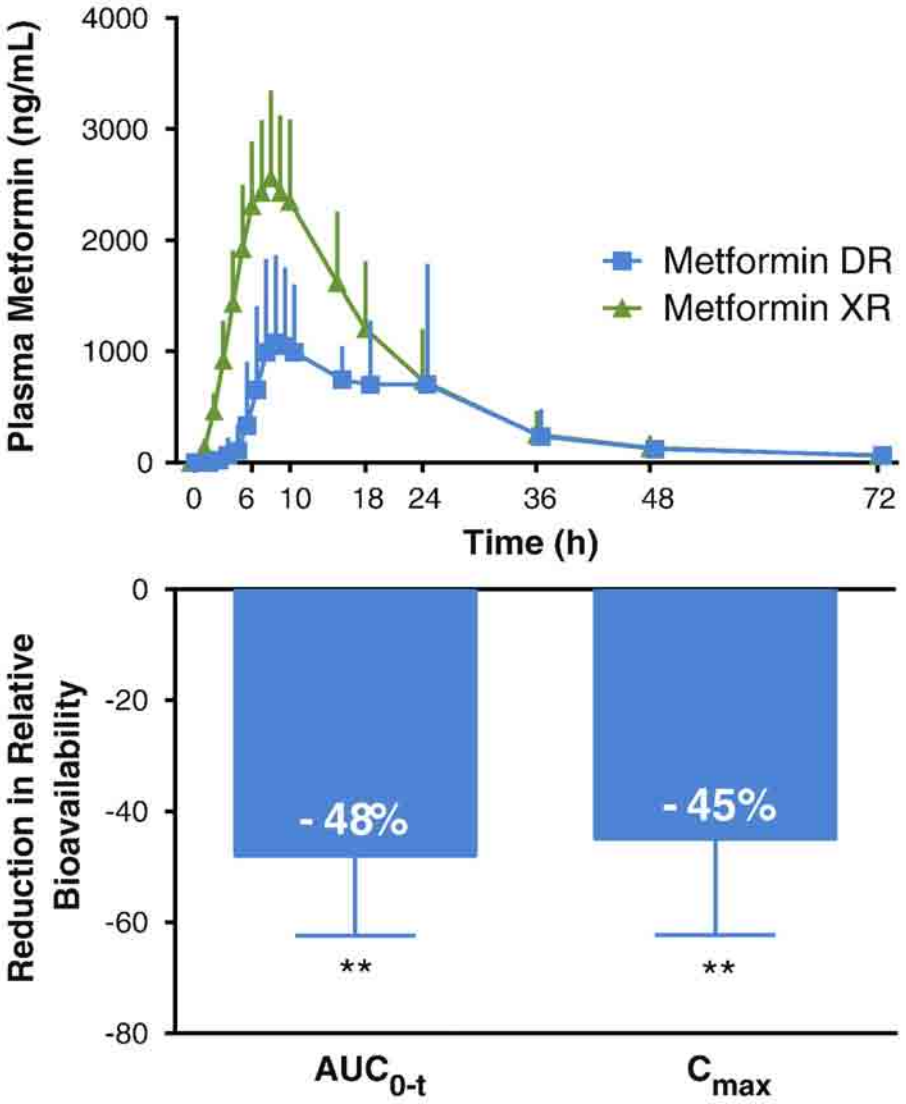
Potential discontinuation

Intercurrent or chronic illness constituting a contraindication

Key: * = Check more frequently in the elderly or patients bordering abnormal.

Triggers for metformin associated lactic acidosis. Lactic acidosis may be secondary to relatively small changes in hydration, kidney function, plasma concentrations of metformin or tissue oxygenation leading to severe lactic ac.





Metformin DR
Delayed release

Metformin XR
Extended release

Plasma metformin concentrations following a single dose of metformin DR and metformin XR in patients with type 2 diabetes and severe renal impairment. Patients with severe renal impairment (eGFR<30mL/min per 1.73m^2) were administered single doses of 1000mg Metformin DR, 1000mg Metformin XR, and Placebo in a cross-over study design. Top panel: Time-course plasma metformin concentration after a single administration of Metformin DR or Metformin XR. Bottom panel: Reduction in metformin bioavailability (Cmax and AUC) with Metformin DR relative to the same dose of Metformin XR

Grazie per l’attenzione !