Associazione Medici Endocrinologi

AACE ITALIAN CHAPTER

17° Congresso Nazionale AME

Joint Meeting with AACE Italian Chapter

Update in Endocrinologia Clinica

ROMA 8 - 11 novembre 2018

Sabato 10 Novembre 2018

Simposio

Infertilità maschile su base metabolica

Farmaci di interesse diabetologico e ricadute sulla funzione riproduttiva maschile

Silvio Settembrini

Servizio di Endocrinologia Diabetologia e Malattie Metaboliche - DS 26

Unità di Nefro - Diabetologia - UOC di Nefrologia e Dialisi

Ospedale dei Pellegrini - Napoli

ASL REGIONE CAMPANIA Azienda Sanitaria Locale Napoli 1

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LE TERAPIE FARMACOLOGICHE DELL'INFERTILITÀ MASCHILE

ame flash
nr. 19 - settembre 2018

Responsabile Editoriale
Renato Cozzi

Francesco Romanelli (francesco.romanelli@uniroma1.it) **& Andrea Sansone**
Dipartimento di Medicina Sperimentale, Sezione di Fisiopatologia Medica, Scienza dell'Alimentazione ed Endocrinologia, Università di Roma Sapienza

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LE TERAPIE FARMACOLOGICHE DELL'INFERTILITÀ MASCHILE

LIMITI, DUBBI E PERPLESSITÀ

La terapia dell'infertilità maschile rappresenta un'area calda della ricerca in ambito andrologico.

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LE TERAPIE FARMACOLOGICHE DELL'INFERTILITÀ MASCHILE

Le terapie farmacologiche dell'infertilità maschile

sono in larga misura dipendenti dall'ezio-patogenesi

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LE TERAPIE FARMACOLOGICHE DELL'INFERTILITÀ MASCHILE

È essenziale ricordare che lo scopo ultimo di un qualsiasi trattamento per l'infertilità maschile consiste nell'aumento del tasso di gravidanze o delle nascite. **Un miglioramento nei parametri seminali**, seppure di notevole entità , **non si traduce automaticamente in un risultato "clinico"**: nei soggetti affetti da azoospermia, un risultato anche di minima entità può consentire alla coppia di considerare il ricorso alla **PMA**; in un uomo con buoni parametri seminali, un ulteriore miglioramento può non portare a nessun giovamento a fronte di costi non trascurabili.

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LE TERAPIE FARMACOLOGICHE DELL'INFERTILITÀ MASCHILE

TERAPIE *OFF-LABEL:* *

Dei numerosi farmaci proposti e sperimentati nel trattamento dell'infertilità maschile, nessuno, al di là delle gonadotropine, ha ottenuto l'approvazione per l'uso nella pratica clinica quotidiana.

*

Clomifene citrato
Tamoxifene
Anastrazolo

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LE TERAPIE FARMACOLOGICHE DELL'INFERTILITÀ MASCHILE

TERAPIE EMPIRICHE : *

I prodotti nutraceutici trovano sempre più spazio nel trattamento dell'infertilità maschile, sebbene siano carenti le evidenze scientifiche a sostegno di una loro reale efficacia.

* **Carnitina, Catalasi, Selenio, N-acetil-cisteina, Coenzima Q10, SuperOssido-Dismutasi, Vitamine C - E**

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BJUI
BJU International

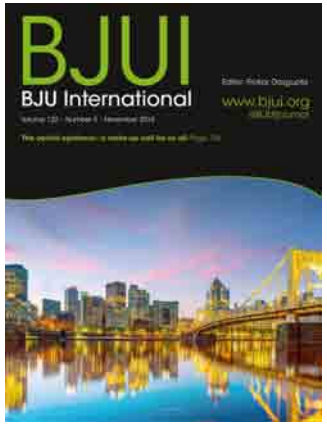
Original Article

Undiagnosed prediabetes is highly prevalent in primary infertile men – results from a cross-sectional study

Luca Boeri, Paolo Capogrosso, Eugenio Ventimiglia, Filippo Pederzoli, Nicola Frego, Walter Cazzaniga, Francesco Chierigo, Massimo Alfano, Lorenzo Piemonti, Paola Viganò, ... See all authors

First published: 16 October 2018 | https://doi.org/10.1111/bju.14558

Conclusions



About 15% of primary infertile men had criteria suggestive of undiagnosed PreDM. A PreDM status was associated with a greater risk of hypogonadism, higher DFI values and iNOA status. Age, FSH values and iNOA status could be considered as useful parameters to recognise men with PreDM and implement early preventive interventions in those men at risk of the consequences from poor glycaemic control.

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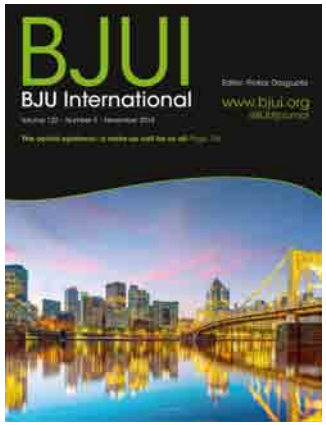
Original Article

Undiagnosed prediabetes is highly prevalent in primary infertile men – results from a cross-sectional study



Abstract

Objective

To study the prevalence and the risk associated with prediabetes (PreDM) in primary infertile men.

Patients and methods

Data from 744 infertile men were analysed. Health-significant comorbidities were scored with the Charlson Comorbidity Index (CCI). Serum hormones were measured in every man. Semen analysis was based on 2010 World Health Organization (WHO) reference criteria. PreDM was defined according to the clinical criteria detailed by the American Diabetes Association (*Diabetes Care* 2014; 37 (Suppl. 1): S81). Descriptive statistics and logistic regression analyses tested the association between PreDM status, hormonal milieu and seminal parameters. The predictive accuracy of all variables was evaluated using the area under the curve, and the clinical net benefit estimated by decision curve analysis (DCA).

Results

Of the 744 men, PreDM was found in 114 (15.4%). Men with PreDM (+PreDM) were older, had higher CCI scores, lower total testosterone and sex hormone-binding globulin but higher follicle-stimulating hormone (FSH) and 17β-oestradiol values compared to those without PreDM (−PreDM) (all $P \leq 0.04$). Higher sperm DNA fragmentation index (DFI; $P = 0.014$) and idiopathic non-obstructive azoospermia (iNOA; $P < 0.001$) were found more frequently in +PreDM men. At multivariable logistic regression analysis, older age, FSH and iNOA (all $P \leq 0.04$) were significantly associated with +PreDM status. DCA demonstrated a clinical net benefit in discriminating men at higher risk of a +PreDM status.

Conclusions

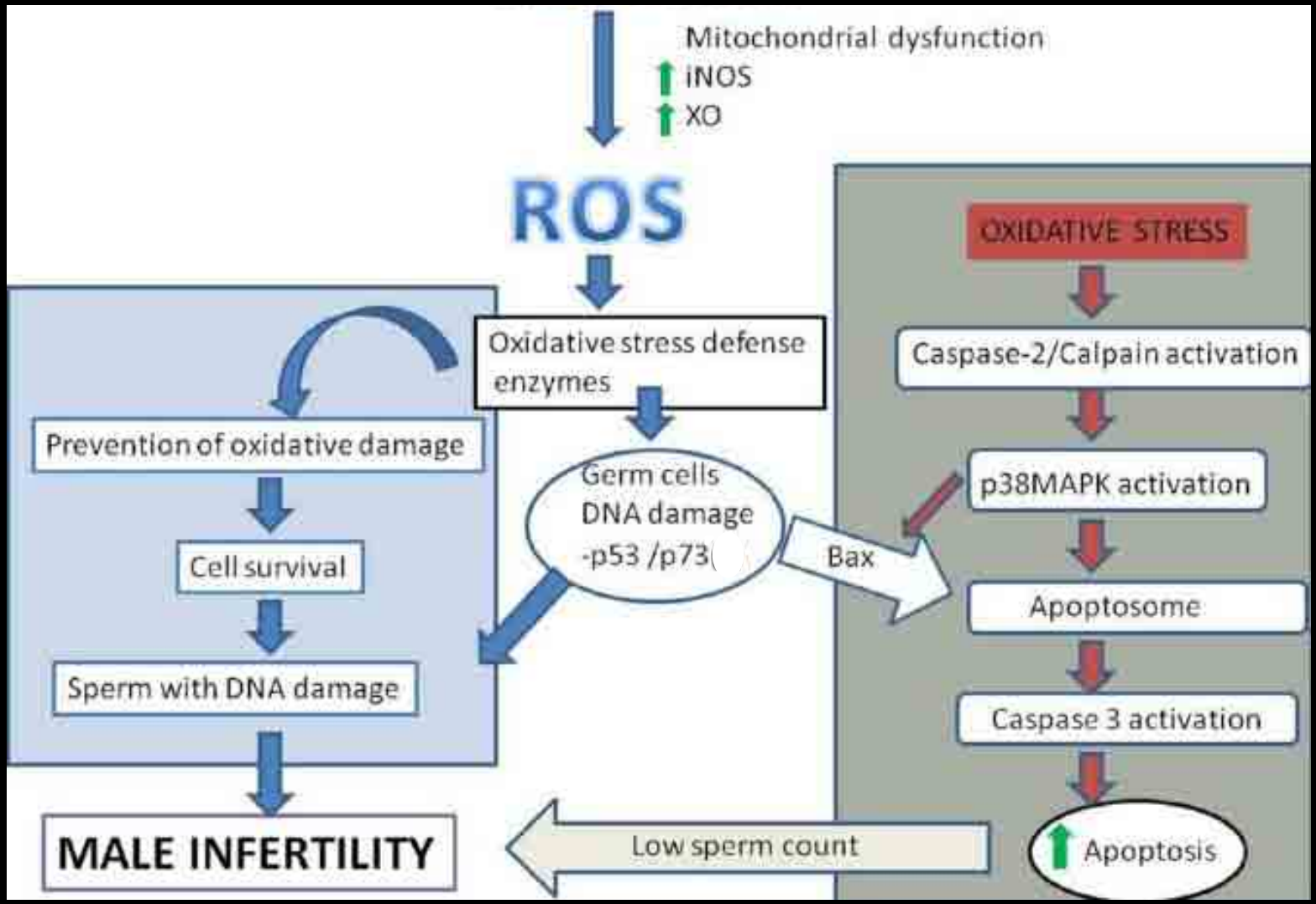
About 15% of primary infertile men had criteria suggestive of undiagnosed PreDM. A PreDM status was associated with a greater risk of hypogonadism, higher DFI values and iNOA status. Age, FSH values and iNOA status could be considered as useful parameters to recognise men with PreDM and implement early preventive interventions in those men at risk of the consequences from poor glycaemic control.

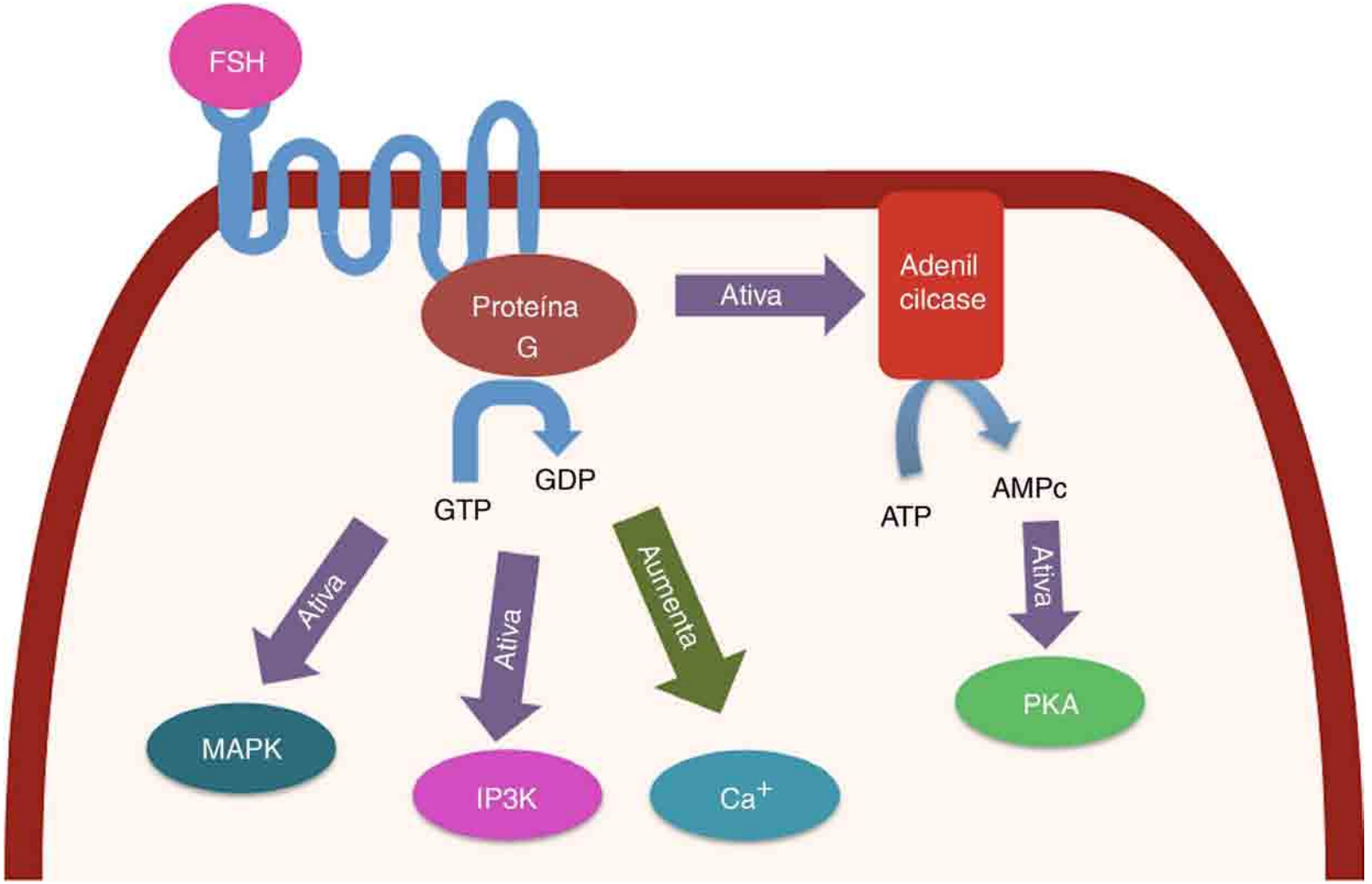
Personalizzazione della terapia???

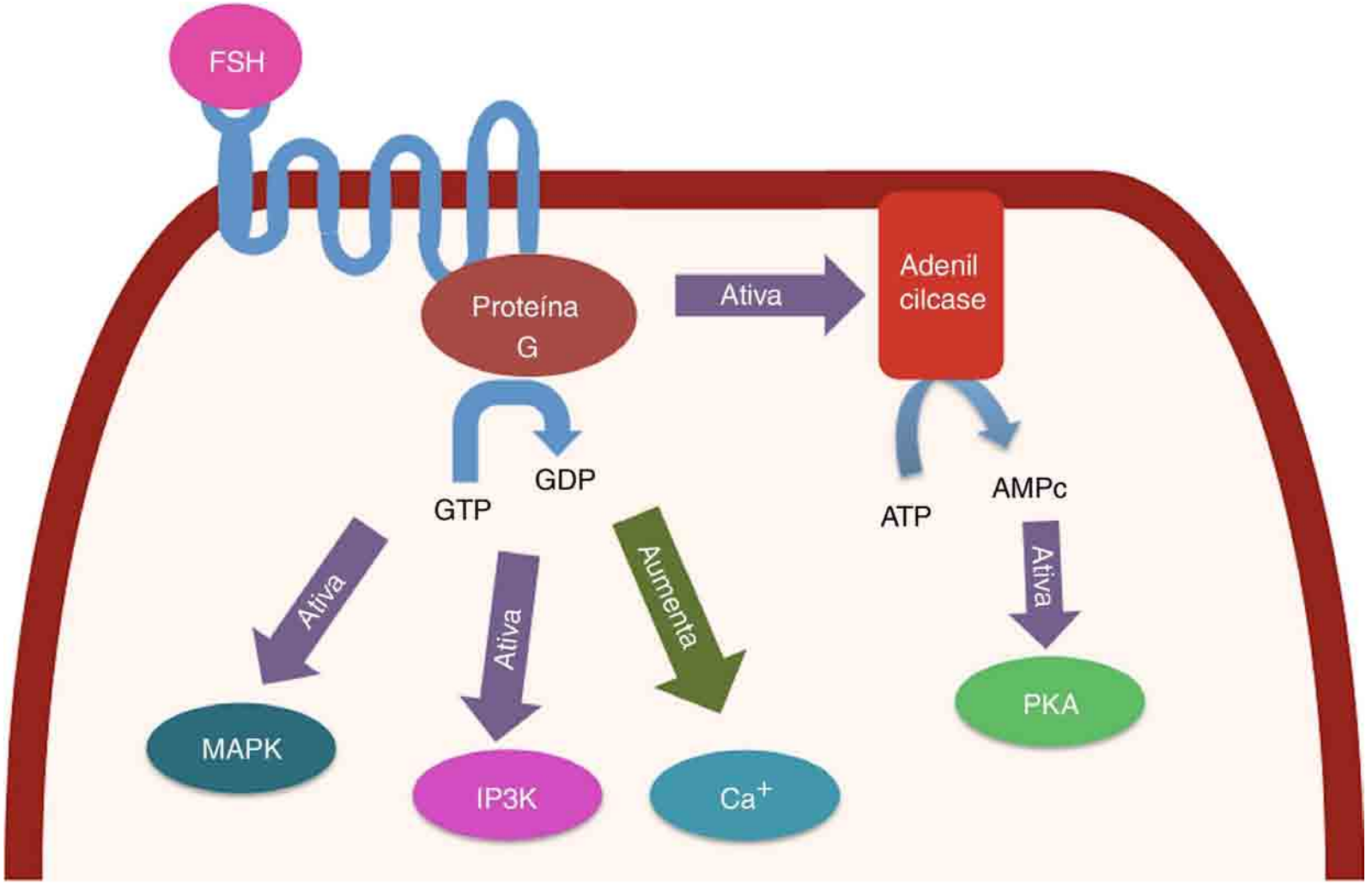
Ogni persona è unica

Ogni percorso è differente

GLUCO - TOXICITY




FSH
Proteína G
Ativa
Adenil cilcase
GTP
GDP
ATP
AMPc
Ativa
Ativa
Ativa
Aumenta
MAPK
IP3K
Ca+
PKA



FSH mimicking effects ?

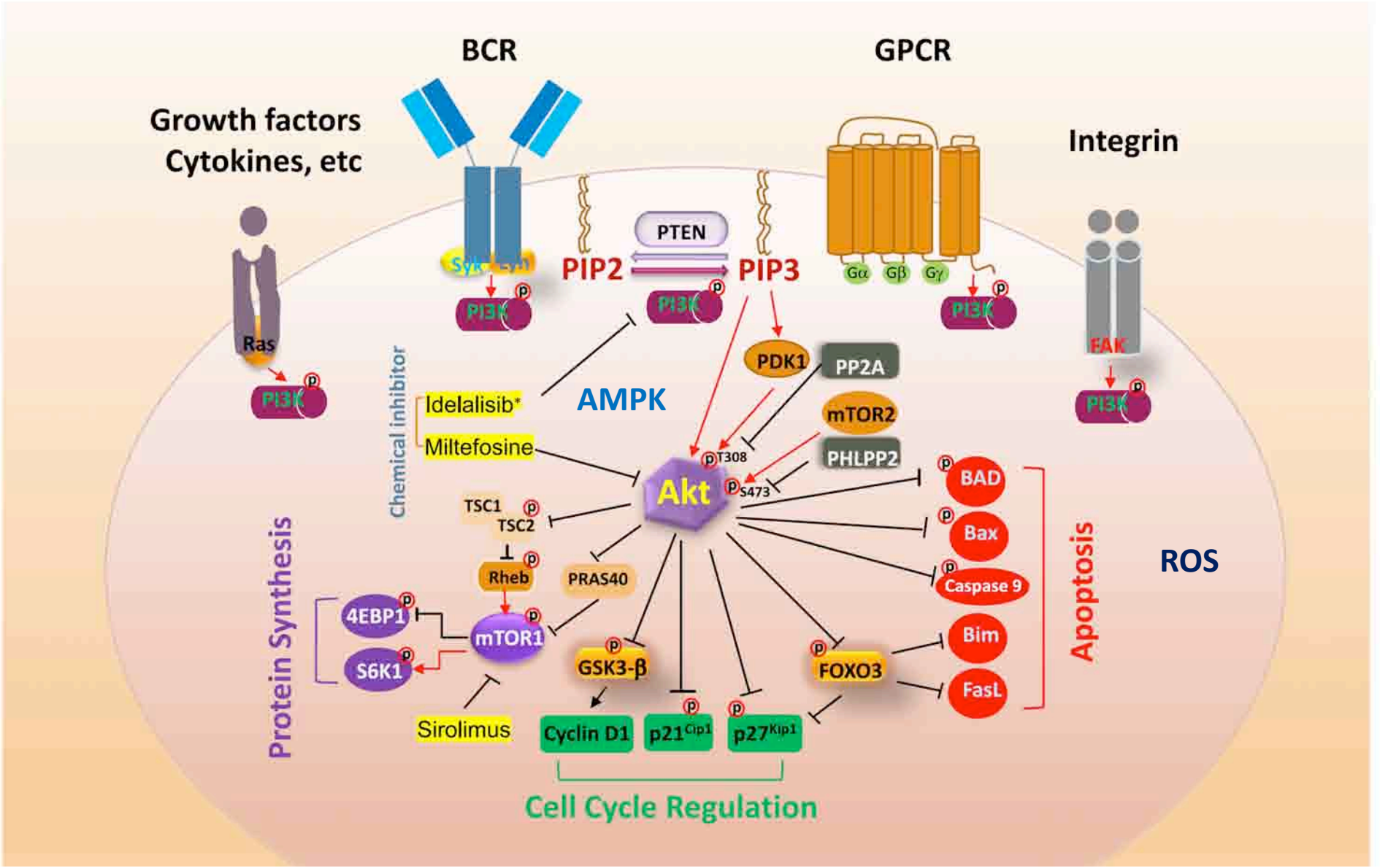


Fig. 1. Receptor-mediated activation of PI3K-Akt pathway and signaling. Binding of ligands to cell surface receptors induces activation of PI3K. Activated PI3K converts membrane-bound PIP2 to PIP3. PTEN dephosphorylates PIP3 to form PIP2. PIP3 recruits PDK1 and Akt to the plasma membrane, resulting in Akt phosphorylation by PDK1. Akt can be dephosphorylated by PP2A and PHLPP2. Activated Akt (a) stimulates protein synthesis by phosphorylation of mTOR inhibitor TSC2, leading to mTOR1 activation, and phosphorylation of 4EBP1 (an inhibitor of translation) and S6K1, (b) stimulates cell cycle progression by phosphorylation of cell cycle inhibitors $p21^{Cip1}$ and $p27^{Kip1}$ for their degradation, and phosphorylation and inactivation of transcriptional factors GSK-3β and FOXO3, leading to increased cyclin D1 and reduced $p27^{Kip1}$ expression, and (c) inhibits apoptosis by phosphorylation and inactivation of proapoptotic proteins BAD, Bax, caspase 9, and transcriptional factor FOXO3 to reduce Bim and FasL expression. * indicates that idelalisib blocks PI3Kδ only.

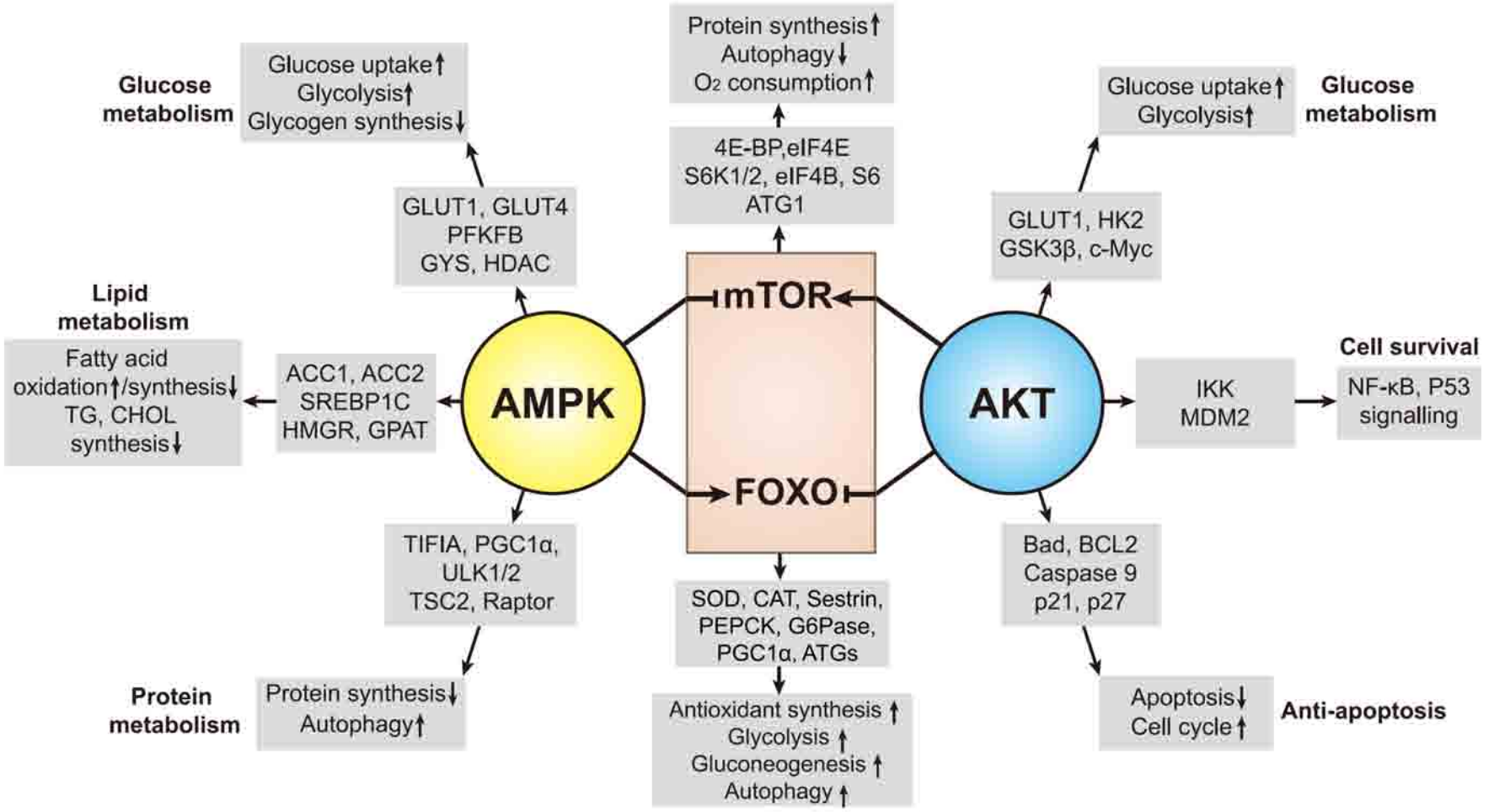
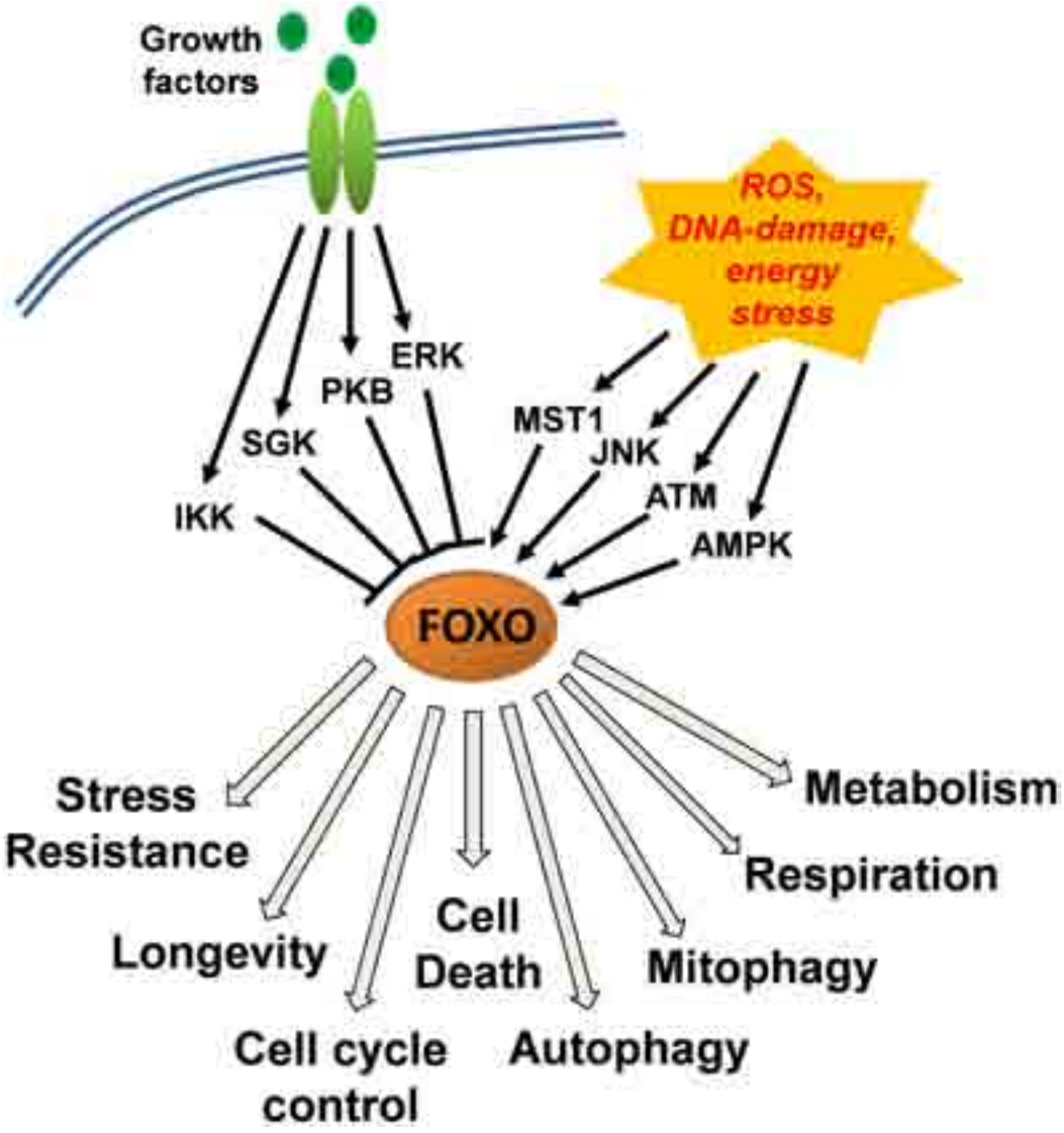
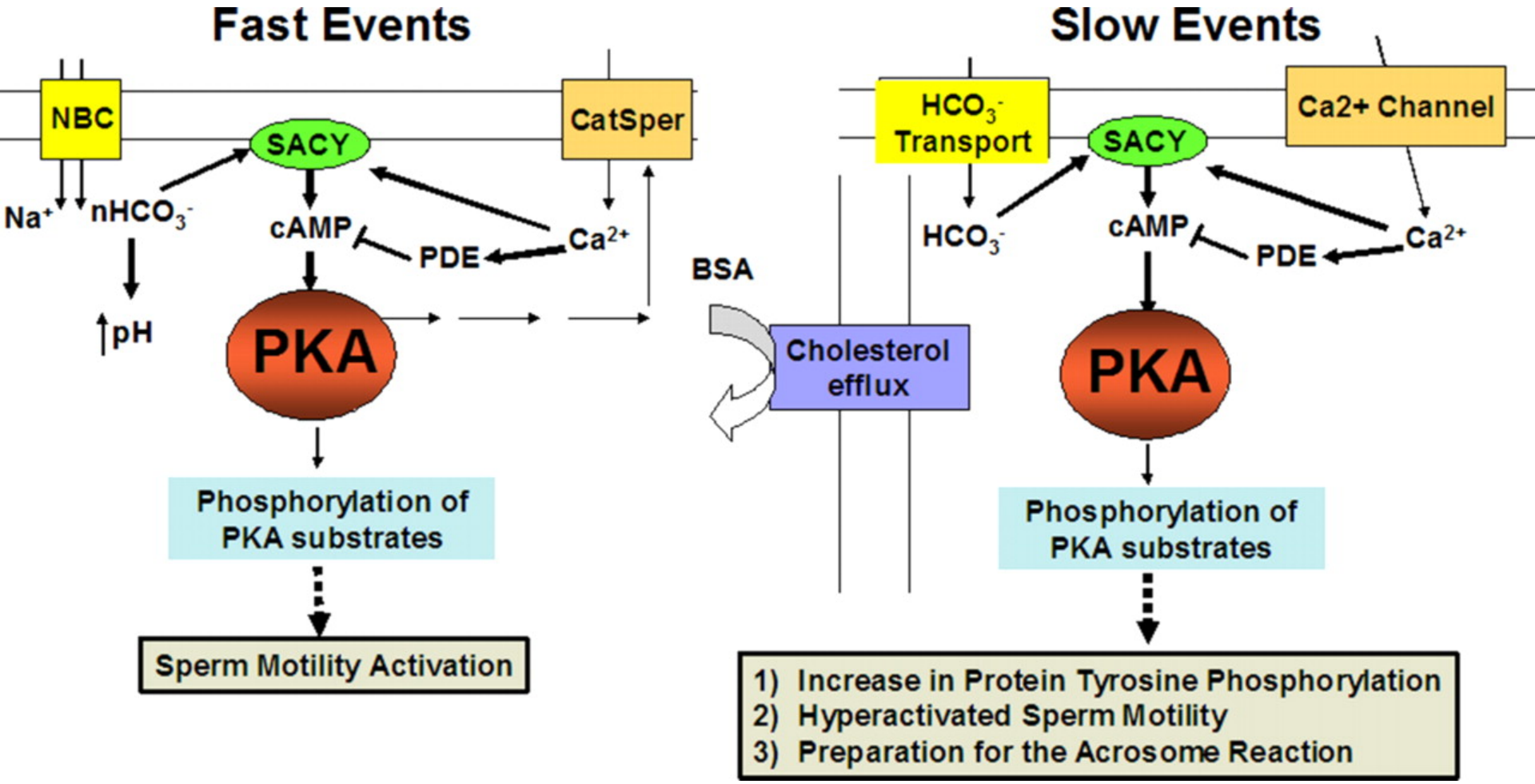
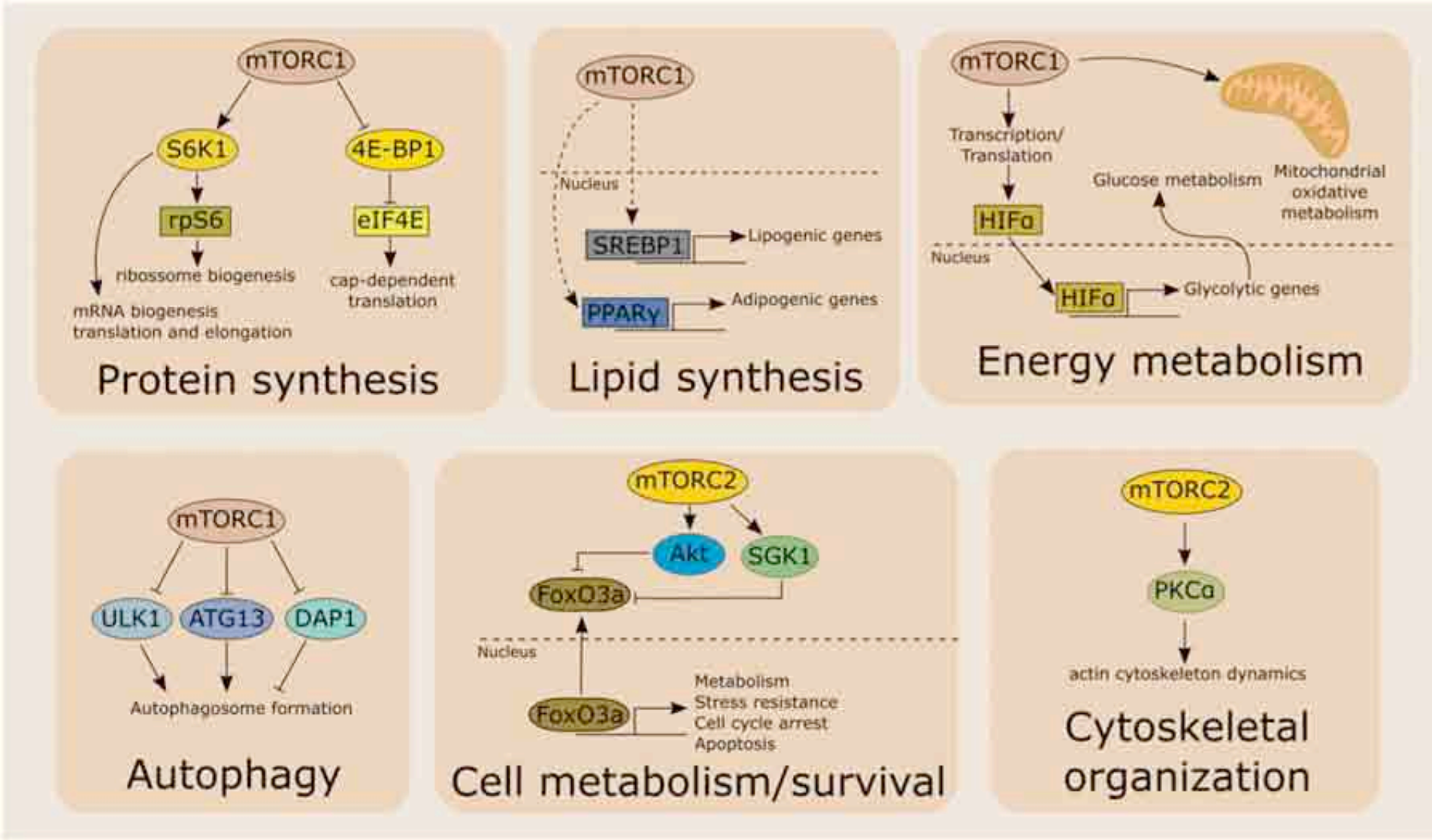


Fig. 2 Cross effects of AMPK and AKT on the cellular metabolism and redox state: The targeted proteins regulated by AMPK and AKT and their regulatory effects are depicted, AMPK is a key player in response to metabolic stress by regulating the metabolism of glucose, lipid and protein. AMPK promotes glucose uptake and glycolysis, facilitating antioxidant production. AMPK also stimulates fatty acid oxidation and limits the fatty acid synthesis. mTOR and FOXO are two main downstream effectors of AMPK. AMPK inhibits mTOR activity, which induces protein synthesis inhibition and autophagy activation. AMPK also promotes FOXO activity to maintain the redox balance through enhanced antioxidant production and glucose metabolism. On the other side, AKT exerts antagonistic effect to regulate mTOR and FOXO activity. AKT stimulates mTOR signaling to promote glucose metabolism and protein synthesis, leading to increased ROS production. Meanwhile, it inhibits FOXO activity and renders cells susceptible to ROS toxicity

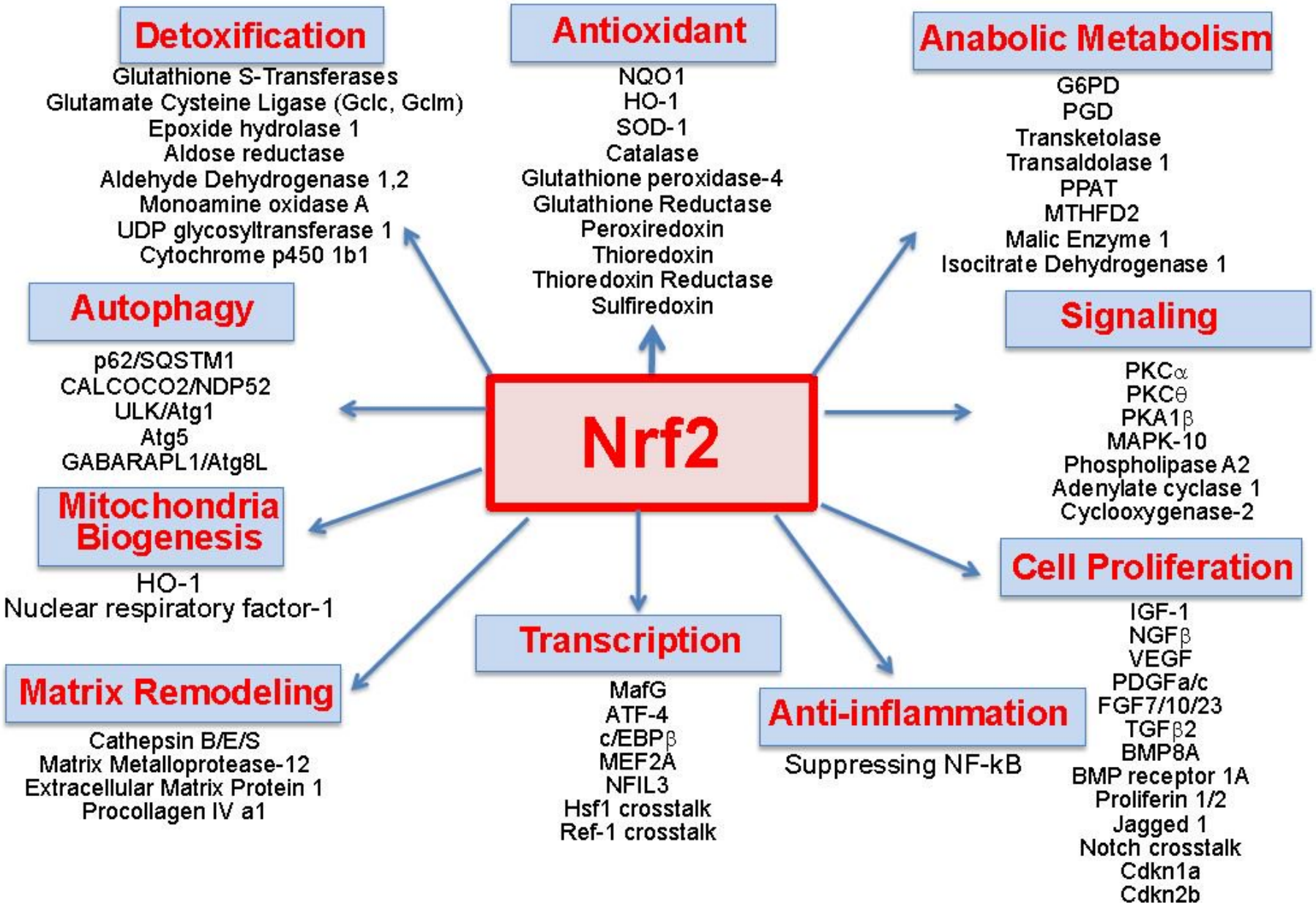

Growth factors
ROS, DNA-damage, energy stress
ERK
PKB
SGK
IKK
MST1
JNK
ATM
AMPK
FOXO
Stress Resistance
Longevity
Cell cycle control
Cell Death
Autophagy
Mitophagy
Respiration
Metabolism


Fast Events
NBC
SACY
CatSper
Na+
nHCO3-
cAMP
PDE
Ca2+
pH
PKA
Phosphorylation of PKA substrates
Sperm Motility Activation
Slow Events
HCO3- Transport
SACY
Ca2+ Channel
HCO3-
cAMP
PDE
Ca2+
BSA
Cholesterol efflux
PKA
Phosphorylation of PKA substrates
1) Increase in Protein Tyrosine Phosphorylation
2) Hyperactivated Sperm Motility
3) Preparation for the Acrosome Reaction



La mTOR, complesso 1, è una protein-chinasi che fosforila serina e treonina, che regola la crescita, la proliferazione, la motilità e la sopravvivenza delle cellule, la sintesi proteica e la trascrizione

Transcription factor nuclear factor-erythroid 2-related factor 2 (NRF2)



AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm

2018

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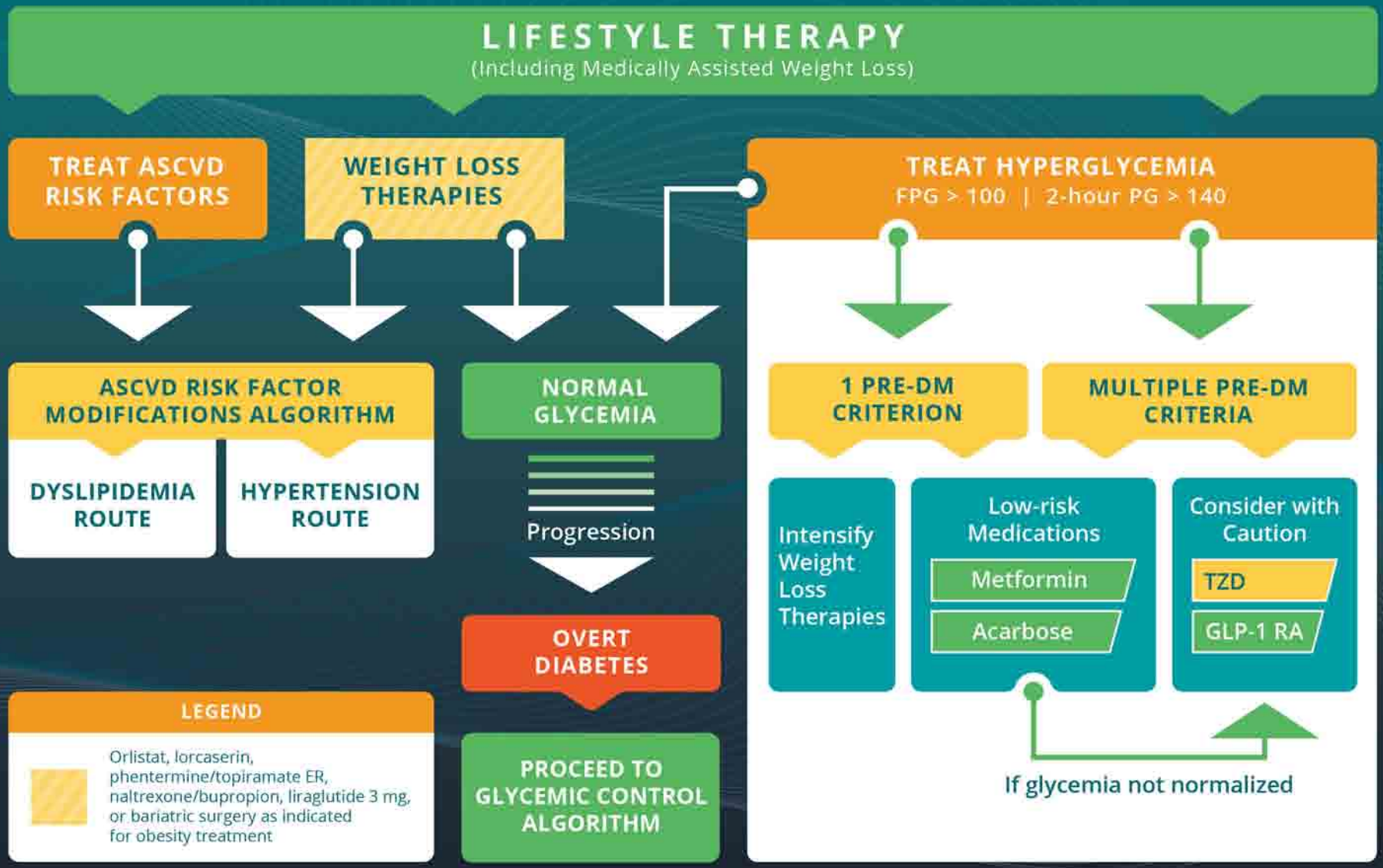
 DOI 10.4158/CS-2017-0153

Prediabetes Algorithm

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)



 DOI 10.4158/CS-2017-0153

Glycemic Control Algorithm

INDIVIDUALIZE GOALS

- **A1C ≤ 6.5%** — For patients without concurrent serious illness and at low hypoglycemic risk
- **A1C > 6.5%** — For patients with concurrent serious illness and at risk for hypoglycemia

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ⚠ TZD
- ⚠ Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ⚠ Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

 DOI 10.4158/CS-2017-0153

REPRODUCTION
REVIEW

Antidiabetic therapies and male reproductive function: where do we stand?

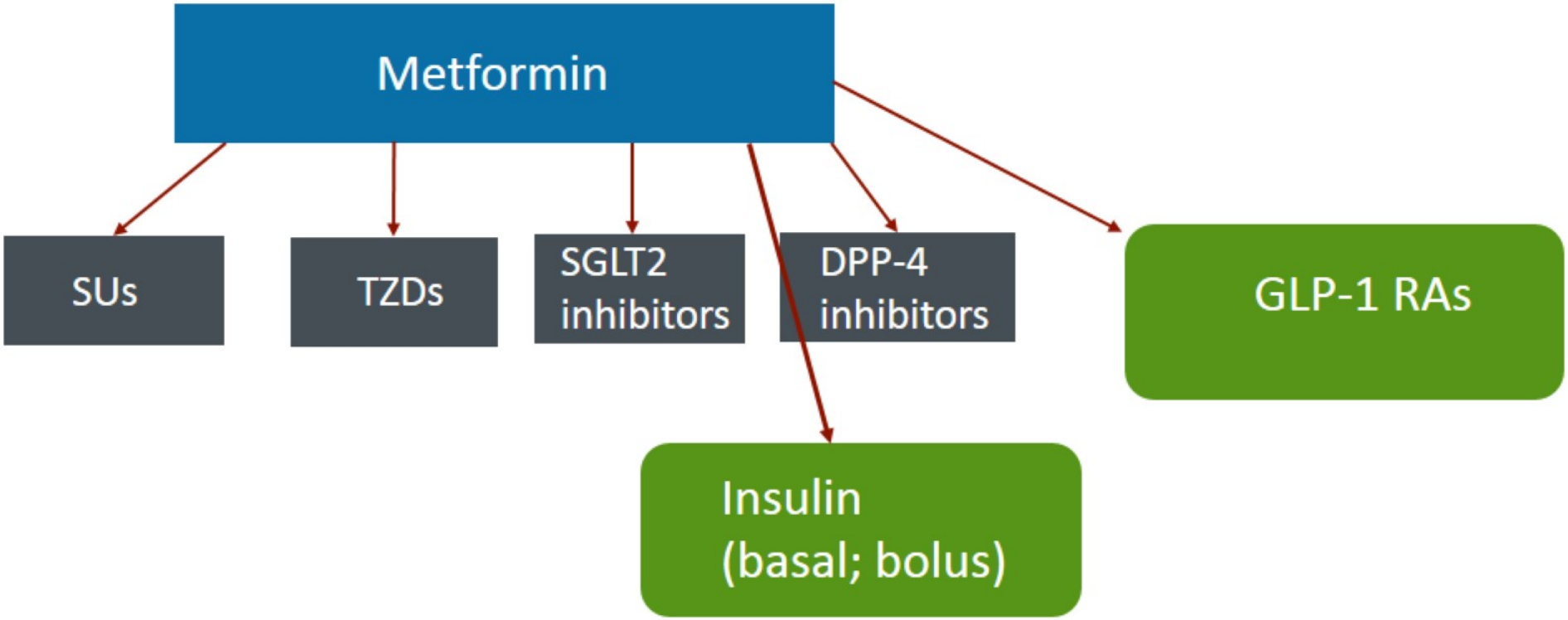
R S Tavares[1,4], S Escada-Rebelo[1,2], A F Silva[1], M I Sousa[1], J Ramalho-Santos[1,3] and S Amaral[1,4]

[1]Biology of Reproduction and Stem Cell Group, CNC-Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal, [2]PhD Programme in Experimental Biology and Biomedicine, CNC, Coimbra, Portugal, [3]Department of Life Sciences, University of Coimbra, Coimbra, Portugal and [4]Institute for Interdisciplinary Research, University of Coimbra, Coimbra, Portugal

Society for Reproduction and Fertility

Reproduction (2018) **155** R13–R37

Commonly Prescribed Antihyperglycemics



Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379.

SciMedCentral

Journal of Endocrinology, Diabetes & Obesity

Review Article

The Effect of Metformin on Reproduction—A Short Review

Winston Crasto*, Pallavi Rao and Helena Gleeson

Department of Diabetes & Endocrinology, University Hospitals of Leicester NHS Trust Leicester, United Kingdom

J Endocrinol Diabetes Obes 2(2): 1038 (2014)

Abstract

Reproductive health is an important domain of women's health care and broadly encompasses conditions which impact fertility, conception or birth of a healthy infant. Although numerous factors or conditions are associated with infertility, polycystic ovary disease is a well recognised cause. In this regard, metformin which belongs to the biguanide group of drugs and is commonly used as first line treatment in type 2 diabetes has also been commonly employed in the management of infertile women with PCOS with beneficial results. This review examines the evidence base of the utility of metformin in PCOS on ovulation and reproductive outcomes and discusses its role in different aspects of management and in future research.

Impact of Metformin on Male Reproduction

Carolina Ferreira[1,2], Mário Sousa[1,3], Ana Rabaça[1,4], Pedro F. Oliveira[1,5], Marco G. Alves[5] and Rosália Sá[1*]

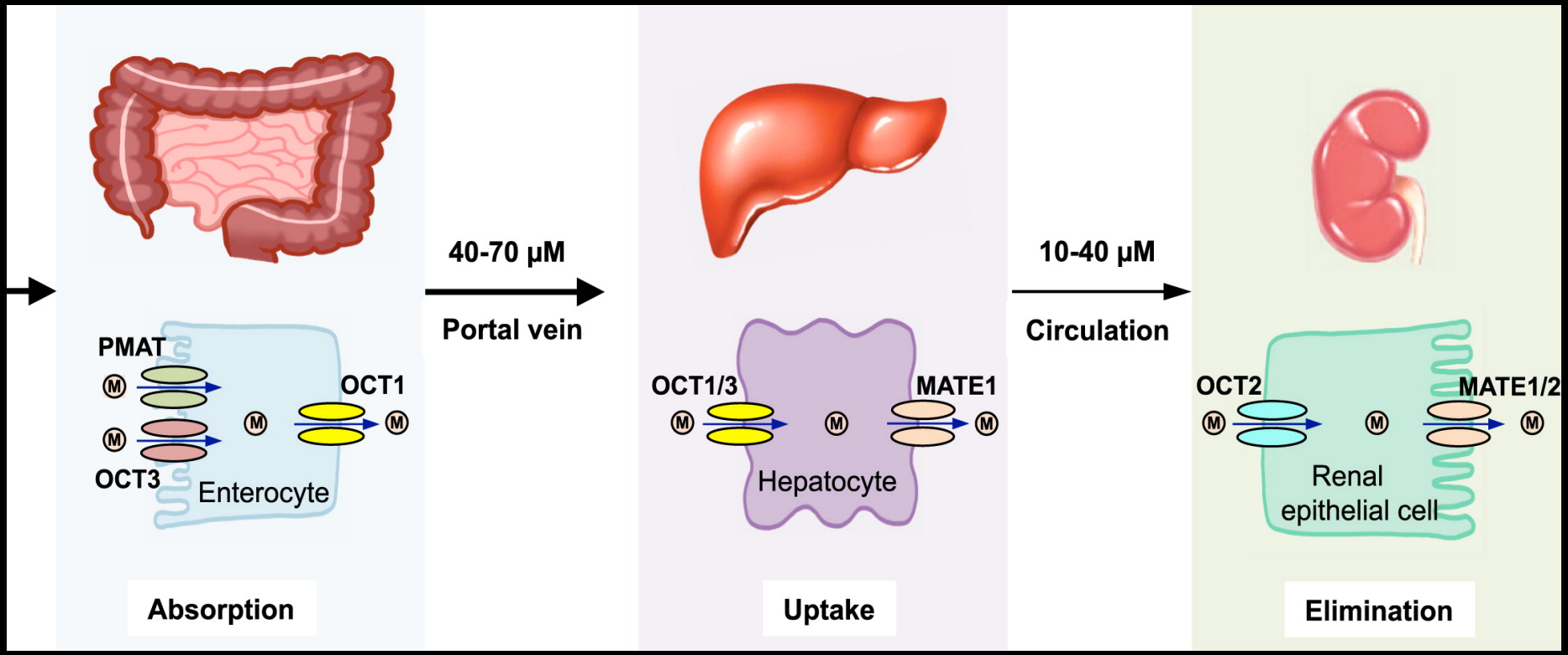
[1]*Department of Microscopy, Laboratory of Cell Biology, Institute of Biomedical Sciences Abel Salazar (ICBAS) and Unit for Multidisciplinary Research in Biomedicine (UMIB), University of Porto, Rua Jorge Viterbo Ferreira 228, 4050-313 Porto, Portugal;* [2]*University of Trás-os-Montes and Alto Douro (UTAD), Quinta de Prados, 5000-801 Vila Real, Portugal;* [3]*Centre for Reproductive Genetics Prof. Alberto Barros, Av. do Bessa 240, 1° Dto. Frente, 4100-009 Porto, Portugal;* [4]*Faculty of Medicine of University of Porto (FMUP), Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal;* [5]*CICS-UBI, Health Sciences Research Centre, Faculty of Health Sciences, University of Beira Interior, Av. Infante D. Henrique, 6200-506 Covilhã, Portugal*

Rosália Sá

Abstract: Male infertility has been increasing over the last decades being nowadays a pressing health problem. Diabetes mellitus (DM) can contribute directly or indirectly to male infertility due to an abnormal spermatogenesis, which results in a decreased sperm quality. Type 2 Diabetes mellitus (T2DM) is responsible for the vast majority of DM cases, being frequently treated with oral antidiabetic drugs. Metformin is the most cost-effective therapy for the treatment of T2DM. This biguanide is an oral insulin-sensitizing agent capable of increasing insulin sensitivity and decreasing plasma fasting insulin levels. The main metabolic action of this drug occurs in the liver. However, it has been shown that metformin acts on a variety of organs including the male reproductive system. With the rising numbers of diabetic individuals among younger populations, there is an increase in the consumption of metformin in individuals of this age group. As a result, it is important to discuss the role of metformin in male fertility. This review presents the most recent data available from studies on the effects of metformin on male reproductive system. Together with the discussion of these effects, their significance to male fertility is also debated.

Current Pharmaceutical Design

***Current Pharmaceutical Design*, 2015, *21*, 3621-3633**



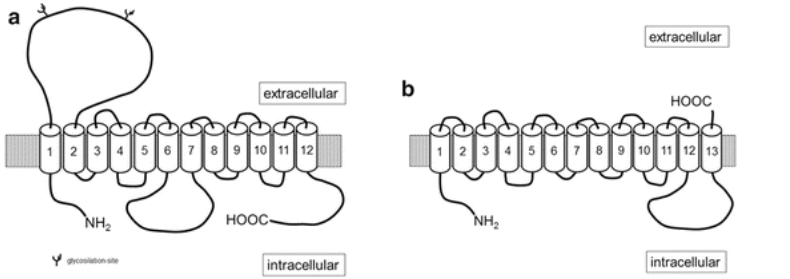
Transport of Metformin by:

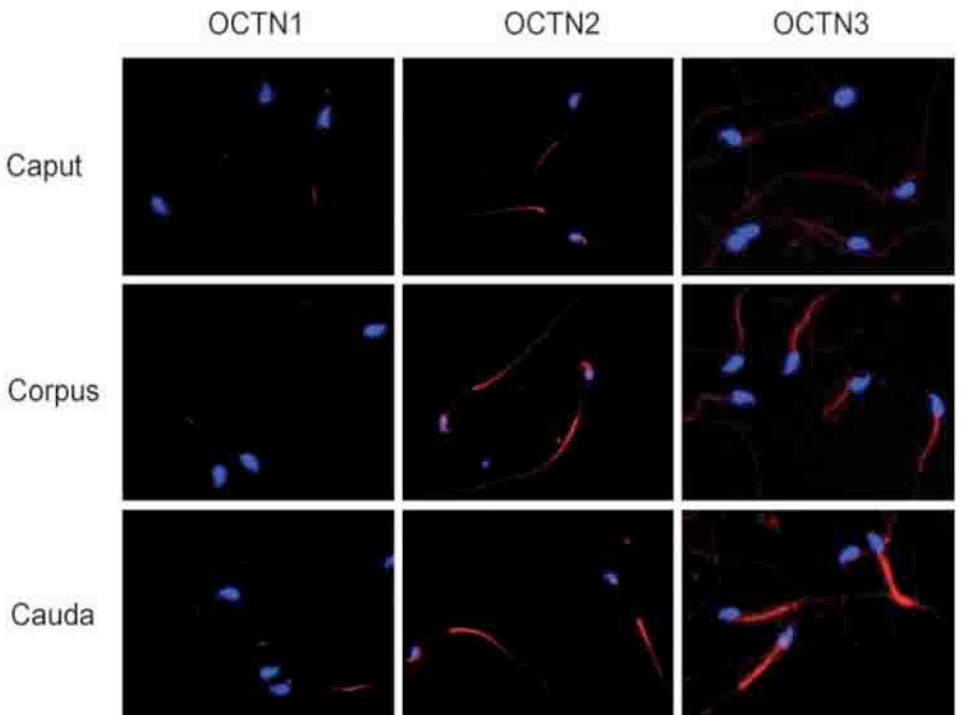
- OCT s 1 – 2 – 3 (organic cation transporters)
- PMAT (plasma membrane monoamine transporter)
- MATE s 1 – 2 (multidrugs and toxin extrusion antiporter)

Biochemical and Biophysical Research Communications
Volume 306, Issue 1, 20 June 2003, Pages 121-128

Characterization of organic cation/carnitine transporter family in human sperm

Wanli Xuan [a], Anne-Marie Lamhonwah [a], Clifford Librach [b], Keith Jarvi [c], Ingrid Tein [a]





Biochemical and Biophysical Research Communications
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Characterization of organic cation/carnitine transporter family in human sperm

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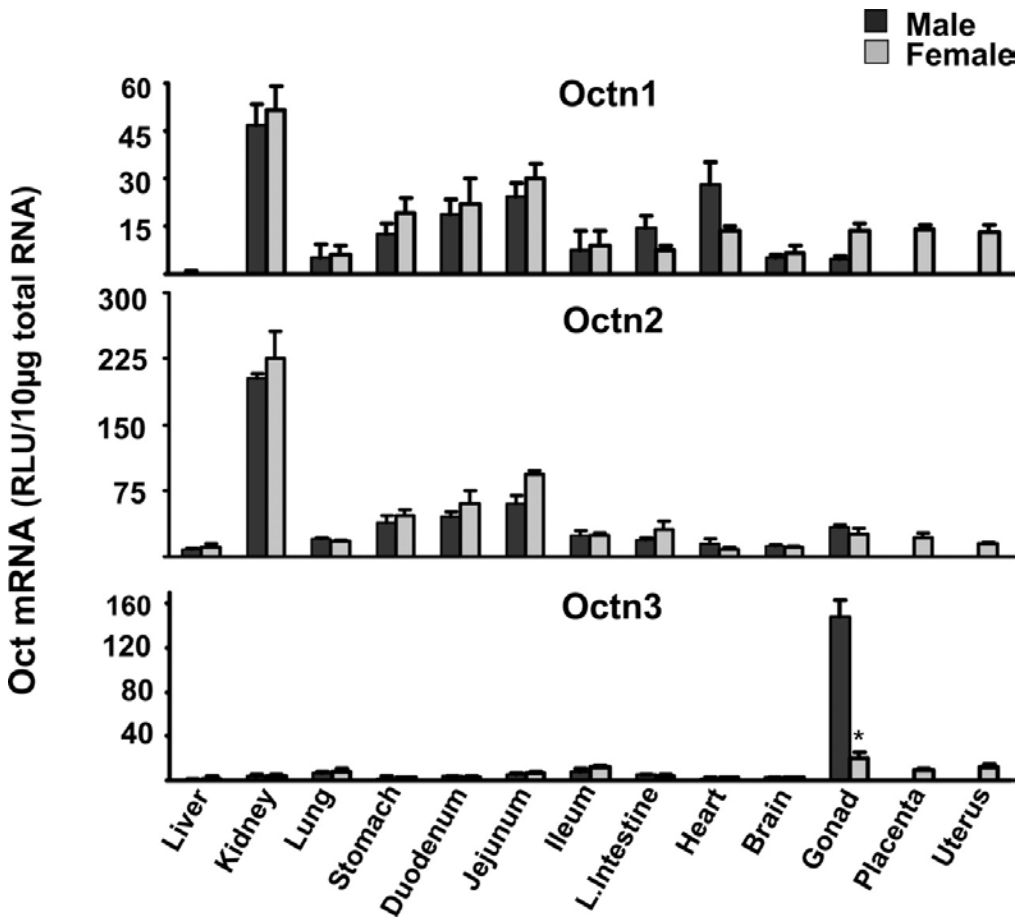
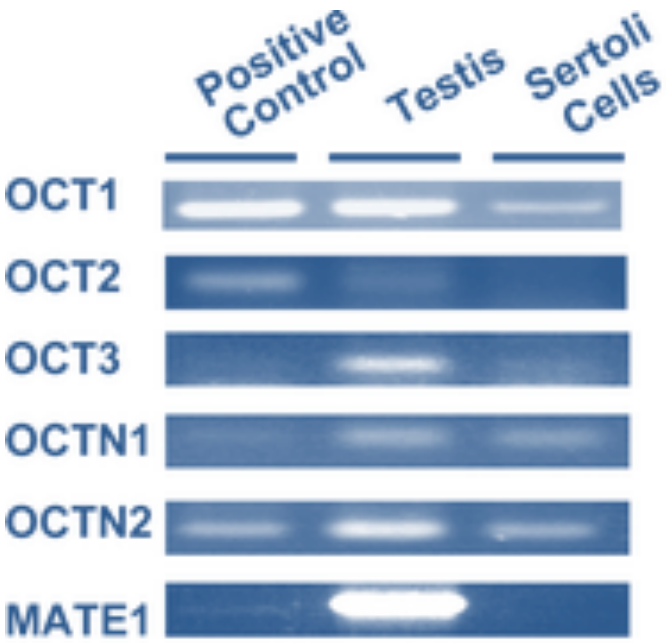
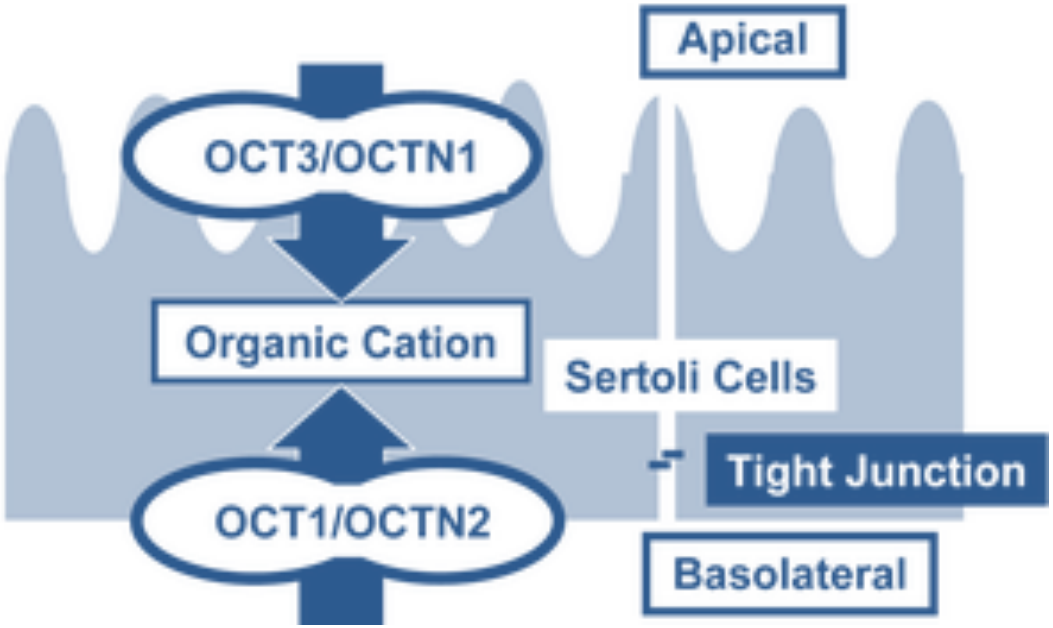
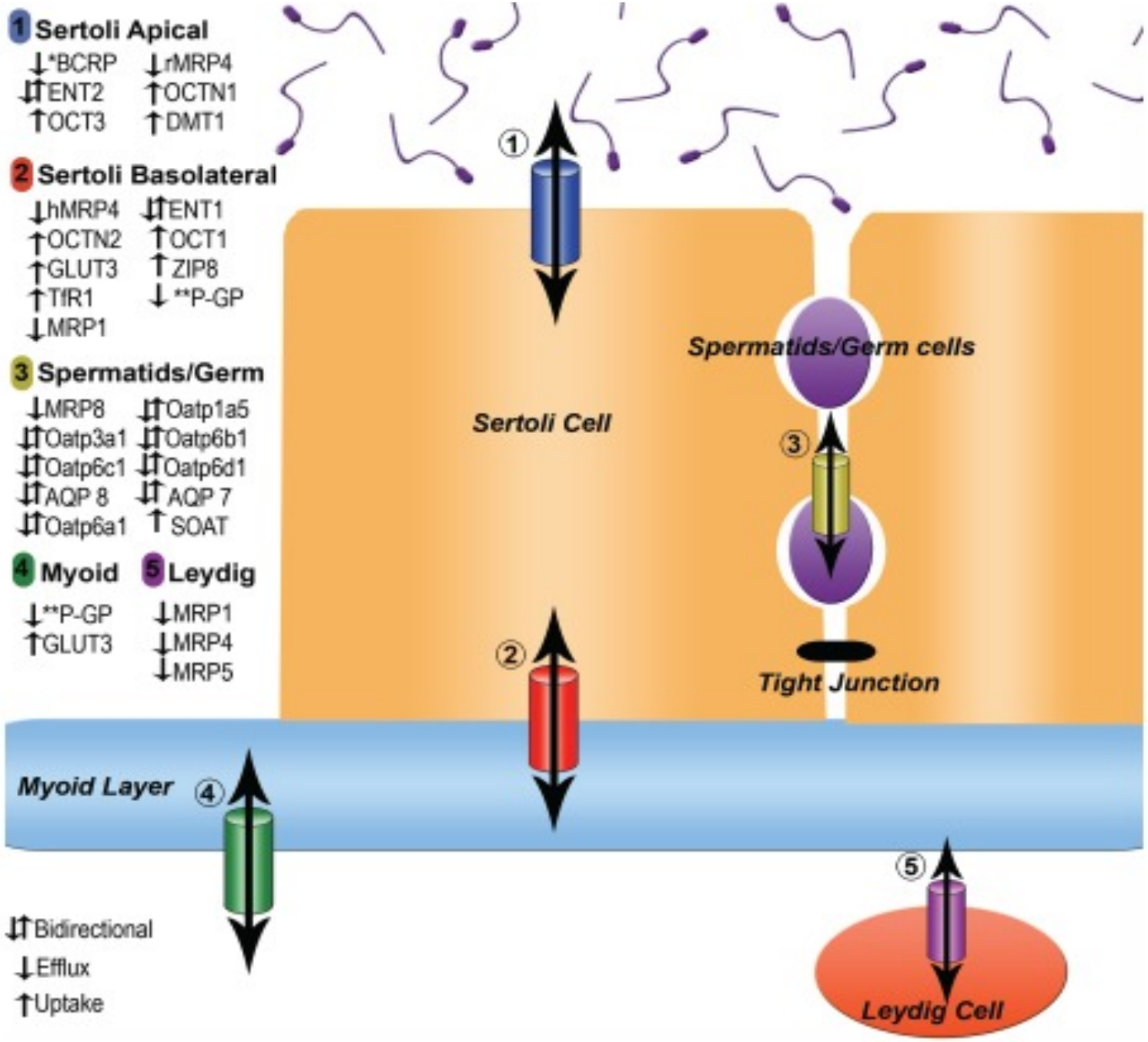
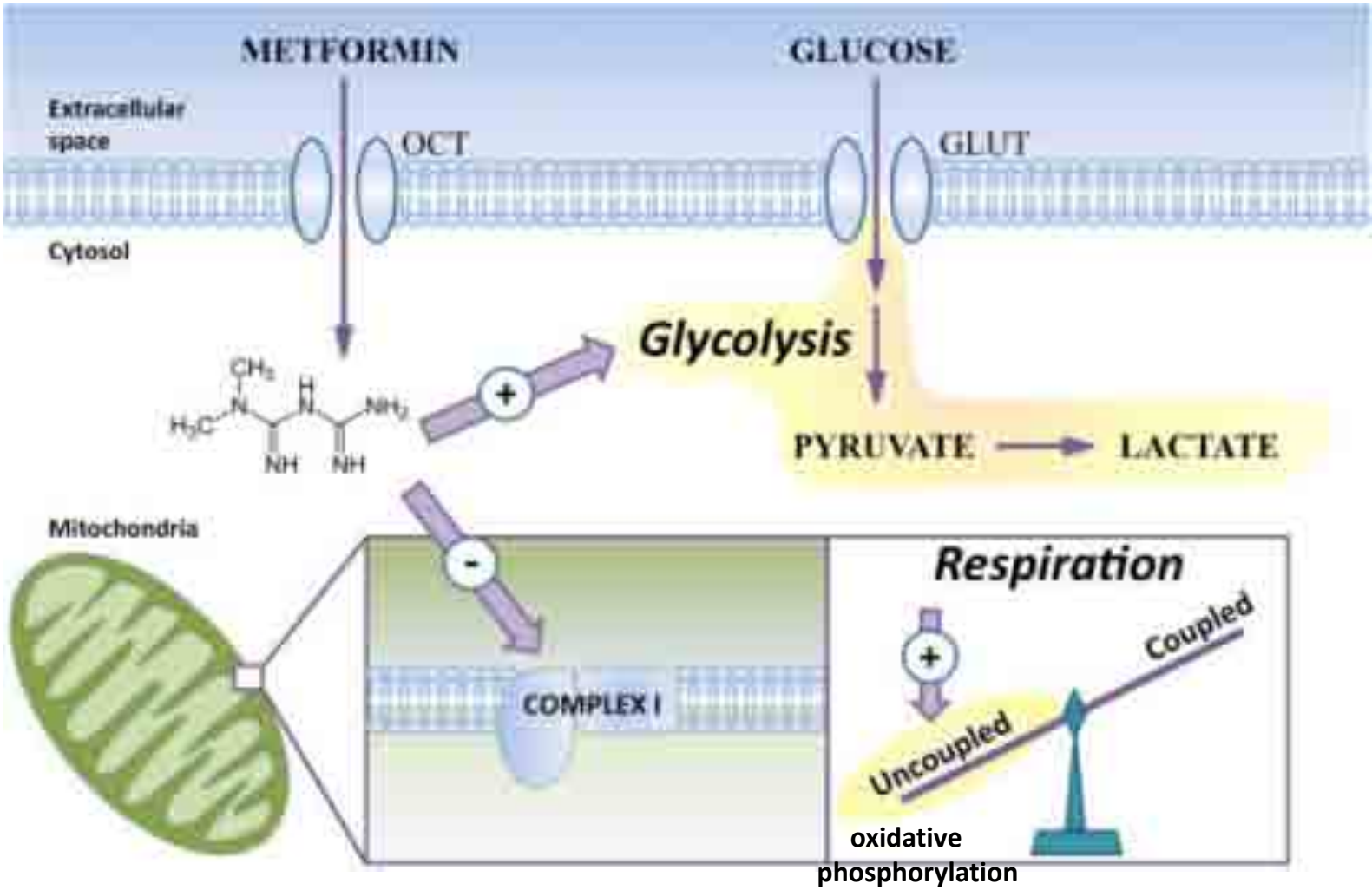



Positive Control
Testis
Sertoli Cells
OCT1
OCT2
OCT3
OCTN1
OCTN2
MATE1

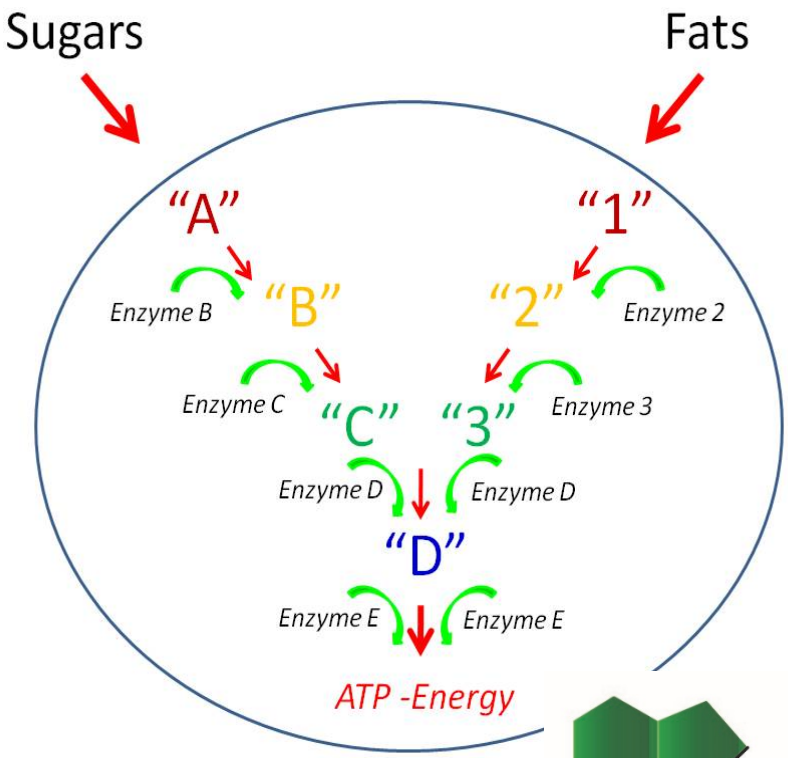

Apical
OCT3/OCTN1
Organic Cation
Sertoli Cells
Tight Junction
OCT1/OCTN2
Basolateral

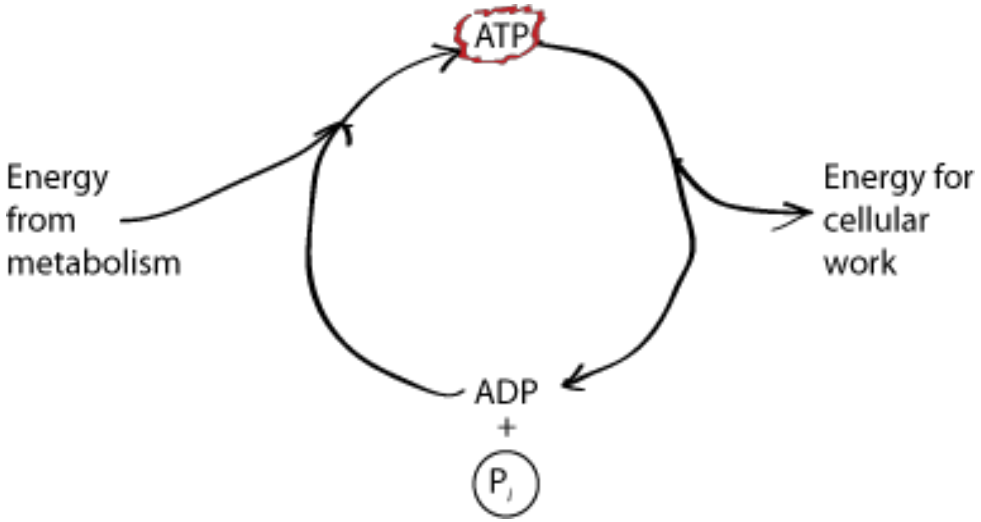

1 Sertoli Apical
↓*BCRP ↓rMRP4
↓↑ENT2 ↑OCTN1
↑OCT3 ↑DMT1
2 Sertoli Basolateral
↓hMRP4 ↓↑ENT1
↑OCTN2 ↑OCT1
↑GLUT3 ↑ZIP8
↑TfR1 ↓**P-GP
↓MRP1
3 Spermatids/Germ
↓MRP8 ↓↑Oatp1a5
↓↑Oatp3a1 ↓↑Oatp6b1
↓↑Oatp6c1 ↓↑Oatp6d1
↓↑AQP 8 ↓↑AQP 7
↓↑Oatp6a1 ↑SOAT
4 Myoid
↓**P-GP
↑GLUT3
5 Leydig
↓MRP1
↓MRP4
↓MRP5
↓↑Bidirectional
↓Efflux
↑Uptake
Sertoli Cell
Spermatids/Germ cells
Tight Junction
Myoid Layer
Leydig Cell
①
②
③
④
⑤

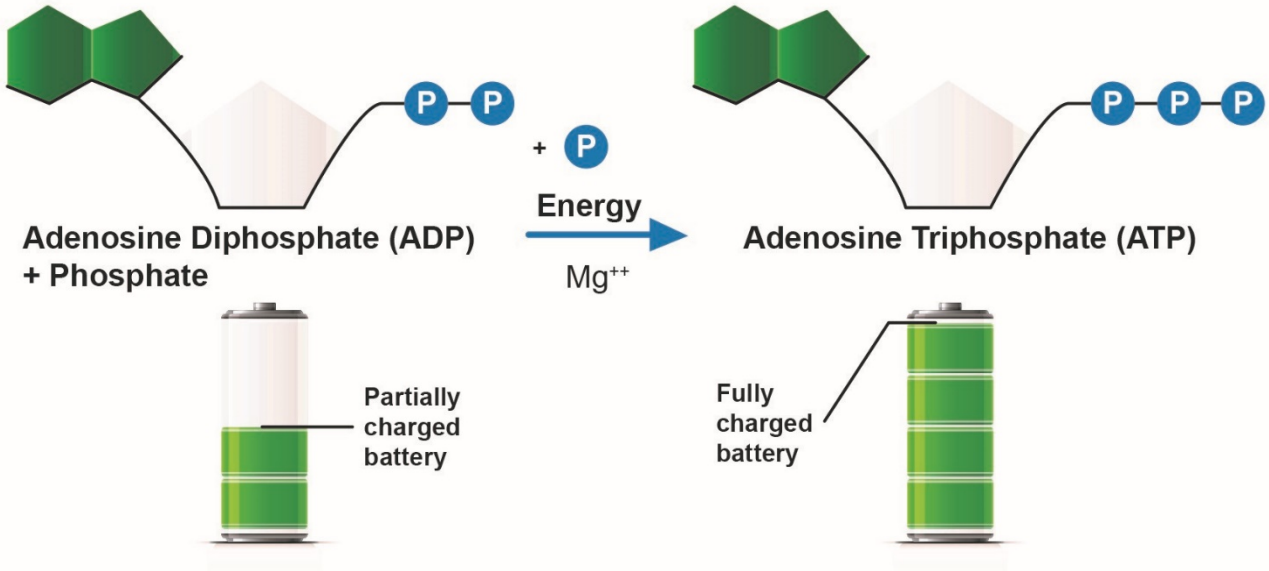


Metformin directly acts on mitochondria and shifts the balance between coupling and uncoupling reactions. Metformin is transported into cells through the OCT family of transporters, where it acts on mitochondria to inhibit complex I-dependent respiration and increase the proportion of uncoupled respiration. Cells respond by increasing glycolysis, ultimately leading to increased lactate production.

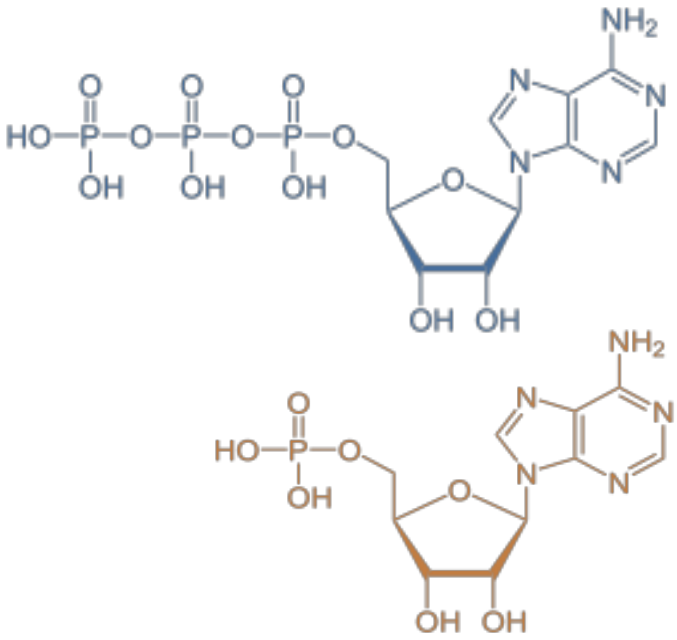
As a result, mitochondrial metabolism becomes energetically inefficient, and cells compensate for this limitation in ATP production by increasing aerobic glycolysis.

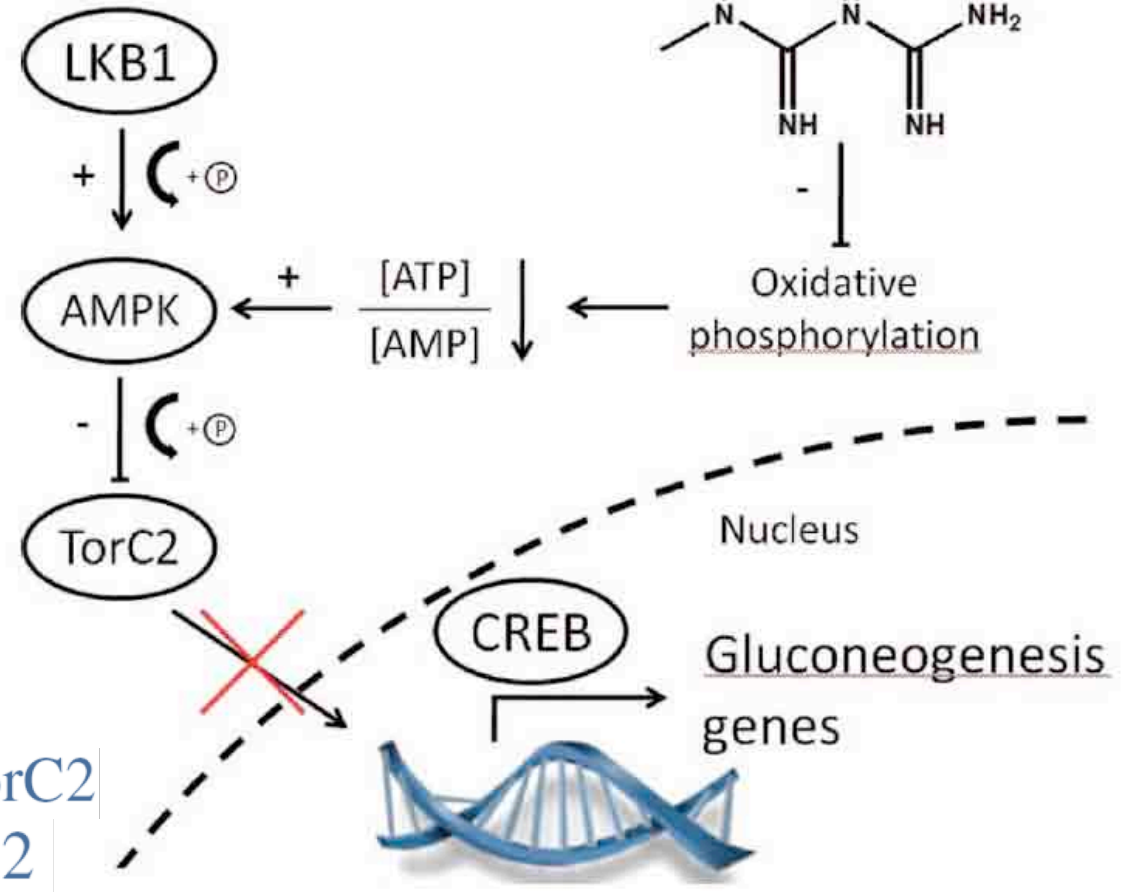

Sugars
Fats
"A"
"1"
Enzyme B
"B"
"2"
Enzyme 2
Enzyme C
"C"
"3"
Enzyme 3
Enzyme D
Enzyme D
"D"
Enzyme E
Enzyme E
ATP -Energy


ATP
Energy from metabolism
Energy for cellular work
ADP
+
P_i


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

kinase and tumor suppressor LKB1



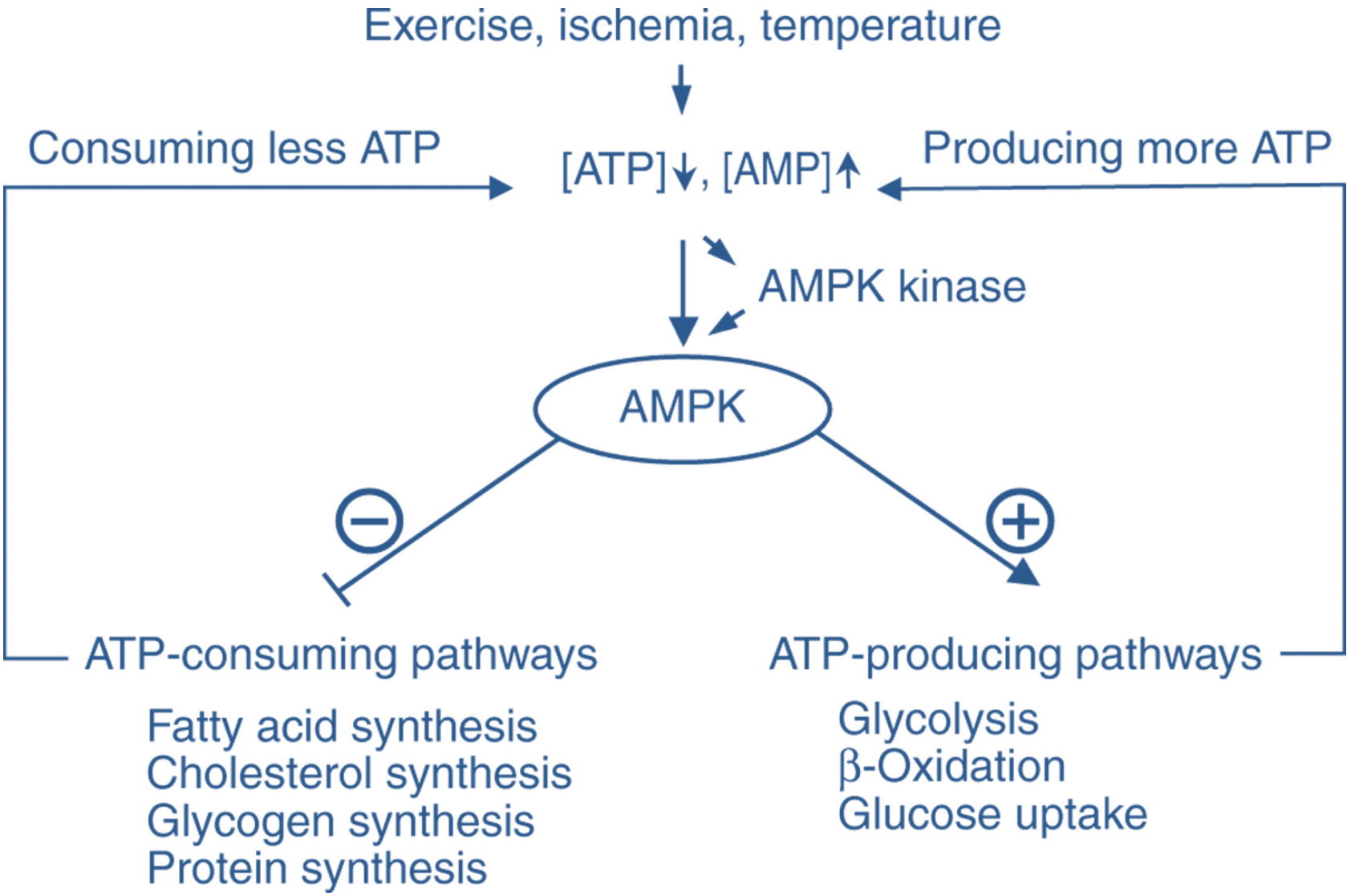


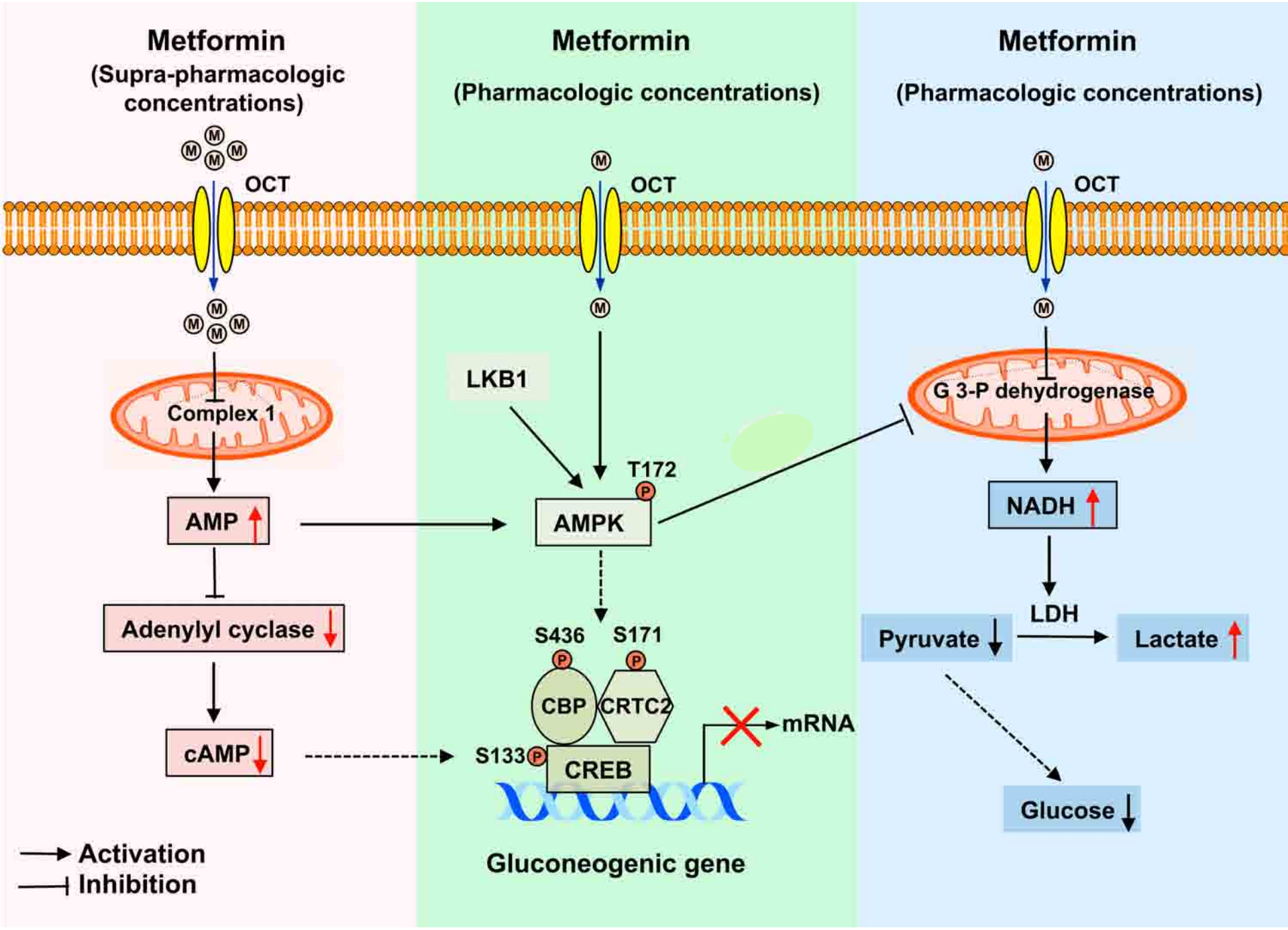
transcriptional activator TorC2

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.

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


Metformin
(Supra-pharmacologic concentrations)
Metformin
(Pharmacologic concentrations)
Metformin
(Pharmacologic concentrations)
OCT
OCT
OCT
M
Complex 1
LKB1
G 3-P dehydrogenase
AMP
AMPK
T172
P
NADH
Adenylyl cyclase
LDH
Pyruvate
Lactate
S436
S171
CBP
CRTC2
mRNA
cAMP
S133
CREB
Glucose
Activation
Inhibition
Gluconeogenic gene

BJP British Journal of Pharmacology

RESEARCH PAPER

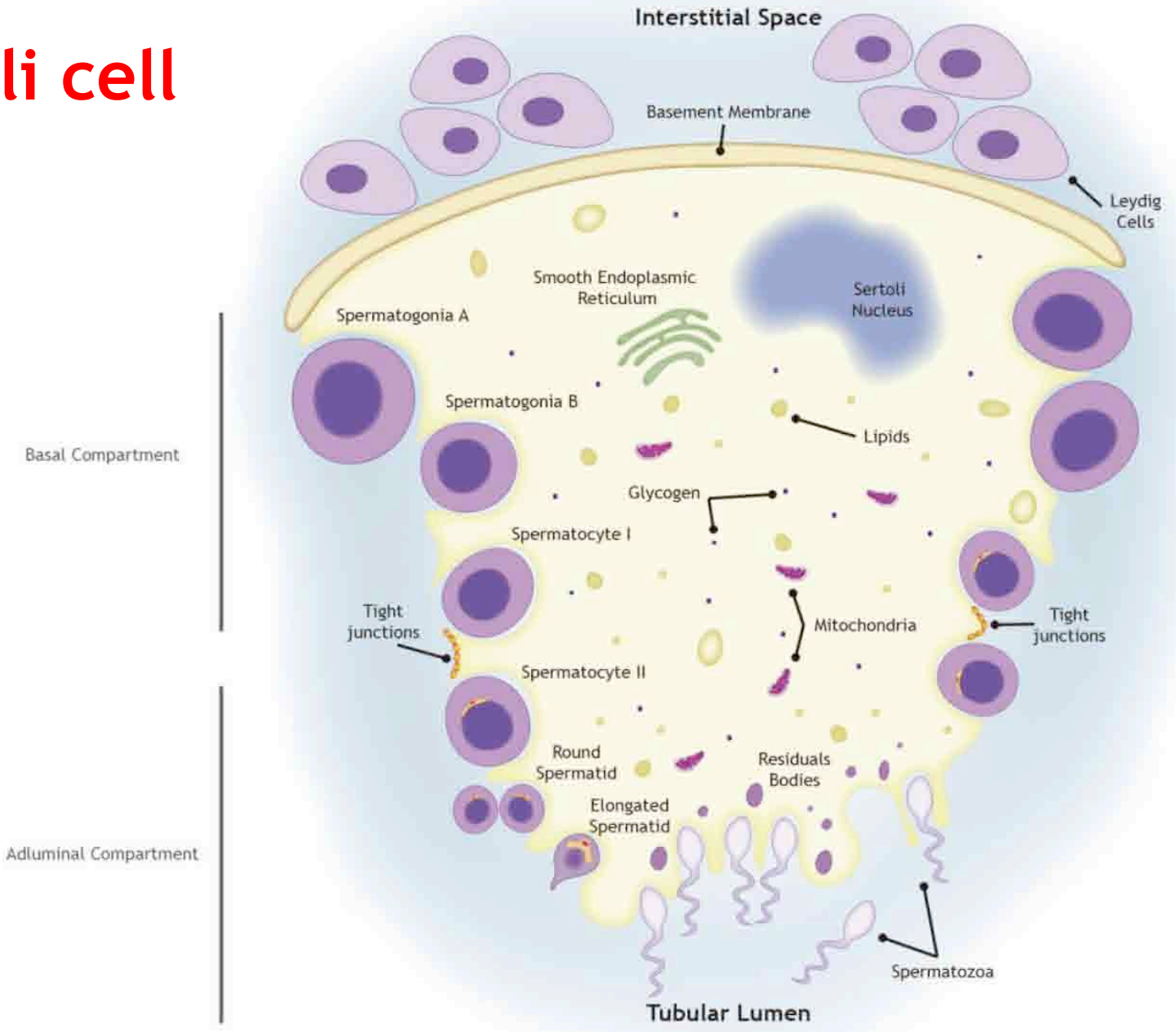
Metformin and male reproduction: effects on Sertoli cell metabolism

M G Alves[1]*, A D Martins[1]*, C V Vaz[1], S Correia[1], P I Moreira[2], P F Oliveira[1] and S Socorro[1]

[1]*CICS-UBI – Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal, and* [2]*CNC – Center for Neuroscience and Cell Biology, University of Coimbra & Laboratory of Physiology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal*

British Journal of Pharmacology (2014) **171** 1033–1042 1033

Sertoli cell



BJP British Journal of Pharmacology

RESEARCH PAPER

Metformin and male reproduction: effects on Sertoli cell metabolism

CONCLUSIONS AND IMPLICATIONS

Our results indicate that metformin: (i) decreases mRNA and protein levels of glycolysis-related transporters in SCs but increases their activity; and (ii) stimulates alanine production, which induces antioxidant activity and maintains the NADH/NAD^+ equilibrium. The increased lactate in metformin-treated SCs provides nutritional support and has an anti-apoptotic effect in developing germ cells. Thus, metformin can be considered as a suitable antidiabetic drug for male patients of reproductive age with T2D.

International Journal of *Molecular Sciences*

Int. J. Mol. Sci. **2018**, *19*, 3293;

MDPI

Review

AMPK Function in Mammalian Spermatozoa

David Martin-Hidalgo [1,2,†], Ana Hurtado de Llera [1,3,†], Violeta Calle-Guisado [1], Lauro Gonzalez-Fernandez [1], Luis Garcia-Marin [1] and M. Julia Bragado [1,*]

[1] Research Group of Intracellular Signaling and Technology of Reproduction (SINTREP), Institute of Biotechnology in Agriculture and Livestock (INBIO G+C), University of Extremadura, 10003 Cáceres, Spain; davidmh@unex.es (D.M.-H.); anahl@unex.es (A.H.d.L.); violetacg@unex.es (V.C.-G.); lgonfer@unex.es (L.G.-F.); ljgarcia@unex.es (L.G.-M.)

International Journal of *Molecular Sciences*

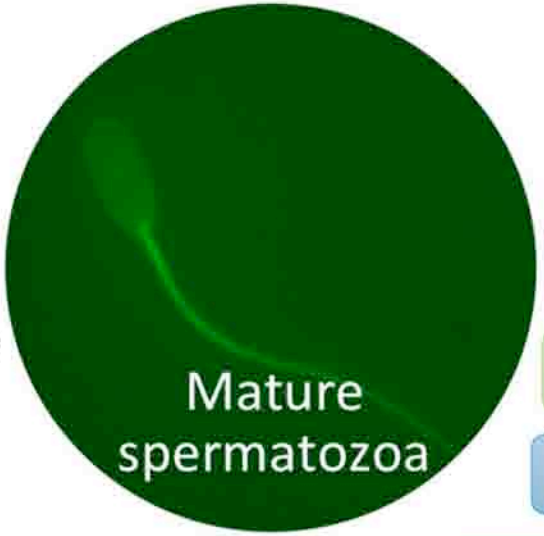
AMPK

Testicular size

Spermatogenesis

Leydig cells:
Testosterone production
Morphology

Sertoli cells:
Number / Survival / Proliferation
Function
Metabolism (Lactate production, glucose transport…)
Morphology



Quality

Fertility

Number

Morphology

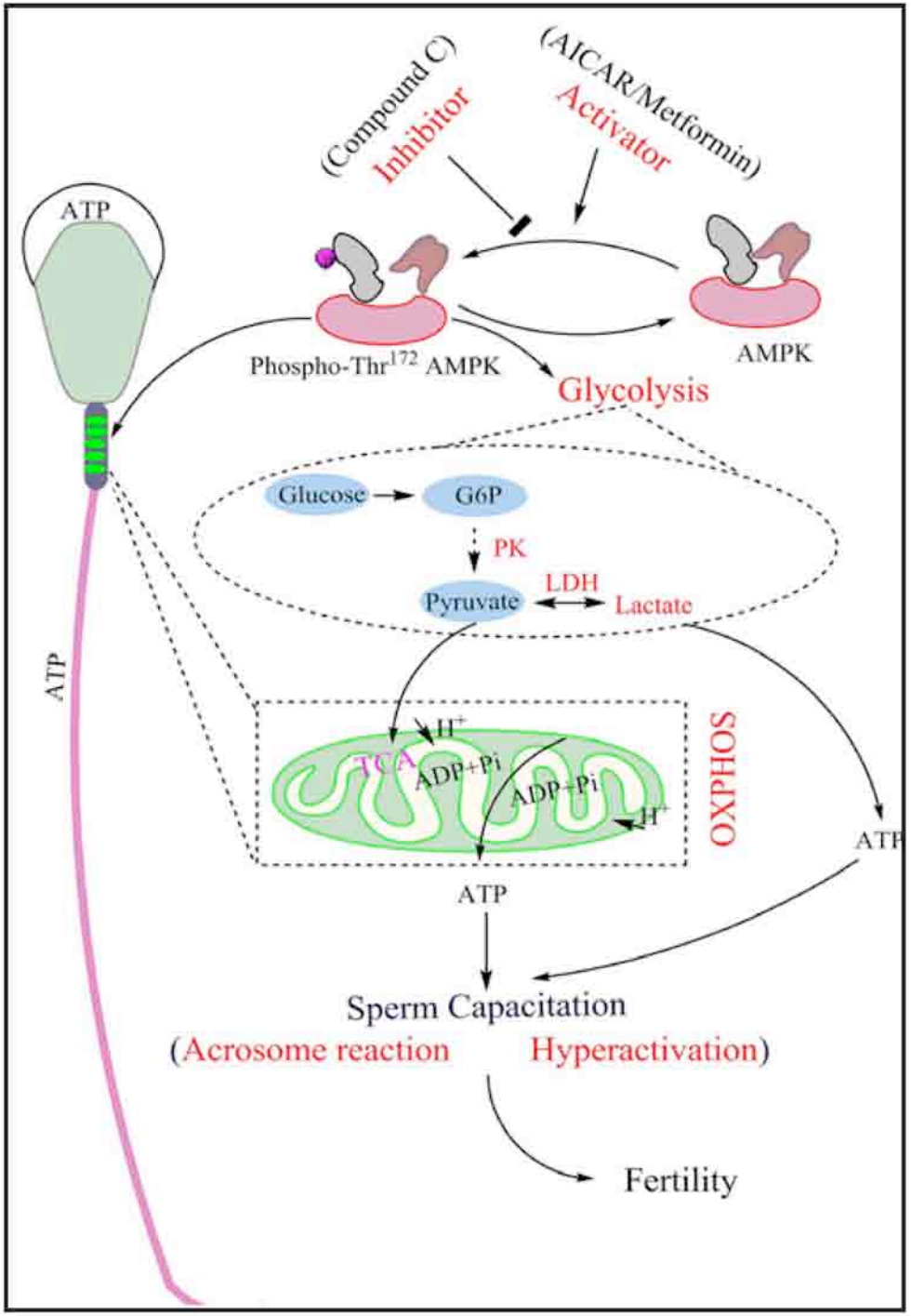
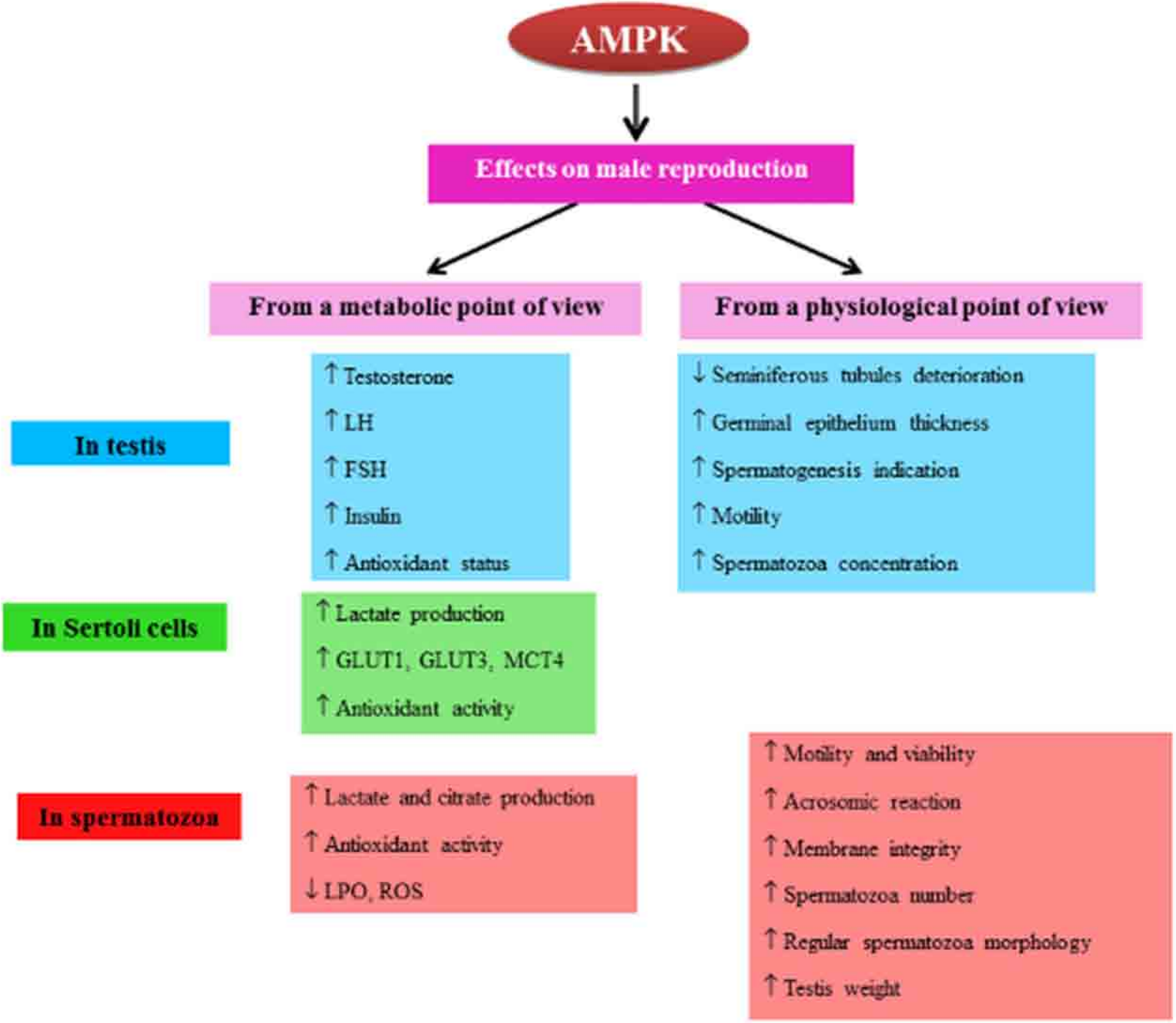
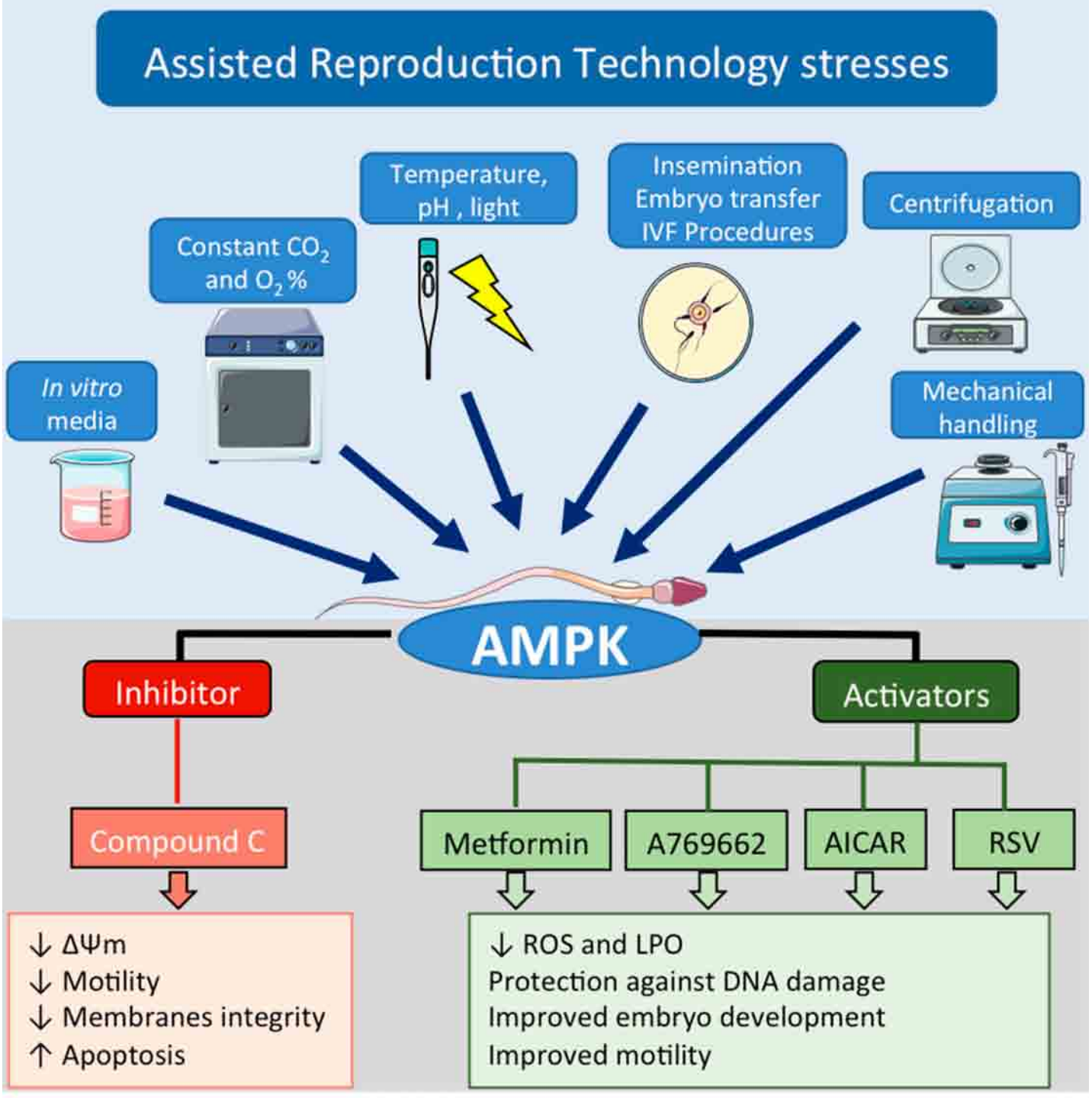


Diagram showing that AMPK regulates sperm functions. AMPK is activated by phosphorylation of the Thr172 residue, which is located at the critical activation loop of the α subunit. AMPK could be modulated by activator (AICAR and Metformin) and inhibitor (Compound C).

Activation of sperm with AMPK activators (AICAR or Metformin) causes increase of phospho-Thr172-AMPK, and results in an enhancing of PK and LDH activity, which improves sperm energy metabolism of glycolysis and oxidative phosphorylation (OXPHOS), then leads to promoting ATP synthesis, thus providing energy for sperm, and thus results in sperm hyperactivation and acrosome reaction.


AMPK
Effects on male reproduction
From a metabolic point of view
From a physiological point of view
In testis
↑ Testosterone
↑ LH
↑ FSH
↑ Insulin
↑ Antioxidant status
↓ Seminiferous tubules deterioration
↑ Germinal epithelium thickness
↑ Spermatogenesis indication
↑ Motility
↑ Spermatozoa concentration
In Sertoli cells
↑ Lactate production
↑ GLUT1, GLUT3, MCT4
↑ Antioxidant activity
In spermatozoa
↑ Lactate and citrate production
↑ Antioxidant activity
↓ LPO, ROS
↑ Motility and viability
↑ Acrosomic reaction
↑ Membrane integrity
↑ Spermatozoa number
↑ Regular spermatozoa morphology
↑ Testis weight


Assisted Reproduction Technology stresses
Temperature, pH , light
Insemination Embryo transfer IVF Procedures
Centrifugation
Constant CO_2 and O_2 %
In vitro media
Mechanical handling
AMPK
Inhibitor
Activators
Compound C
Metformin
A769662
AICAR
RSV
↓ ΔΨm
↓ Motility
↓ Membranes integrity
↑ Apoptosis
↓ ROS and LPO
Protection against DNA damage
Improved embryo development
Improved motility

Asian Journal of Andrology (2015) 17, 942–947

www.asiaandro.com; www.ajandrology.com

Open Access

INVITED REVIEW

Sperm Biology

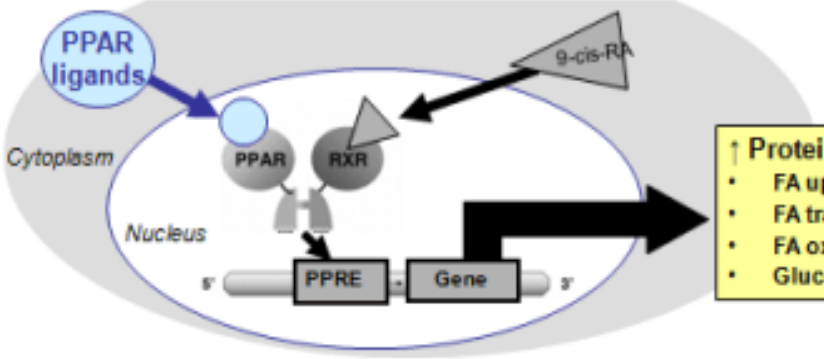
Peroxisome proliferator-activated receptor gamma signaling in human sperm physiology

Li-Li Liu[1,2], Hua Xian[2], Jing-Chen Cao[1], Chong Zhang[1], Yong-Hui Zhang[1], Miao-Miao Chen[1], Yi Qian[1,2], Ming Jiang[1,3]

Peroxisome proliferator-activated receptor gamma (*PPARγ*) is a member of the *PPARs*, which are transcription factors of the steroid receptor superfamily. *PPARγ* acts as an important molecule for regulating energy homeostasis, modulates the hypothalamic-pituitary-gonadal (HPG) axis, and is reciprocally regulated by HPG. In the human, *PPARγ* protein is highly expressed in ejaculated spermatozoa, implying a possible role of *PPARγ* signaling in regulating sperm energy dissipation. *PPARγ* protein is also expressed in Sertoli cells and germ cells (spermatocytes). Its activation can be induced during capacitation and the acrosome reaction. This mini-review will focus on how *PPARγ* signaling may affect fertility and sperm quality and the potential reversibility of these adverse effects.

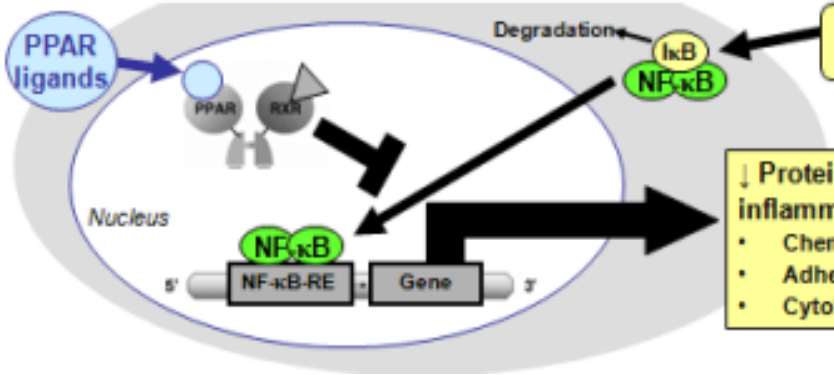
Asian Journal of Andrology (2015) **17**, 942–947; doi: 10.4103/1008-682X.150253; published online: 7 April 2015

Stimulatory effect of PPAR on gene expression

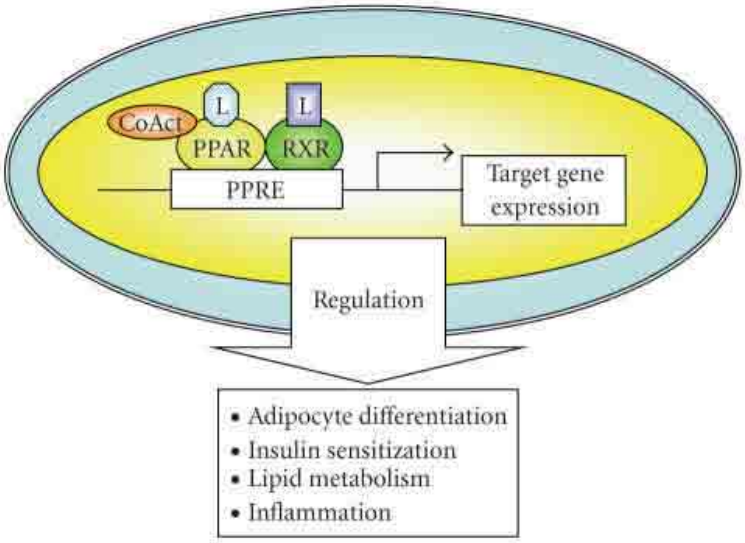


↑ Proteins involved in …
- FA uptake
- FA trafficking
- FA oxidation
- Glucose uptake

Inhibitory effect of PPAR on gene expression



↓ Proteins mediating inflammatory response
- Chemokines
- Adhesion molecules
- Cytokines



Trans- activation	Trans- repression
Lipid metabolism	Anti-inflammatory properties
Glucose homeostasis	

Asian Journal of Andrology (2015) 17, 942–947

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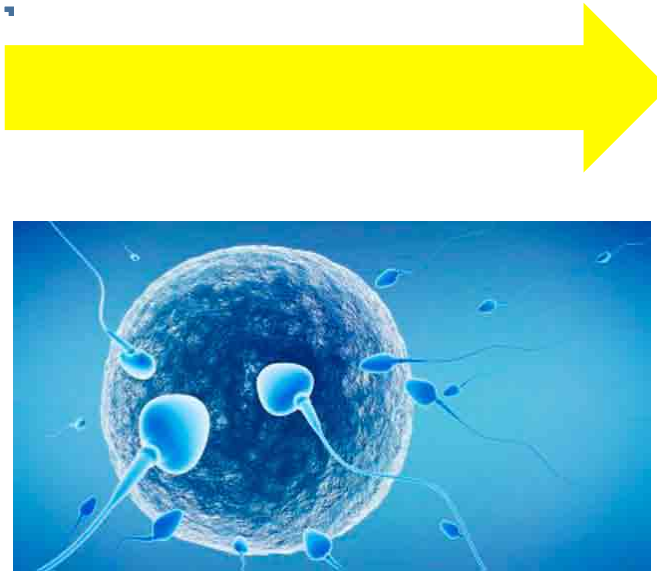
Asian Journal of Andrology

Open Access

INVITED REVIEW

Peroxisome proliferator-activated receptor gamma signaling in human sperm physiology

PPARs G influences sperm biology and physiology by regulating:



motility
capacitation
acrosome reaction
survival
metabolism

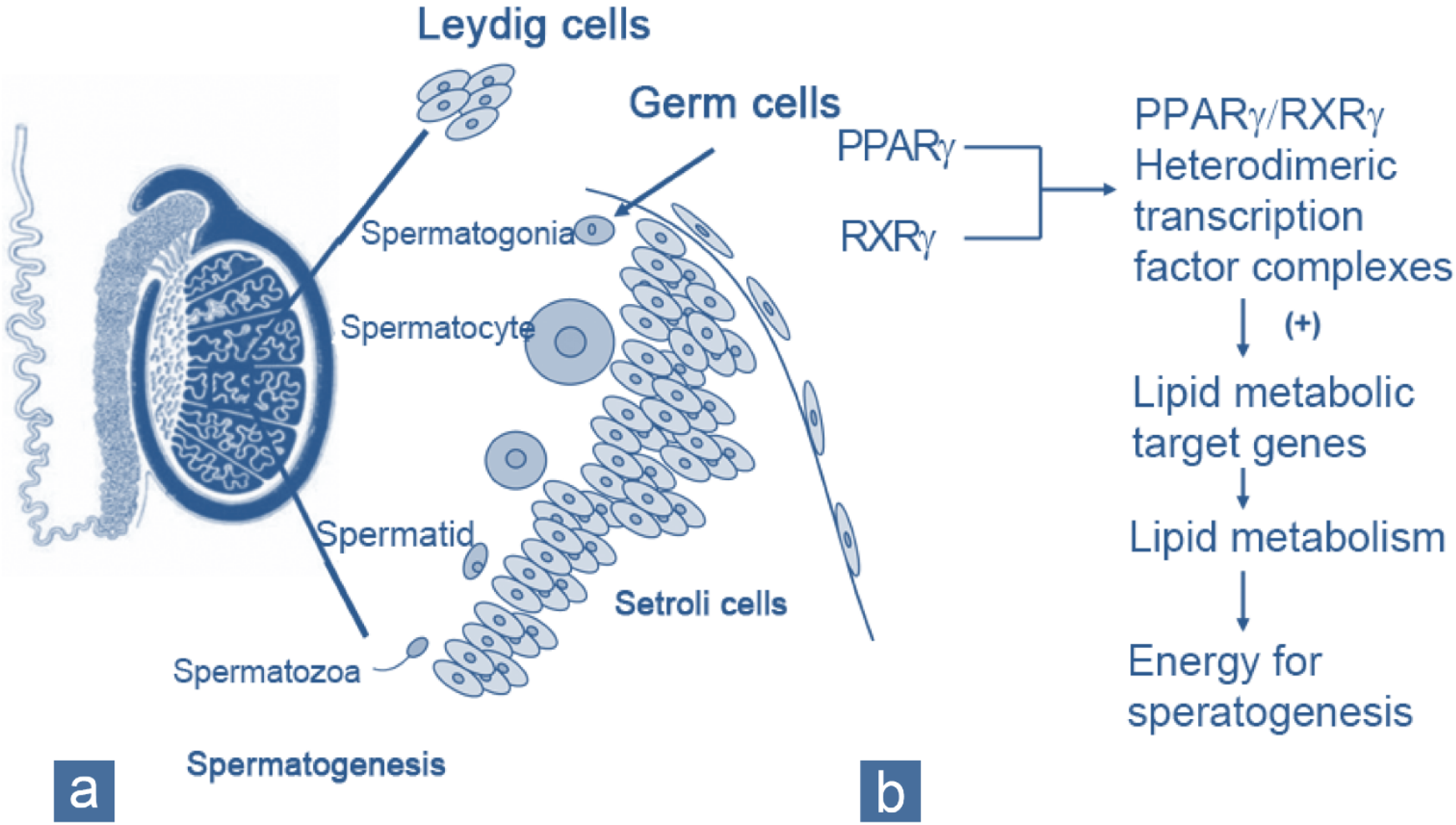


Figure 2: Expression patterns of PPARg shows in the testis. (**a**) In the testis, *PPARγ* protein is detected at high expression in Sertoli cells and weak expression in spermatocytes. The names of cells expressing *PPARγ* are underlined. (**b**) *PPARγ* forms obligate heterodimers with *RXRγ* for regulation of lipid metabolic target genes, providing energy for spermatogenesis. *PPARγ*: peroxisome proliferator-activated receptor gamma; *RXRγ*: retinoid X receptor gamma.

Asian Journal of Andrology

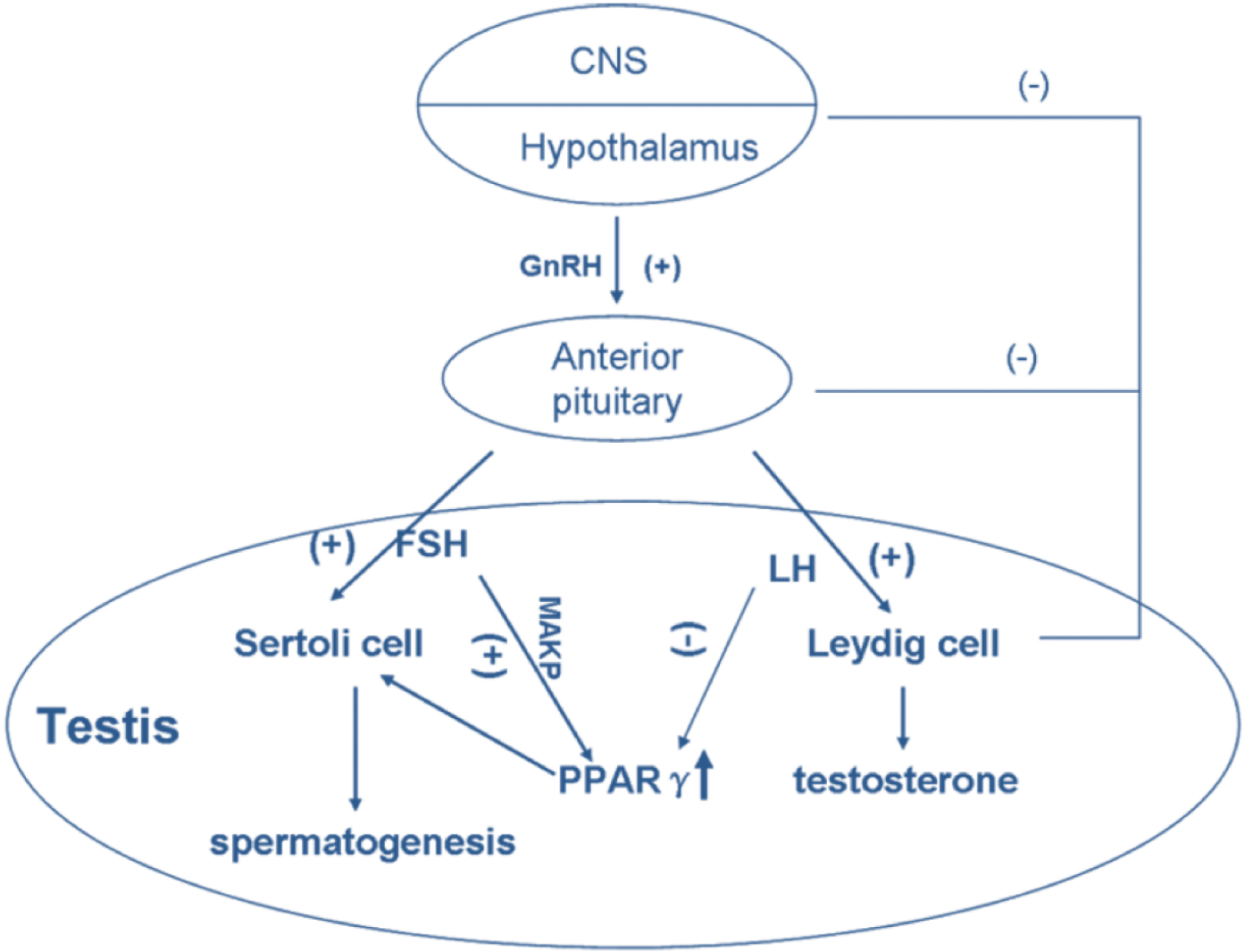


Figure 1: *PPARγ* functions in hypothalamic-pituitary-gonadal axis. Pulsatile GnRH production signals gonadotroph cells in the anterior pituitary to produce *FSH* and *LH* that then act on the testis to regulate spermatogenic potential. *FSH* up-regulates the expression of *PPARγ* through *MAPK* signaling pathways while *LH* inhibits the function of *PPARγ* via various pathways. High expression of testosterone suppresses the secretion of *LH* by negative feedback, providing a relatively persistent high-expression of *PPARγ*. *PPARγ*: peroxisome proliferator-activated receptor gamma; *FSH*: follicle-stimulating hormone; *LH*: luteinizing hormone; *MAPK*: mitogen-activated protein kinase.

Asian Journal of Andrology

The International Journal of Biochemistry & Cell Biology 79 (2016) 52–60

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

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

Pioglitazone increases the glycolytic efficiency of human Sertoli cells with possible implications for spermatogenesis

M.J. Meneses[a,b], R.L. Bernardino[a], R. Sá[a], J. Silva[c], A. Barros[c,d,e], M. Sousa[a,c], B.M. Silva[b], P.F. Oliveira[a,e], M.G. Alves[b,*]

[a] Department of Microscopy, Laboratory of Cell Biology and Unit for Multidisciplinary Research in Biomedicine (UMIB), Abel Salazar Institute of Biomedical Sciences (ICBAS), University of Porto, 4050-313 Porto, Portugal

A B S T R A C T

Pioglitazone is a synthetic agonist for the nuclear receptor peroxisome proliferator-activated receptor γ used to treat type 2 diabetes mellitus. Recently we reported that antidiabetic drugs regulate the nutritional support of spermatogenesis by Sertoli cells. Herein, we investigate the effects of pioglitazone on human Sertoli cells metabolism. Human Sertoli cells were cultured in the presence of pioglitazone (1, 10, 100 μM). Protein levels of phosphofructokinase 1, lactate dehydrogenase, hexokinase, glucose transporters (GLUT1, GLUT2, GLUT3), monocarboxylate transporter 4 and oxidative phosphorylation complexes were determined by Western blot. Lactate dehydrogenase and alanine aminotransferase activity were assessed and metabolite production and consumption determined by proton nuclear magnetic resonance. Mitochondrial membrane potential was also determined. Glucose consumption more than doubled in human Sertoli cells stimulated with pioglitazone 100 μM. Mitochondrial complex II protein levels increased 50% with exposure to pioglitazone (100 μM) in human Sertoli cells, though mitochondrial membrane potential was decreased by 32%. The pharmacological concentration of pioglitazone (10 μM) almost doubled lactate production and established crucial correlations among key intervenient of glycolysis. Moreover, in the same concentration, alanine aminotransferase decreased more than 80%. Our results suggest that pioglitazone (10 μM) increases the efficiency of the glycolytic flux and lactate production by human Sertoli cells, which is essential to sustain and preserve the spermatogenic event. Thus, pioglitazone may improve male fertility and thus, be considered a suitable antidiabetic drug for men in reproductive age.

NRC Research Press

Canadian Journal of Physiology and Pharmacology

ARTICLE

Taurine and pioglitazone attenuate diabetes-induced testicular damage by abrogation of oxidative stress and up-regulation of the pituitary–gonadal axis

Sanaa M. Abd El-Twab, Hanaa M. Mohamed, and Ayman M. Mahmoud

Abstract: Chronic hyperglycemia is associated with impairment of testicular function. The current study aimed to investigate the protective effects and the possible mechanisms of taurine and pioglitazone against diabetes-induced testicular dysfunction in rats. Diabetes was induced by streptozotocin injection. Both normal and diabetic rats received taurine (100 mg/kg) or pioglitazone (10 mg/kg) orally and daily for 6 weeks. Diabetic rats showed a significant ($P < 0.001$) increase in glycosylated hemoglobin, glucose, homeostasis model of insulin resistance, and pro-inflammatory cytokines. Serum insulin, testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were significantly ($P < 0.001$) decreased in diabetic rats. Taurine and pioglitazone alleviated hyperglycemia, decreased pro-inflammatory cytokines, and increased circulating levels of insulin, testosterone, LH, and FSH. Gene and protein expression of LH and FSH receptors and cytochrome P450 17α-hydroxylase (CYP17) was significantly ($P < 0.001$) down-regulated in testes of diabetic rats, an effect which was significantly increased after administration of taurine and pioglitazone. In addition, taurine and pioglitazone significantly decreased lipid peroxidation and DNA damage, and enhanced activity of the antioxidant enzymes in testes of diabetic rats. In conclusion, taurine and pioglitazone exerted protective effects against diabetes-induced testicular damage through attenuation of hyperglycemia, inflammation, oxidative stress and DNA damage, and up-regulation of the pituitary/gonadal axis.

Can. J. Physiol. Pharmacol. **94**: 651–661 (2016)

International Journal of Medical Laboratory 2018;5(1):19-34.

International Journal of Medical Laboratory
Shahid Sadoughi University of Medical Sciences

Original Article

Modulatory Effect of Pioglitazone on Sperm Parameters and Oxidative Stress, Apoptotic and Inflammatory Biomarkers in Testes of Streptozotocin-Induced Diabetic Rats

Farin Malekifard[1*] Ph.D., Nowruz Delirezh[1] Ph.D.
Ali Soleimanzadeh[2] D.V.Sc.

[1]Department of Microbiology, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran.
[2]Department of Theriogenology, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran.

International Journal of Medical Laboratory 2018;5(1):19-34.
International Journal of Medical Laboratory
Shahid Sadoughi University of Medical Sciences

Original Article

Modulatory Effect of Pioglitazone on Sperm Parameters and Oxidative Stress, Apoptotic and Inflammatory Biomarkers in Testes of Streptozotocin-Induced Diabetic Rats

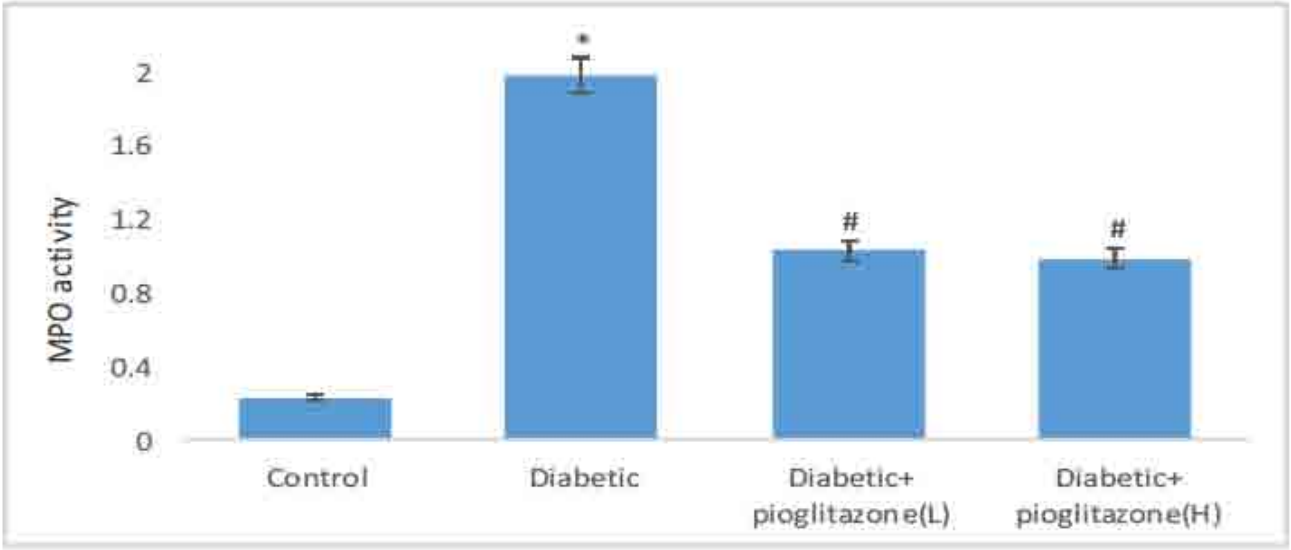


Fig. 4. Effect of low (1 mg/kg) and high (10 mg/kg) doses of pioglitazone on testicular myeloperoxidase activity (MPO) in streptozotocin-induced diabetic rats. Data are represented as mean±SEM *$p<0.05$ vs. control; #$p<0.05$ vs. diabetic. pioglitazone (L)= low dose of pioglitazone; pioglitazone (H)= high dose of pioglitazone

Middle East Fertility Society Journal (2015) **20**, 271–279

Middle East Fertility Society

Middle East Fertility Society Journal

www.mefsjournal.org
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ORIGINAL ARTICLE

PPAR-γ agonist pioglitazone improves semen quality and testicular histomorphometrics with partial reversal of hyperglycaemia in alloxan-induced diabetic rats

O.B. Akinola [a,*], O.O. Dosumu [b], S.A. Sanusi [a], T.F. Ajayi [a], T.H. Olajide [a]

[a] *Department of Anatomy, Faculty of Basic Medical Sciences, College of Health Sciences, University of Ilorin, Ilorin, Nigeria*
[b] *Department of Anatomy, College of Medicine, University of Lagos, Nigeria*

GLP-1

- **Exenatide: a mechanism via improving mitochondrial function involving the GLP-1 receptor/cAMP/ PKA pathway**
- **Increased SOD levels and decreased MDA levels and action against oxidative stress induced by H2O2 increasing the concentration of antioxidant defense enzymes and inhibiting cell apoptosis**

AJRI American Journal of Reproductive Immunology
Official Journal of the American Society for Reproductive Immunology

Volume74, Issue5 November 2015 - Pages 457-466

GLP-1 Receptor Agonist Exenatide Attenuates the Detrimental Effects of Obesity on Inflammatory Profile in Testis and Sperm Quality in Mice

Problem

Male obesity has been linked to subfecundity. This study is to investigate the effects of GLP-1 receptor (GLP-1R) agonist exenatide on sperm quality in high-fat diet (HFD)-induced obese mice.

Method of study

After 12 weeks of chow diet (CD) or HFD challenge, mice on HFD were allocated to either saline or exenatide (24 nmol/kg/day) interventions for 8 weeks. Sperm quality and the inflammatory profile of testis were compared among three groups.

AJRI American Journal of Reproductive Immunology
Official Journal of the American Society for Reproductive Immunology

Volume74, Issue5 November 2015 - Pages 457-466

GLP-1 Receptor Agonist Exenatide Attenuates the Detrimental Effects of Obesity on Inflammatory Profile in Testis and Sperm Quality in Mice

Results

Obesity reduced the quality of sperm and changed the inflammatory profile characterized by increased mRNA expression levels of TNF-α, MCP-1, and F4/80 in testis. Exenatide intervention reduced the expression of pro-inflammatory cytokines and improved the quality of sperm.

Conclusion

HFD-induced obesity leads to the impairment of sperm quality and increased inflammation of testis in mice, and the abnormal physiology can be attenuated by exenatide treatment. Exenatide treatment may bring additional profits to obese and diabetes men by improving sperm function.

AJRI American Journal of Reproductive Immunology
Official Journal of the American Society for Reproductive Immunology

Volume74, Issue5 November 2015 - Pages 457-466

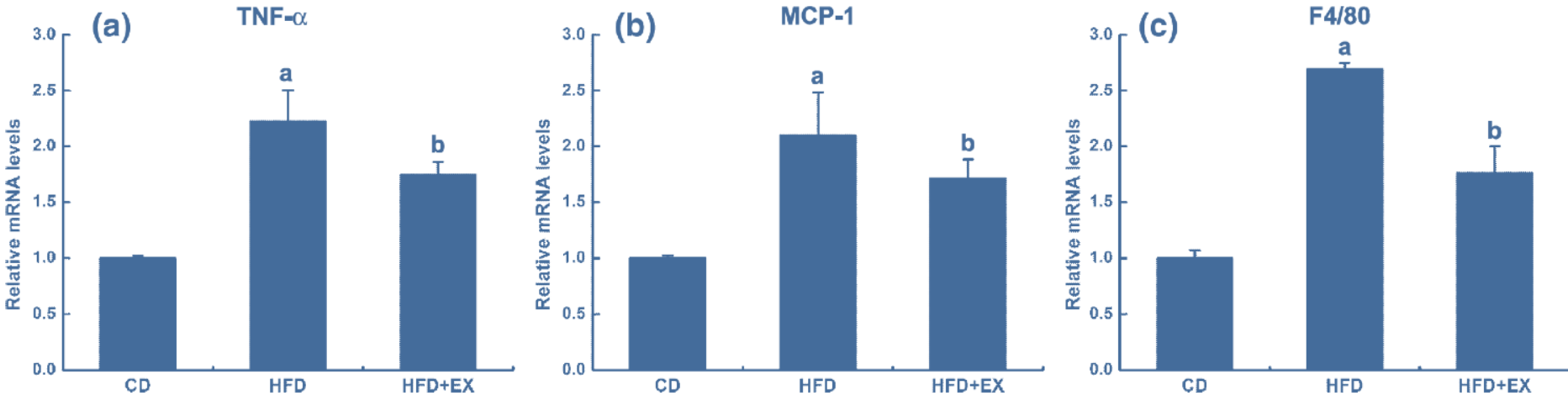

Fig. 4 Effect of diet and exenatide on pro-inflammatory cytokines expression levels in testis. Data were presented as mean ± S.E.M. (n = 5–6). CD, control diet; HFD, high-fat diet; HFD + EX, high-fat diet + exenatide. [a]means $P < 0.05$, HFD group versus CD group; [b]means $P < 0.05$, HFD + EX group versus HFD group. Relative mRNA expression of TNF-α, MCP-1, and F4/80 was all elevated in testis from obese mice compared to CD mice. After exenatide treatment, pro-inflammatory genes expression in testis was reduced to the level compared to that in the CD group.

AJRI American Journal of Reproductive Immunology
Official Journal of the American Society for Reproductive Immunology
Volume74, Issue5 November 2015 - Pages 457-466

JC-1 is a novel cationic carbocyanine dye that accumulates in mitochondriaJC-1 is a lipophilic, cationic dye that can selectively enter into mitochondria and reversibly change color from green to red as the membrane potential increases

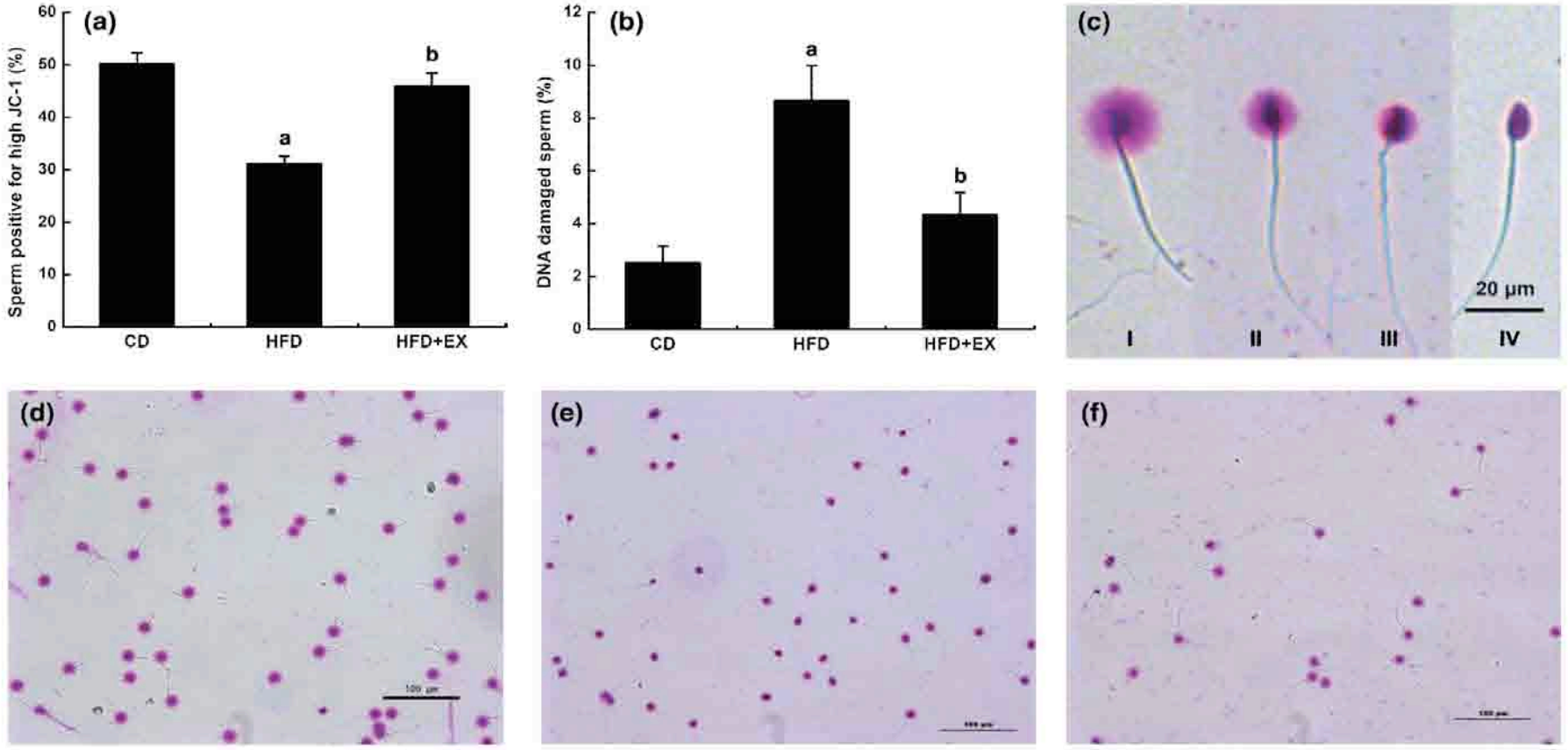

Fig. 2 Effect of diet and exenatide on sperm MMP and DNA damage. Data were presented as mean ± S.E.M. (n = 5–6). CD, control diet; HFD, high-fat diet; HFD + EX, high-fat diet + exenatide. [a]means $P < 0.05$, HFD group versus CD group; [b]means $P < 0.05$, HFD + EX group versus HFD group. (a) Percentage of sperm positive for high JC-1 per treatment group. (b) SCD data from semen samples of different groups. (c) Four DNA dispersion patterns of sperm obtained with the SCD procedure. (i) Nuclei with large DNA dispersion halos, (ii) nuclei with medium halos, (iii) nuclei with very small halos, and (iv) nuclei with no halo. (d–f) SCD test patterns of sperm in different intervention groups.

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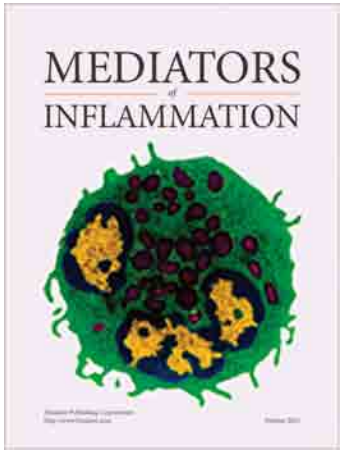
http://dx.doi.org/10.1155/2016/3094642



Review Article

Anti-Inflammatory Effects of GLP-1-Based Therapies beyond Glucose Control

Young-Sun Lee[1] and Hee-Sook Jun[1,2,3]

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[3]*Gachon Medical Research Institute, Gil Hospital, Incheon 405-760, Republic of Korea*

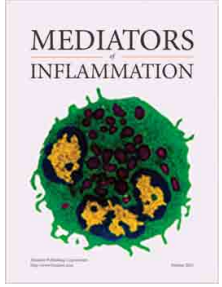
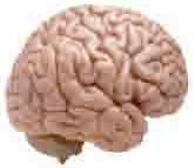


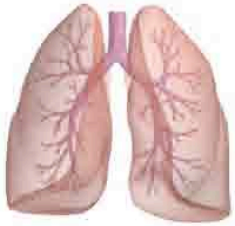
FIGURE 1: Molecular signals underlying the anti-inflammatory effects of GLP-1-based drugs. DPP-4 inhibitors increase GLP-1 levels in plasma. GLP-1 and GLP-1 receptor (GLP-1R) agonists bind to the GLP-1 receptor, which blocks PKC or NF-κB activation and subsequent expression of NLRP3, IL-1β, TNF-α, IL-6, VCAM-1, IFN-γ, and MCP-1. In addition, GLP-1R signaling activates cAMP/Ca^{2+}, CAMKKβ, and pAMPK, which induces anti-inflammatory effects on monocyte adhesion.



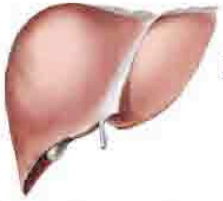
Brain

Alzheimer's disease,
Parkinson's disease:
TNF-α, IL-1β, IL-6 ↓

Lung

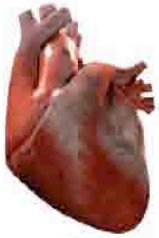


Asthma:
TNF-α, IL-4, IL-5, IL-13 ↓



Liver

Nonalcoholic steatohepatitis
(NASH):
CRP, TNF-α, IL-1β, IL-6 ↓

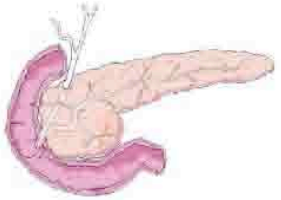


Atherosclerosis
cardiovascular disease:
NOS-2, COX-2, VCAM-1,
TNF-α, IL-6, PAI-1 ↓

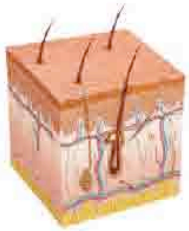
Vascular system

GLP-1
anti-inflammation

Diabetes:
TNF-α, IL-1β, IL-6, IP-10 ↓

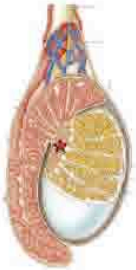


Pancreas



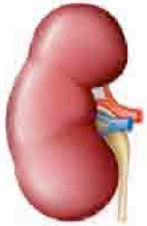
Psoriasis:
iNKT cells ↓

Skin



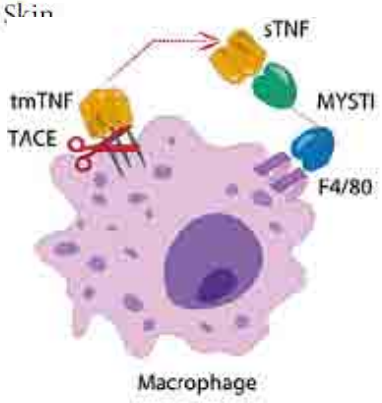
Testis:
TNF-α, MCP-1, F4/80 ↓

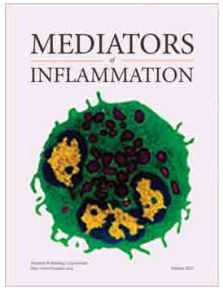
Testis



Nephropathy:
TNF-α, IL-1β, ICAM-1 ↓

Kidney





***F4/80* macrophage *marker* Ag – Rec.**

ANDROLOGY

ISSN: 2047-2919

ANDROLOGY

ORIGINAL ARTICLE

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E-mail vitogiagulli@alice.it

Keywords:
erectile dysfunction, glucagon-like peptide-1 agonist, hypogonadism, obesity, testosterone replacement therapy, type 2 diabetes mellitus

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doi: 10.1111/andr.12099

Adding liraglutide to lifestyle changes, metformin and testosterone therapy boosts erectile function in diabetic obese men with overt hypogonadism

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Biochimica et Biophysica Acta 1863 (2017) 585–597

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Review

Nrf2 signaling pathway: Pivotal roles in inflammation

Syed Minhaj Uddin Ahmed [a,1], Lin Luo [b,c,1], Akhileshwar Namani [a], Xiu Jun Wang [b], Xiuwen Tang [a,*]

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[b] Department of Pharmacology, School of Medicine, Zhejiang University, Hangzhou 310058, PR China
[c] School of Pharmacy, Nantong University, Nantong 226001, PR China

Highlights

- Nrf2 involves in inflammatory diseases.
- Crosstalk between Nrf2 and NF-κB pathways.
- Nrf2 regulates NLRP3 inflammasome activity.
- Nrf2 pathway could be therapeutically exploited.

Biochimica et Biophysica Acta 1863 (2017) 585–597

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[a] Department of Biochemistry, School of Medicine, Zhejiang University, Hangzhou 310058, PR China
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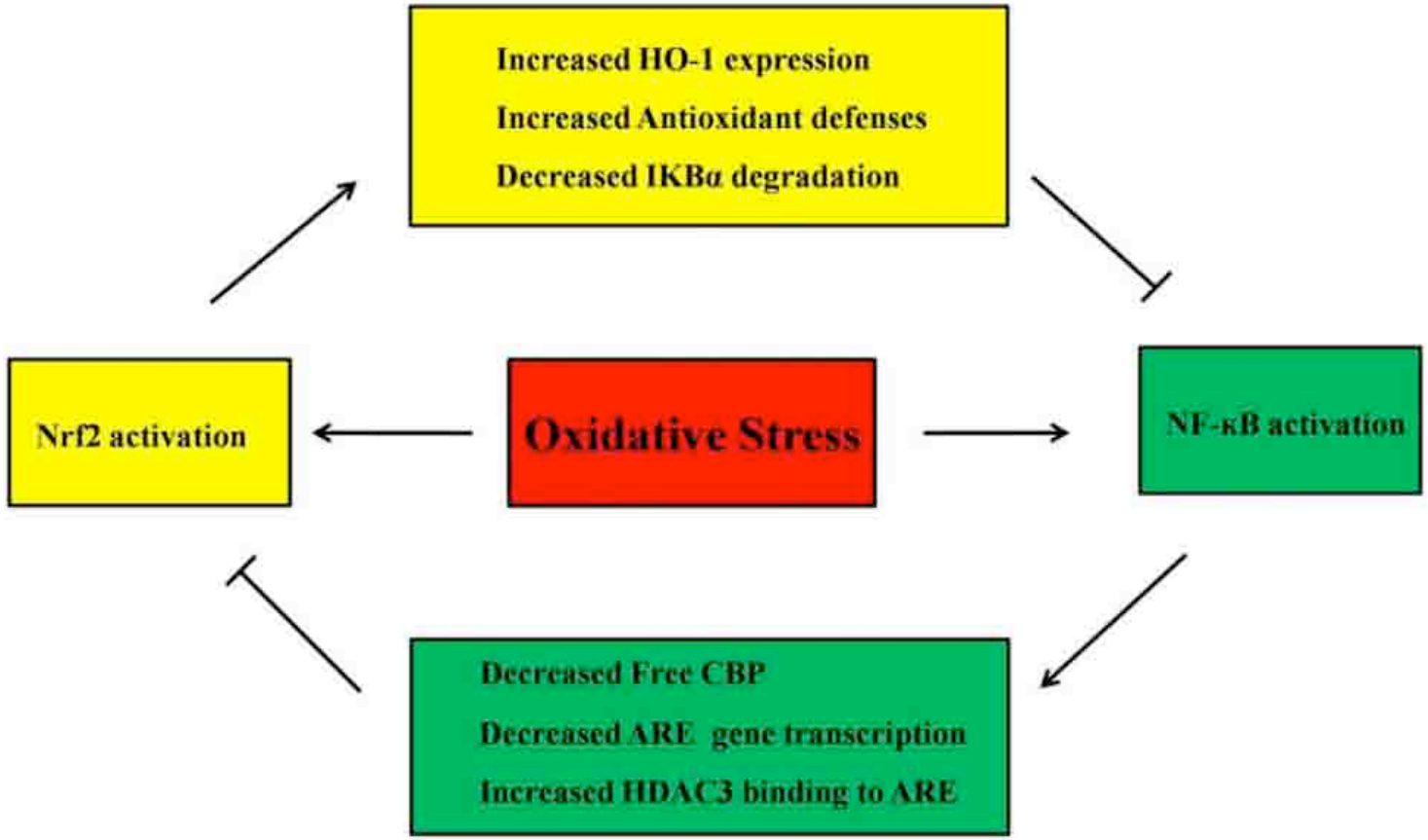
[c] School of Pharmacy, Nantong University, Nantong 226001, PR China



International Journal of
Molecular Sciences

MDPI

Review

Effects of Glucagon-Like Peptide-1 on Oxidative Stress and Nrf2 Signaling

Yoon Sin Oh [1] and Hee-Sook Jun [2,3,4,*]

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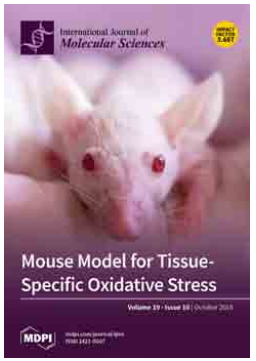
International Journal of
Molecular Sciences



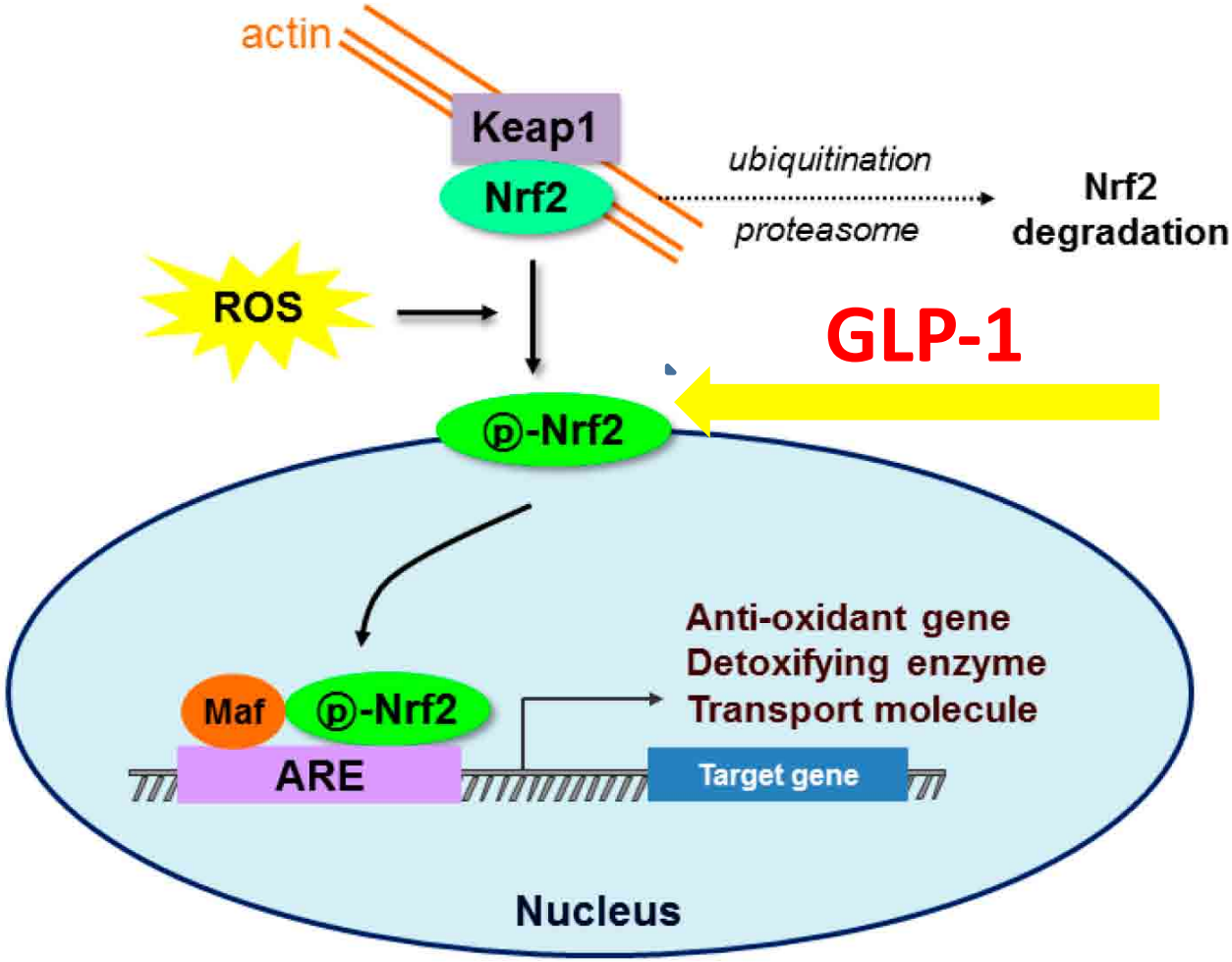


Figure 1. Schematic diagram of the Nrf2-Keap1-ARE signaling pathway. Under normal conditions, nuclear erythroid-2 like factor-2 (Nrf2) is constantly ubiquitinated through Kelch-like ECH-associated protein1 (Keap1) and degraded in the proteasome. After exposure to oxidative stress (ROS), Keap1 is inactivated and Nrf2 becomes phosphorylated. Phosphorylated Nrf2 (p-Nrf2) accumulates in the nucleus and binds to antioxidant response element (ARE) sites, subsequently activating many genes including antioxidants, detoxifying enzymes, and transport molecules.

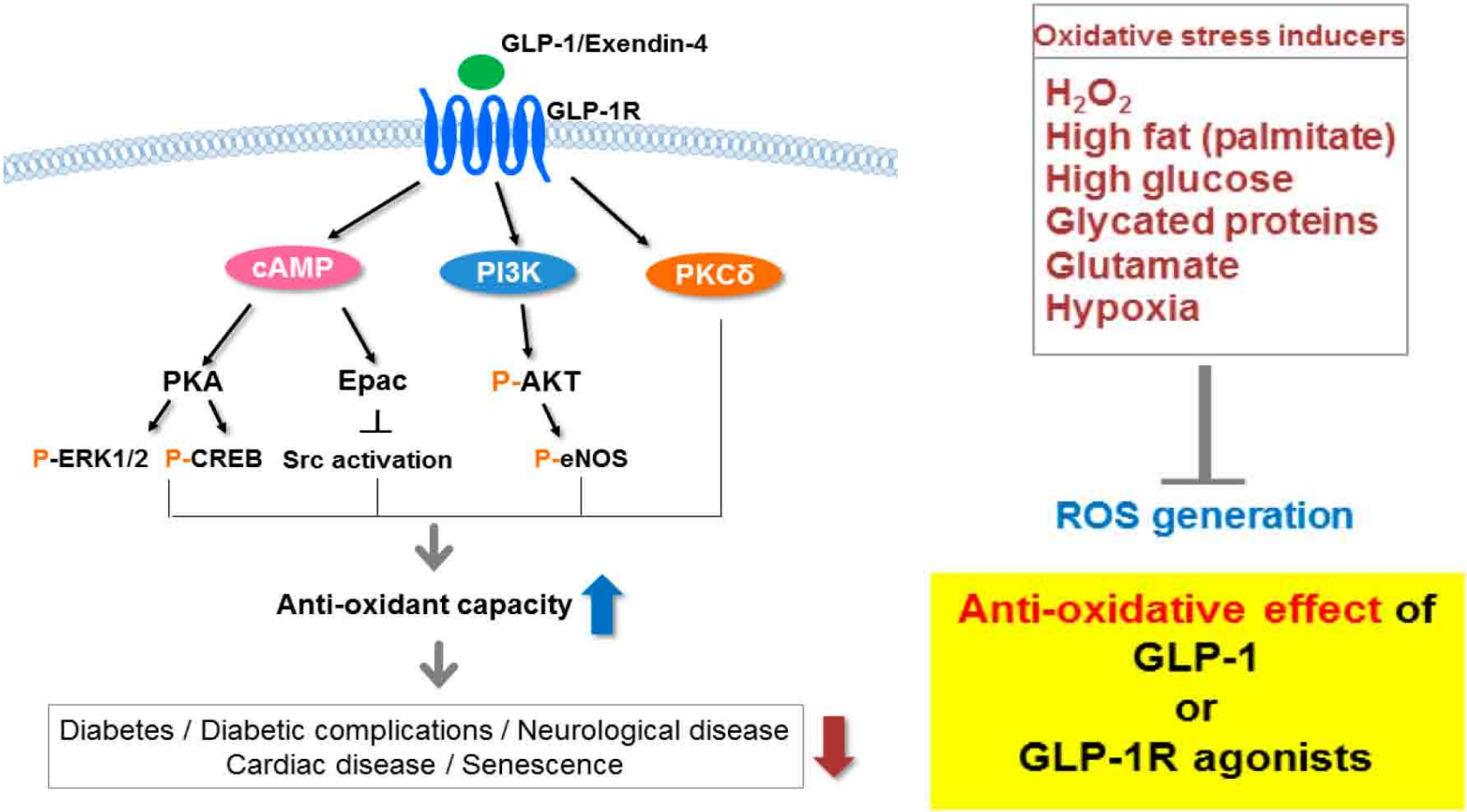
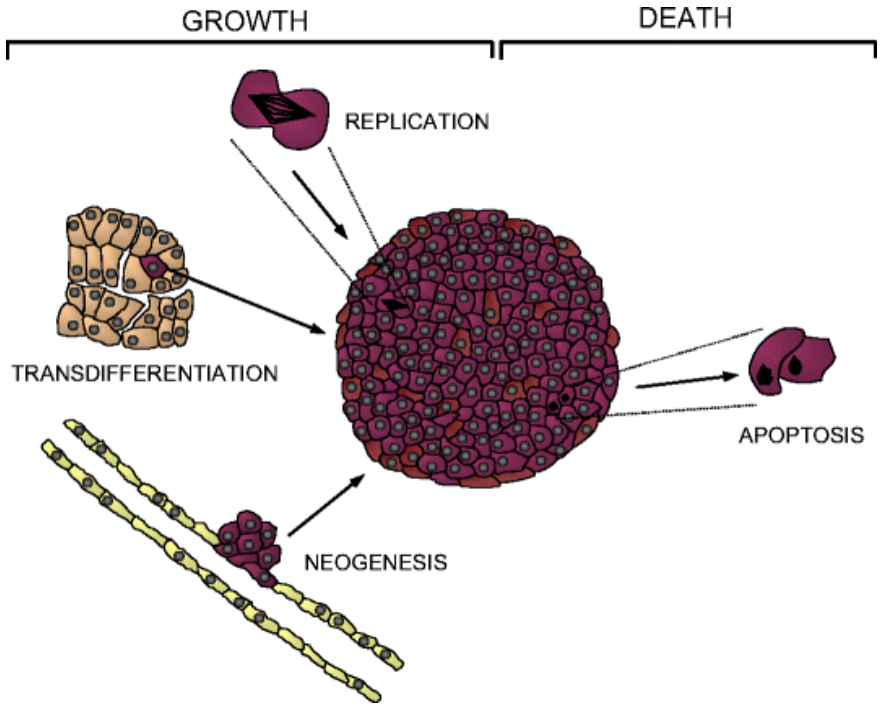
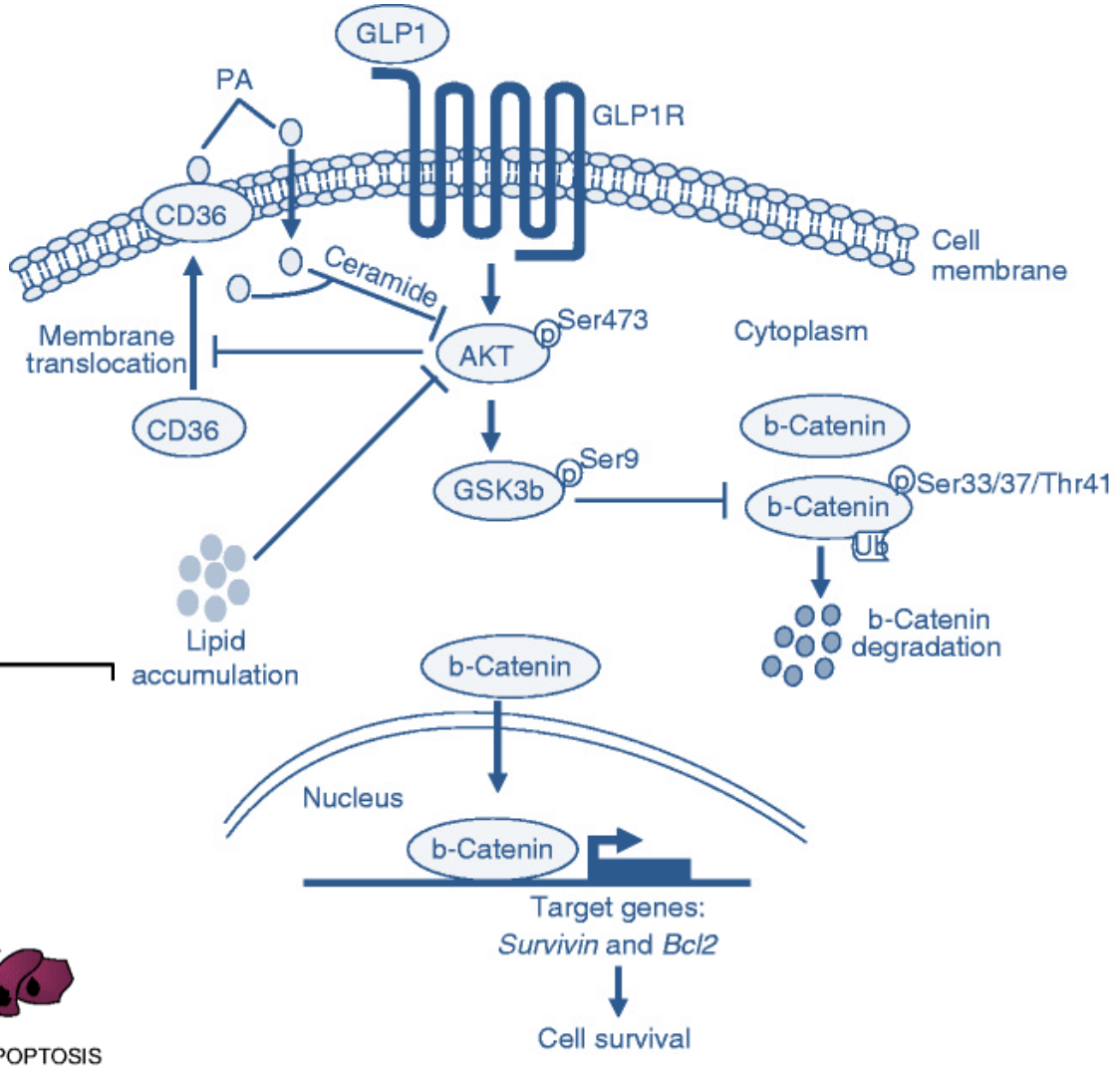


Figure 2. Signaling pathways underlying the antioxidative effects of the GLP-1 receptor. GLP-1 and exendin-4 (a GLP-1 receptor agonist) bind to the GLP-1 receptor (GLP-1R) and stimulate cyclic adenosine monophosphate (cAMP), phosphoinositide 3-kinase (PI3K) and protein kinase C (PKC)δ, subsequently activating a number of pathways including protein kinase A (PKA), exchange protein kinase activated by cAMP2 (Epac2) and protein kinase B (AKT). These pathways increase the antioxidant capacity in various tissues and reduce diabetes, diabetic complications, neurological disease, cardiac disease, and senescence. p, phosphorylation; ERK, extracellular signal-regulated kinase; CREB, cAMP response element binding protein; Src, sarcoma; eNOS, endothelial nitric oxide synthase 3.

ROLE OF GLP-1 IN THE LIFE AND DEATH OF PANCREATIC BETA CELLS

- Stimulates insulin secretion
- Induces replication of islet cells
- Promotes islet-cell neogenesis from pancreatic ductal cells
- Inhibits apoptosis





Toxicology and Applied Pharmacology 362 (2019) 1–8

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

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

Metabolic dynamics of human Sertoli cells are differentially modulated by physiological and pharmacological concentrations of GLP-1

Ana D. Martins[a,b], Mariana P. Monteiro[b,c], Branca M. Silva[d], Alberto Barros[e,f,g], Mário Sousa[a,b,e], Rui A. Carvalho[h], Pedro F. Oliveira[a,b,g], Marco G. Alves[a,b,*]

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[h] Department of Life Sciences, Faculty of Sciences and Technology and Centre for Functional Ecology, University of Coimbra, Coimbra, Portugal

Toxicology and Applied Pharmacology 362 (2019) 1–8

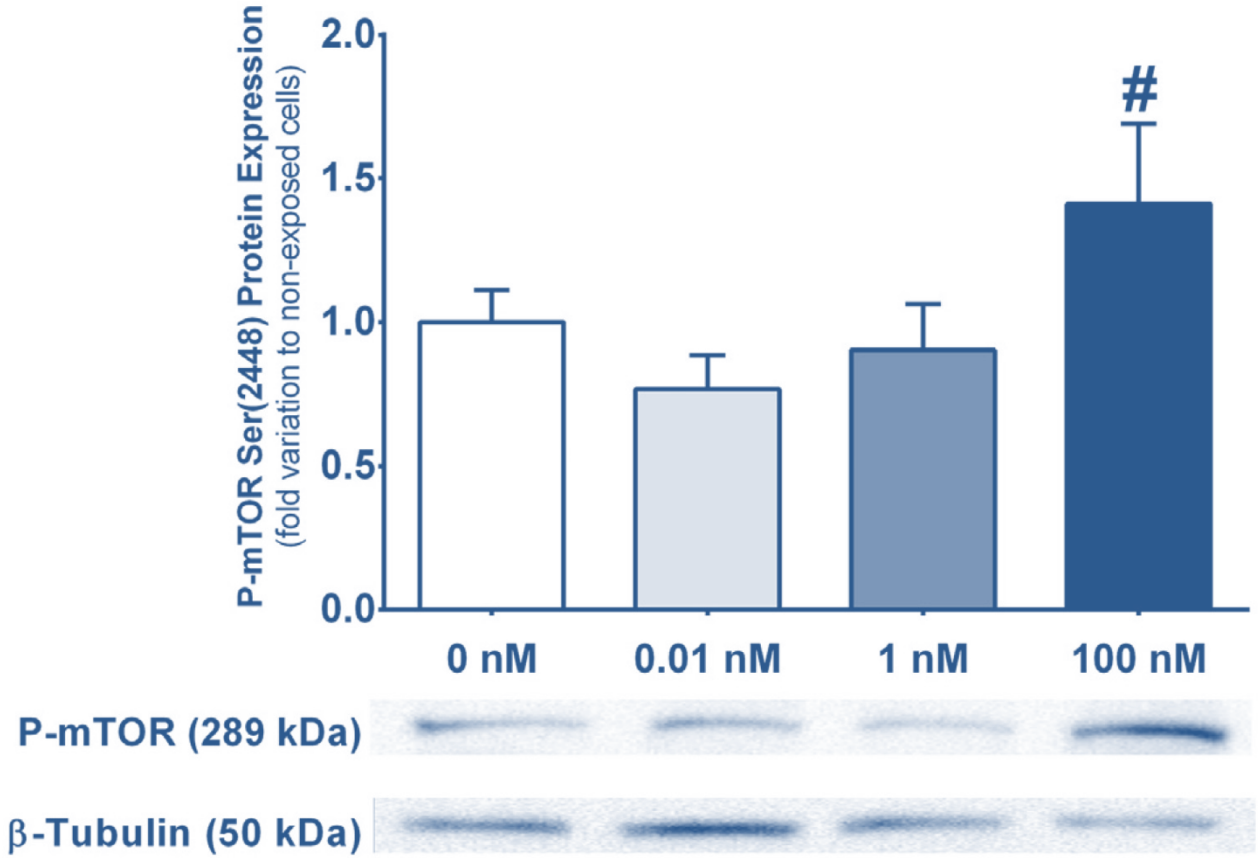
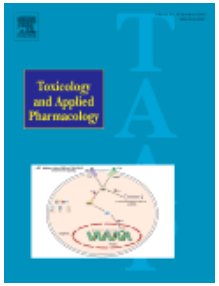


Fig. 5. Effect of glucagon like peptide-1 (GLP-1) on mammalian target of rapamycin (mTOR) signalling pathway. The protein expression levels of phosphorylated mTOR (Ser2448) in human Sertoli cells after exposure to increasing concentrations of GLP-1 are represented. Figure shows pooled data of independent experiments, indicating the expression levels of P-mTOR. Figure also show representative Western Blot experiments. Results are expressed as mean ± SEM (n = 6 for each condition). Significantly different results ($p < .05$) are as indicated: # relative to 0.01 nM.



Toxicology and Applied Pharmacology 362 (2019) 1–8

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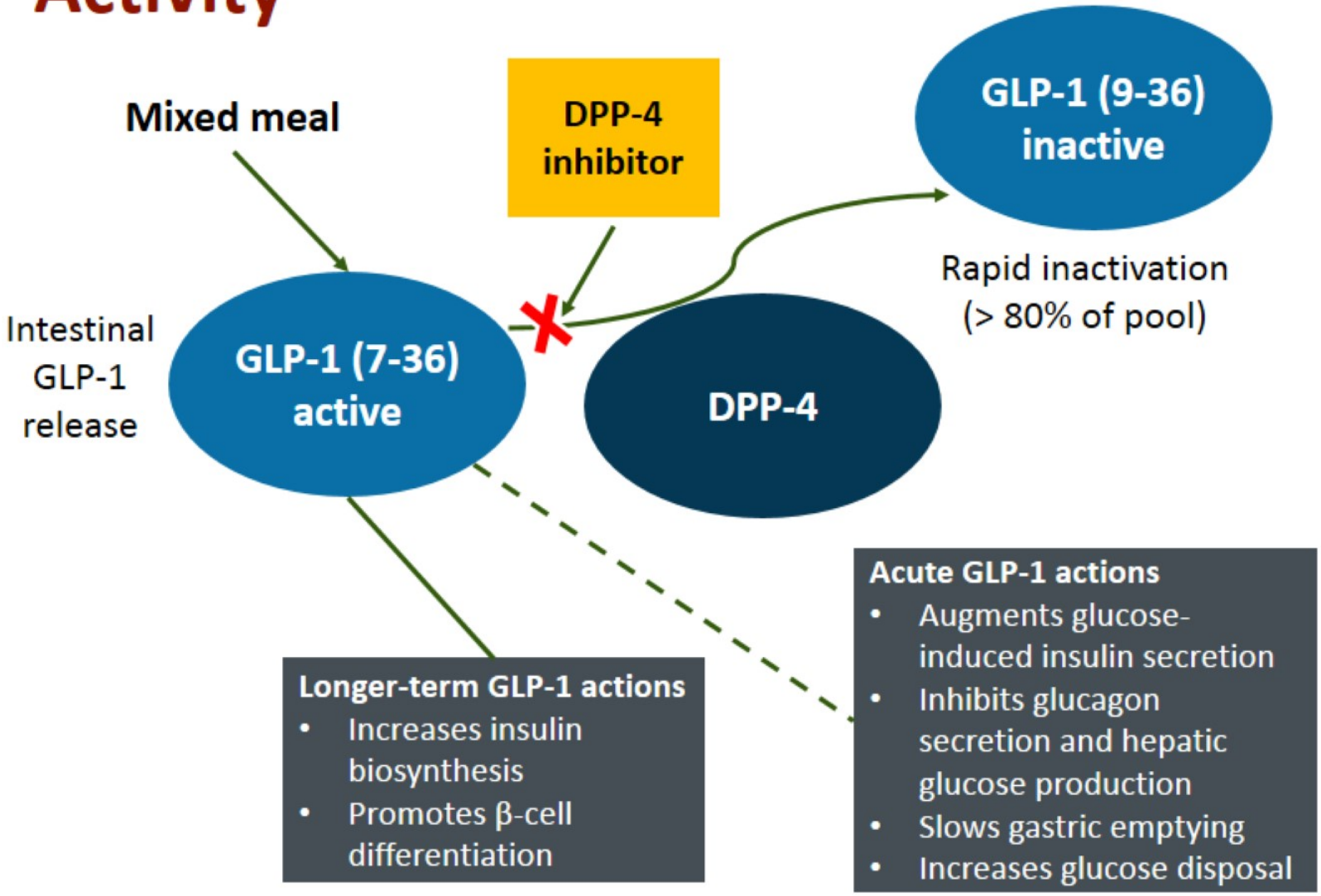
Metabolic dynamics of human Sertoli cells are differentially modulated by physiological and pharmacological concentrations of GLP-1

In conclusion, GLP-1 was able to modulate glucose metabolism and bioenergetics, promoting the production of lactate by hSCs. Moreover, exposure to the highest concentration of GLP-1 decreased oxidative damage in these cells. Also, the absence of toxic effects of GLP-1 at this concentration in hSCs, allied to a decrease in oxidative damage, adds a possible positive impact on male fertility. Still, further experiments are needed to clarify the effects of GLP-1 in male reproductive health and to determine if the effects observed *in vitro* translate to *in vivo*. Taking in consideration the decline of fertility rates parallel to the increasing prevalence of obesity, it is crucial to understand how GLP-1 affects male fertility. The use of GLP-1 analogues for obesity treatment could also be valuable to counteract the negative impact of adiposity related metabolic dysregulation in male reproductive function and arise as an additional target for medical intervention.

The Role of DPP-4 Inhibition in GLP-1 Activity



Drucker DJ. *Diabetes Care*. 2003;26:2929-2940.

Journal of Diabetes

Journal of Diabetes •• (2013) ••••

REVIEW ARTICLE

Dipeptidyl peptidase-4 inhibitors: Multitarget drugs, not only antidiabetes drugs

Yunjuan ZHAO, Lin YANG, and Zhiguang ZHOU

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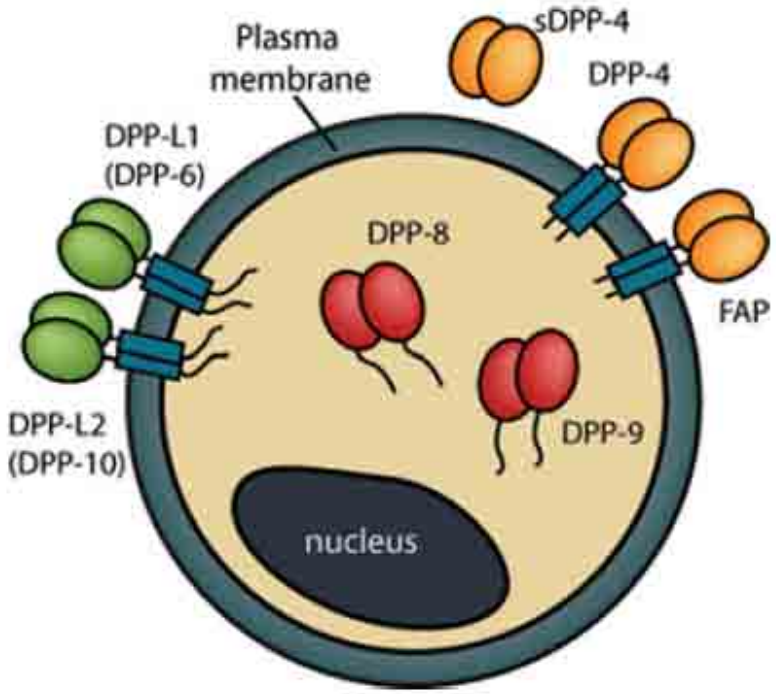
doi: 10.1111/1753-0407.12063

Abstract

Dipeptidyl peptidase (DPP)-4 inhibitors are a new class of antidiabetic agents that reduce blood glucose by preventing the degradation of the endogenous incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. Protection by DPP-4 inhibitors of β-cell function has been demonstrated in patients with type 2 diabetes. Because DPP-4 is an enzyme widely expressed in humans, DPP-4 inhibitors are speculated to be multitarget agents. However, other potential therapeutic benefits of DPP-4 inhibitors remain unknown. Recently, some therapeutic effects of DPP-4 inhibitors, such as immune regulation, cardiovascular protection, and anti-inflammatory effects, have been observed. This article provides a systematic and comprehensive review of current research into the newly found effects and mechanism of action of DPP-4 inhibitors in a therapeutic context.

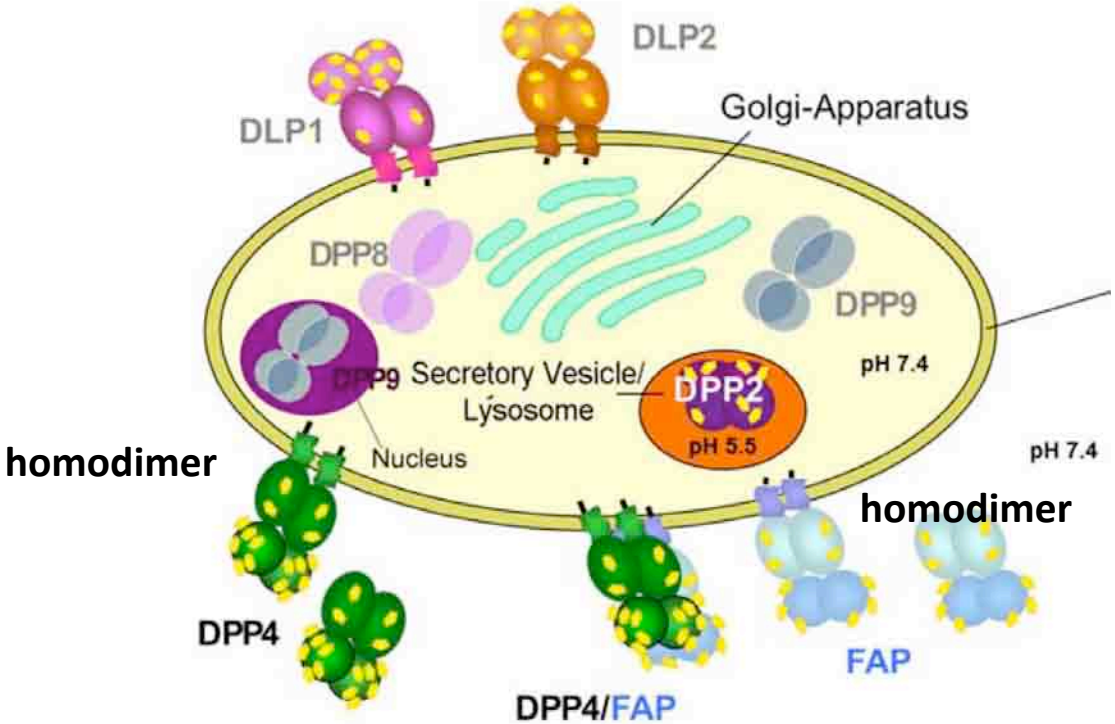
Keywords: anti-inflammatory, cardiovascular protection, dipeptidyl peptidase-4 inhibitors, immunomodulatory.

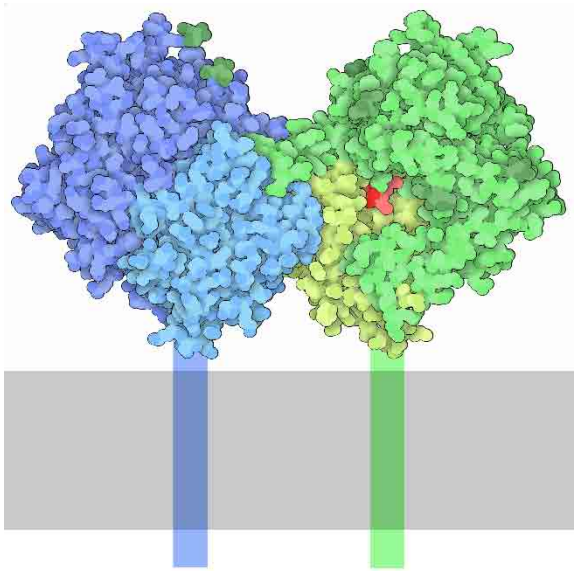


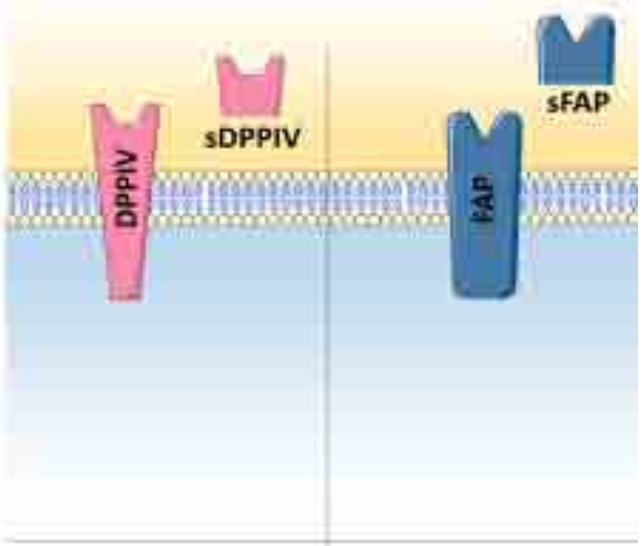
DPP-4 enzymatic activity is very high in the kidney.

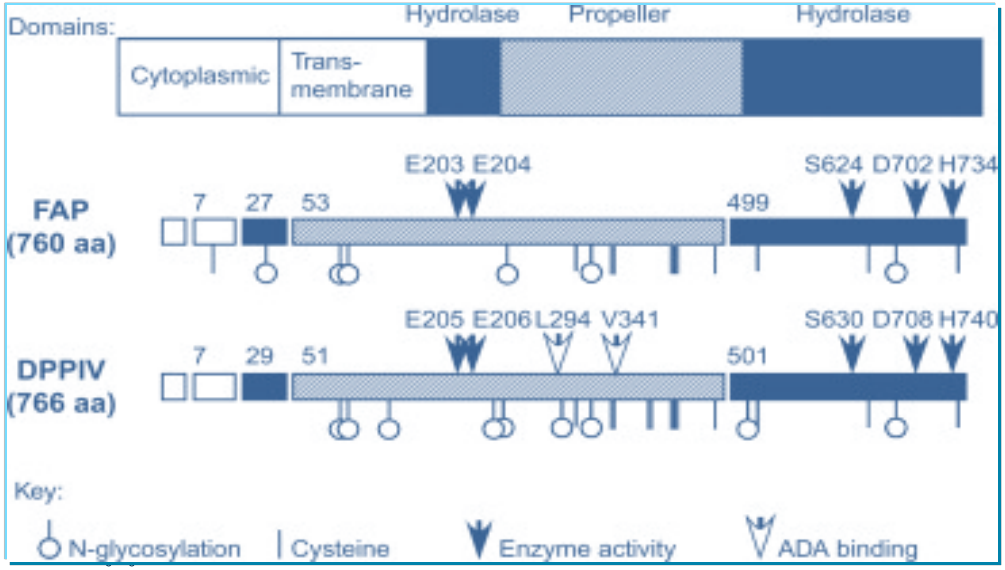
DPP4 activity (nmol min^{-1} g $tissue^{-1}$)	
Kidney	1460·8 ± 54·9
Liver	119·7 ± 9·6
Pancreas	11·2 ± 0·8
Epididymal fat	19·7 ± 2·8

Kirino Y et al. Journal of Endocrinology (2009) 200, 53–61









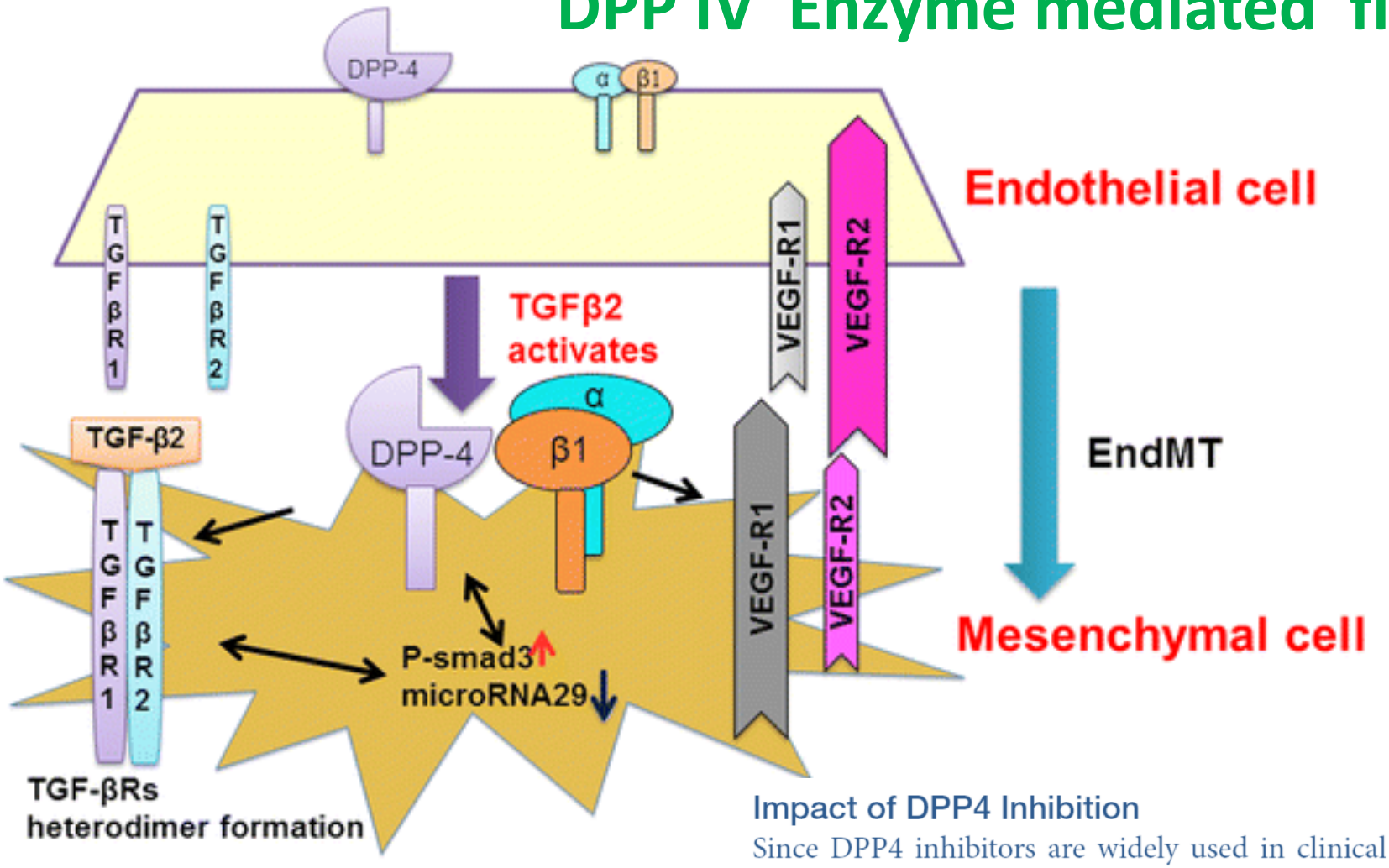
DPPIV, CD26

- Glucose homeostasis (46)
- Collagen metabolism (41)
- T cell activation (164, 165)
- MERS-Cov receptor (52)

FAP, seprase

- Tissue remodeling (47)
- Key regulator in tumor growth and metastasis (47)

DPP IV Enzyme mediated fibrosis



Impact of DPP4 Inhibition

Since DPP4 inhibitors are widely used in clinical practice, this drug was also investigated as a potential new therapeutic strategy against the development of liver fibrosis and steatosis. Kaji and collaborators demonstrated that sitagliptin markedly inhibits liver fibrosis development in rats via suppression of hepatic stellate cell proliferation and collagen synthesis (158). These suppressive effects were associated with dephosphorylation of ERK1/2, p38, and Smad2/3 in the hepatic stellate cells.

SCIENTIFIC REPORTS

OPEN

Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: a systematic review and meta-analysis

Jiali Liu[1], Ling Li[1], Sheyu Li[2], Pengli Jia[1], Ke Deng[1], Wenwen Chen[1] & Xin Sun[1]

Previous trial evidence suggested potential risk of serious urinary tract infections (UTIs) and genital infections in type 2 diabetes patients using sodium glucose co-transporter-2 inhibitors (SGLT2) inhibitors. We conducted a systematic review and meta-analysis to assess the effects of SGLT2 inhibitors on UTIs and genital infections in patients with type 2 diabetes. In total, 77 RCTs involving 50,820 participants were eligible. The meta-analyses of randomized controlled trials (RCTs) showed no significant difference in UTIs between SGLT2 inhibitors versus control (2,526/29,086 vs. 1,278/14,940; risk ratio (RR) 1.05, 95% confidence interval (CI) 0.98 to 1.12; moderate quality evidence), but suggested increased risk of genital infections with SGLT2 inhibitors (1,521/24,017 vs. 216/12,552; RR 3.30, 95% CI 2.74 to 3.99; moderate quality evidence). Subgroup analyses by length of follow up (interaction $p = 0.005$), type of control (interaction $p = 0.04$) and individual SGLT2 inhibitors (interaction $p = 0.03$) also showed statistically significant differences in genital infections. The upcoming major trials may provide important additional insights on UTIs, and more efforts are needed to address comparative effects of each individual SGLT2 inhibitors on the infections.

SCIENTIFIC REPORTS

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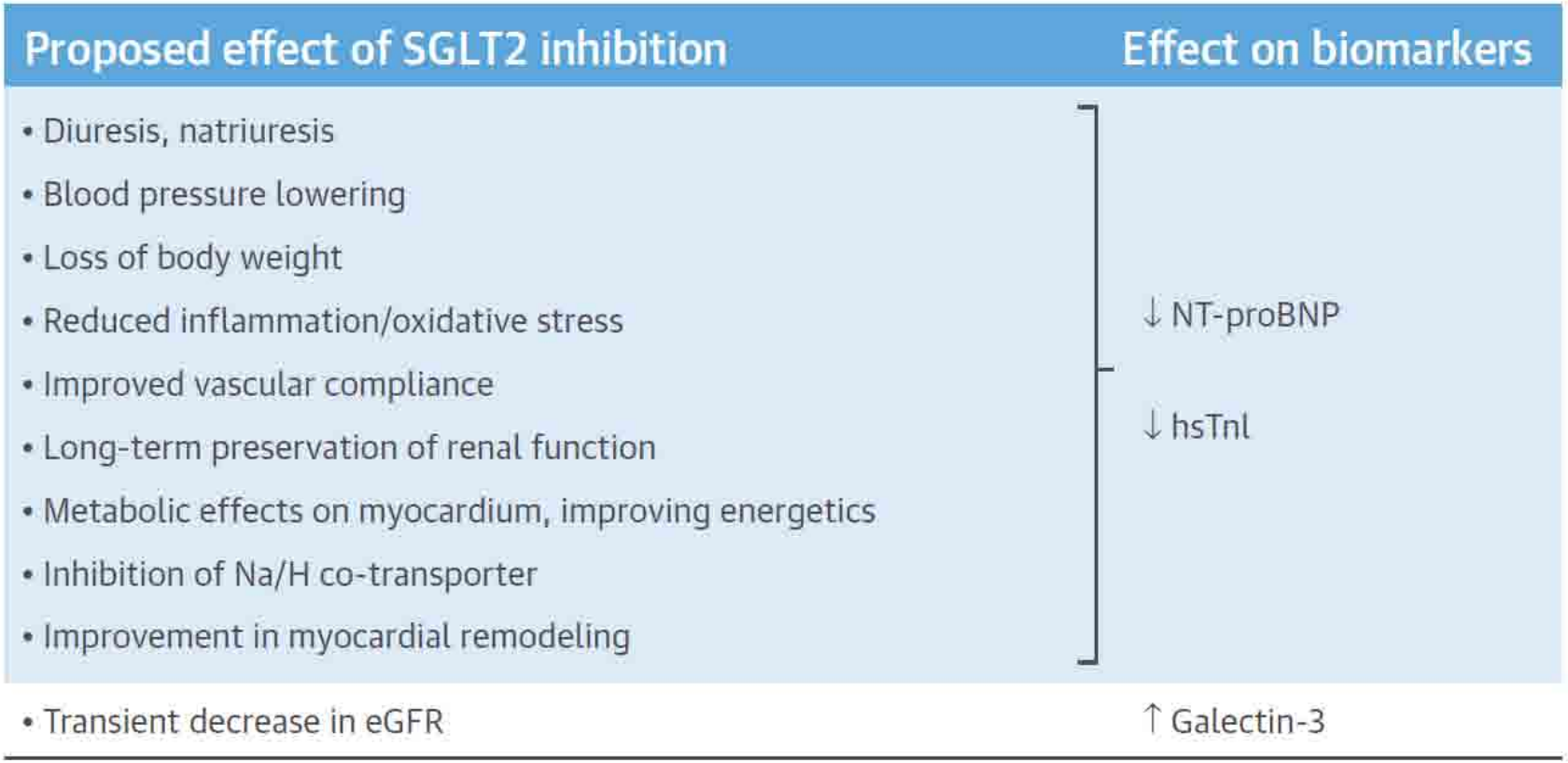

Januzzi, Jr., J.L. et al. J Am Coll Cardiol. 2017;70(6):704–12.

Through its beneficial effects on the heart, canagliflozin prevented a rise in N-terminal pro–B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin I (hsTnI). Possibly through transient reduction in estimated glomerular filtration rate (eGFR), galectin-3 increased modestly. Na/H = sodium/proton; SGLT2 = sodium glucose co-transporter 2.

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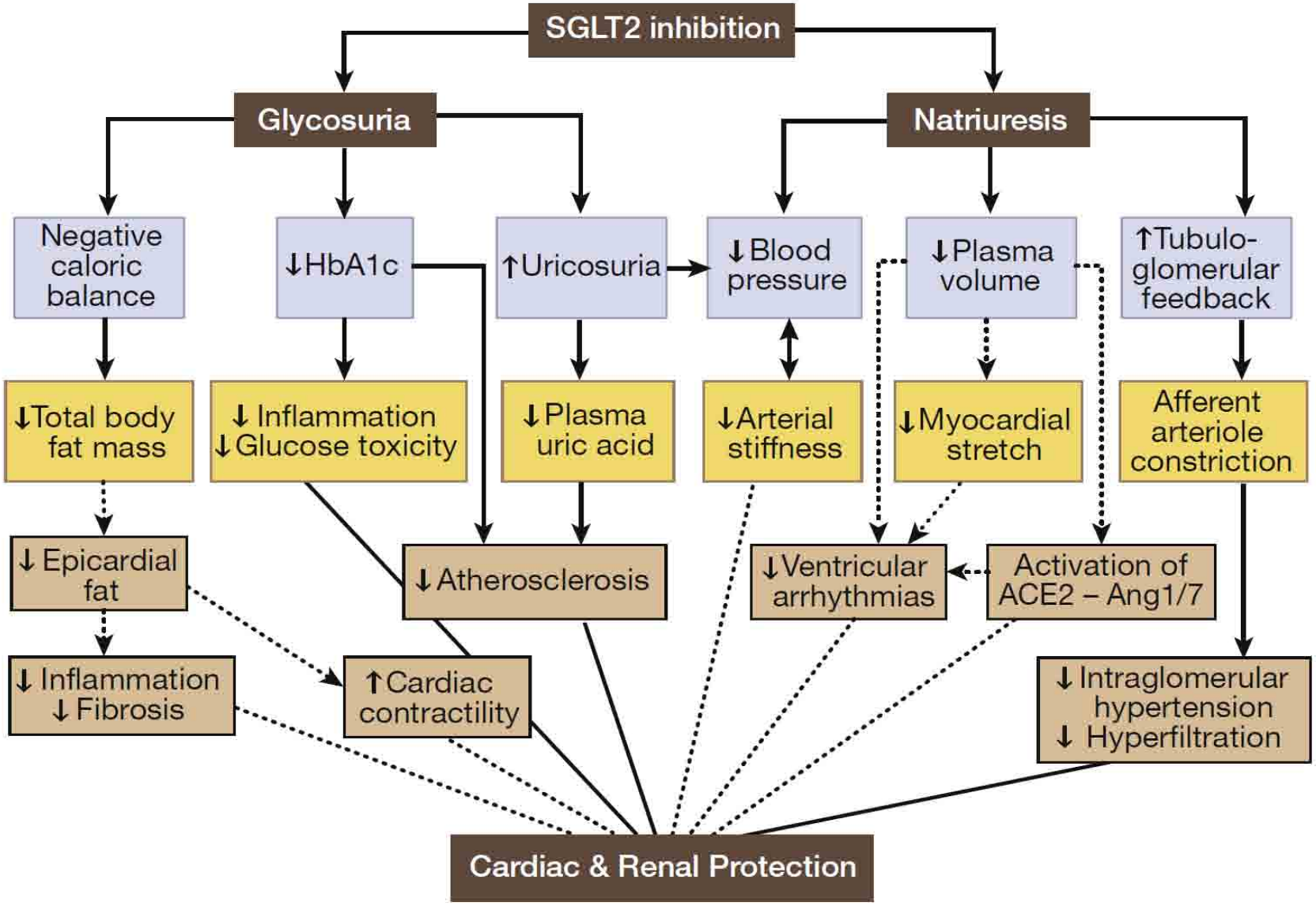
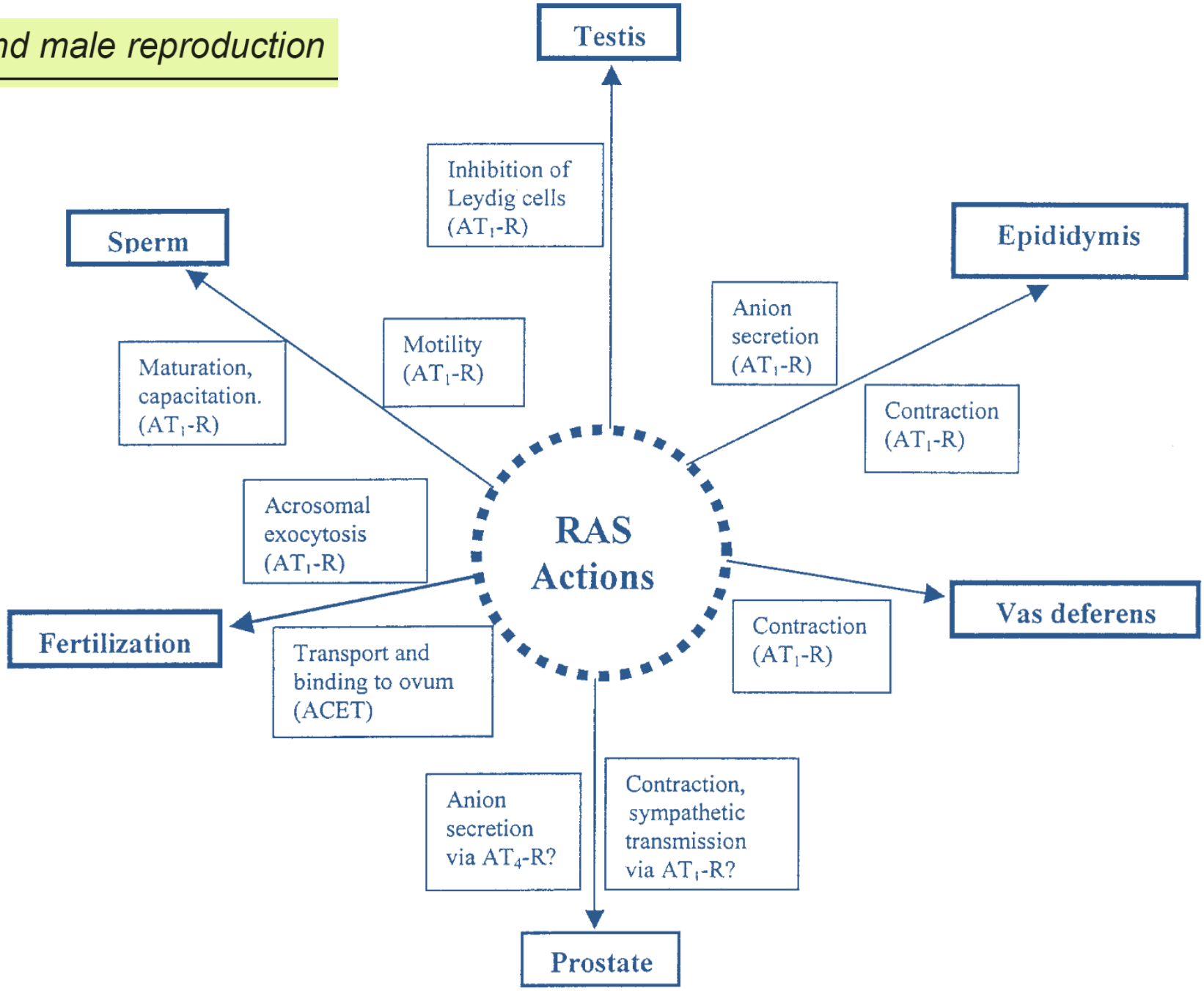
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY


SGLT2 inhibition
Glycosuria
Natriuresis
Negative caloric balance
↓HbA1c
↑Uricosuria
↓Blood pressure
↓Plasma volume
↑Tubulo-glomerular feedback
↓Total body fat mass
↓ Inflammation
↓Glucose toxicity
↓Plasma uric acid
↓Arterial stiffness
↓Myocardial stretch
Afferent arteriole constriction
↓ Epicardial fat
↓ Atherosclerosis
↓Ventricular arrhythmias
Activation of ACE2 – Ang1/7
↓ Inflammation
↓ Fibrosis
↑Cardiac contractility
↓ Intraglomerular hypertension
↓ Hyperfiltration
Cardiac & Renal Protection

RAS and male reproduction



Int. J. Mol. Sci. **2013**, *14*, 21071-21086; doi:10.3390/ijms141021071

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International Journal of
Molecular Sciences
ISSN 1422-0067
www.mdpi.com/journal/ijms

Review

Angiotensin-Converting Enzymes Play a Dominant Role in Fertility

Pei-Pei Pan, Qi-Tao Zhan, Fang Le, Ying-Ming Zheng and Fan Jin*

Department of Reproductive Endocrinology, Women's Hospital, School of Medicine, Zhejiang University, 1 Xueshi Road, Hangzhou 310006, China;
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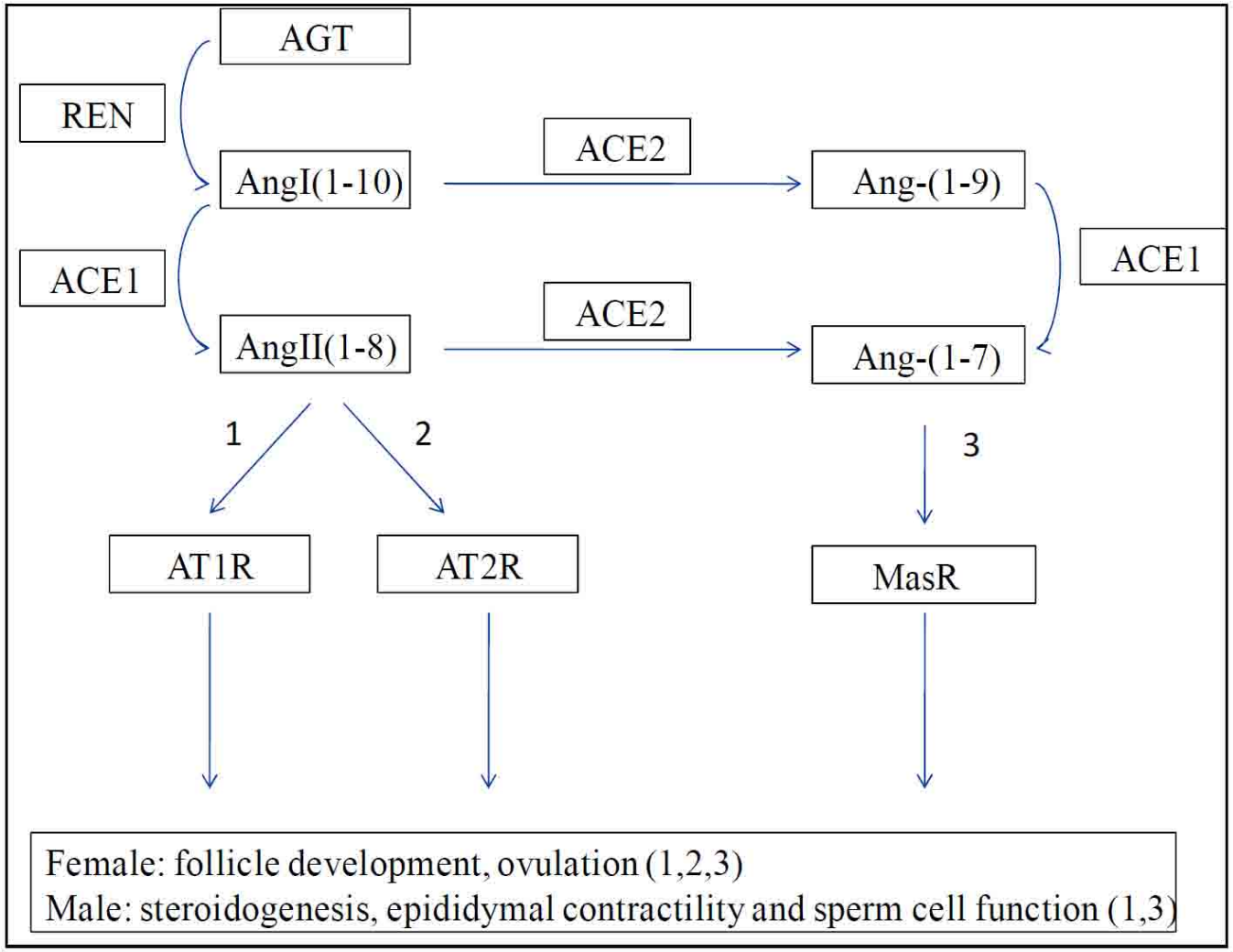
International Journal of
Molecular Sciences



1. Corona, G.; Rastrelli, G.; Morelli, A.; Vignozzi, L.; Mannucci, E.; Maggi, M. Hypogonadism and metabolic syndrome. *J. Endocrinol. Invest.* **2011**, *34*, 557–567.

3. Lotti, F.; Corona, G.; Degli Innocenti, S.; Filimberti, E.; Scognamiglio, V.; Vignozzi, L.; Forti, G.; Maggi, M. Seminal, ultrasound and psychobiological parameters correlate with metabolic syndrome in male members of infertile couples. *Andrology* **2013**, *1*, 229–239.

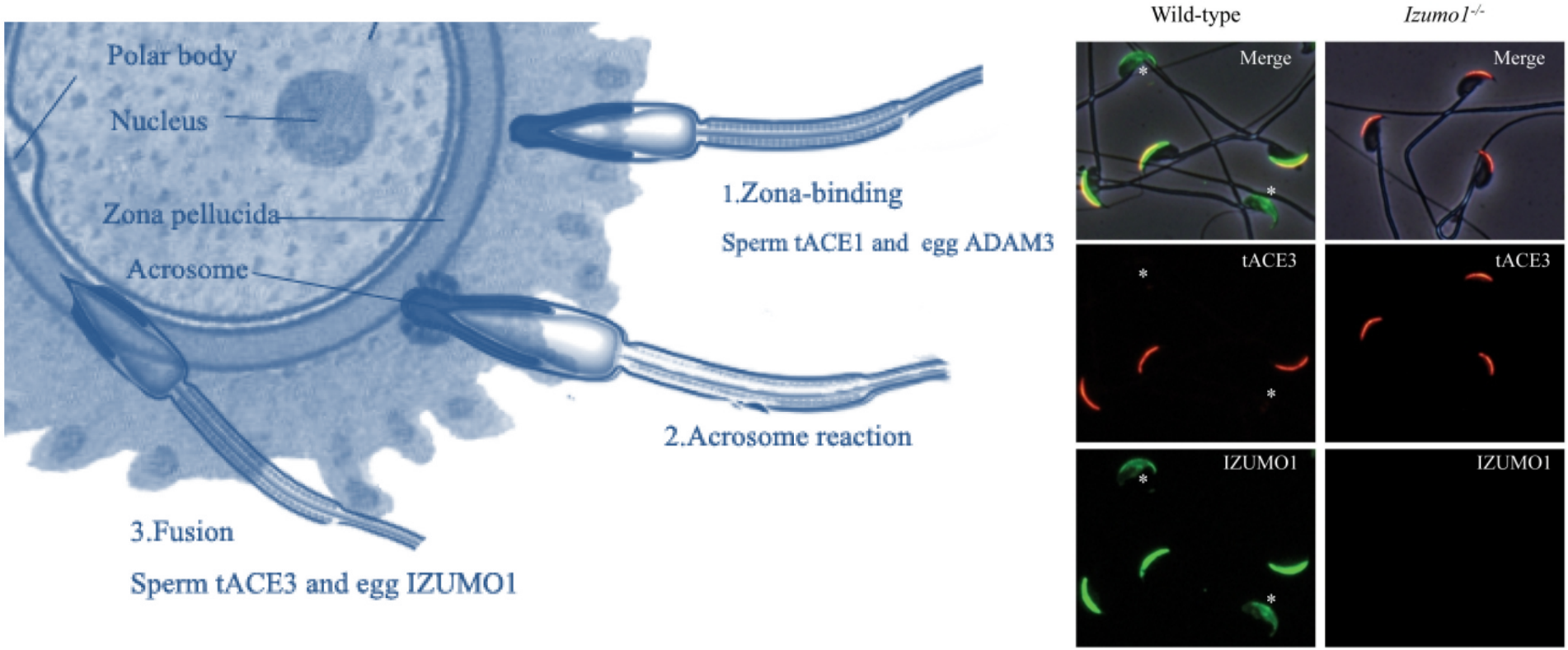


Figure 2. Mechanisms of sperm–egg interaction. tACE1 and ADAM3 are dispensable factors for the binding of sperm to the zona pellucida, whereas tACE3 and IZUMO1 play important roles in the fusion of gametes to sperm. ADAM: a disintegrin and metalloprotease; ZP: zona pellucida; tACE1: testis angiotensin-converting enzyme 1; tACE3: testis angiotensin-converting enzyme 3.

IZUMO 1: Izumo sperm-egg fusion 1, sperm-specific protein, Immunoglobulin G domain, is essential for sperm-egg plasma membrane binding and fusion

ACE3 inhibits MEK-ERK1/2 signaling pathway

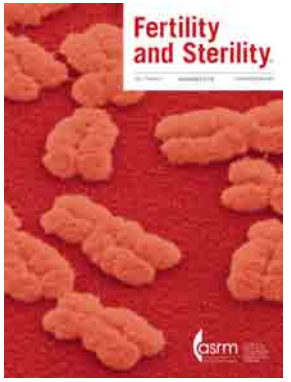
ORIGINAL ARTICLES: ANDROLOGY

Fertility and Sterility®

Angiotensin II type 2 receptor is expressed in human sperm cells and is involved in sperm motility

Marta Gianzo, J.D.,[a] Iraia Muñoa-Hoyos, J.D.,[a] Itziar Urizar-Arenaza, J.D.,[a] Zaloa Larreategui, J.D.,[b] Fernando Quintana, J.D.,[b] Nicolás Garrido, Ph.D.,[c] Nerea Subirán, Ph.D.,[a] and Jon Irazusta, Ph.D.[a]

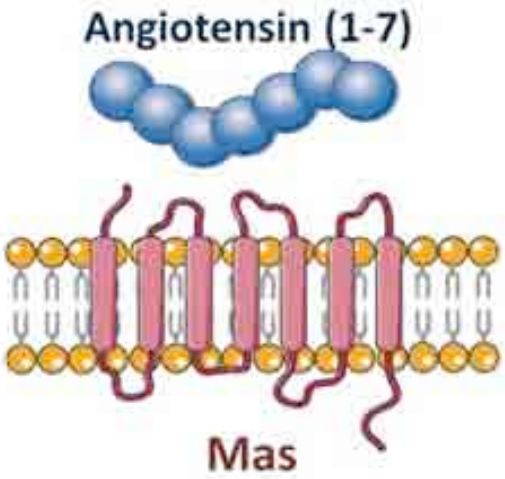
[a] Department of Physiology, Faculty of Medicine and Dentistry, University of the Basque Country (UPV/EHU), Leioa, Bizkaia; [b] IVI Clinic Bilbao, Leioa, Bizkaia; and [c] Laboratory of the Andrology and Semen Bank, IVI Clinic Valencia, Valencia, Spain



VOL. 105 NO. 3 / MARCH 2016 608

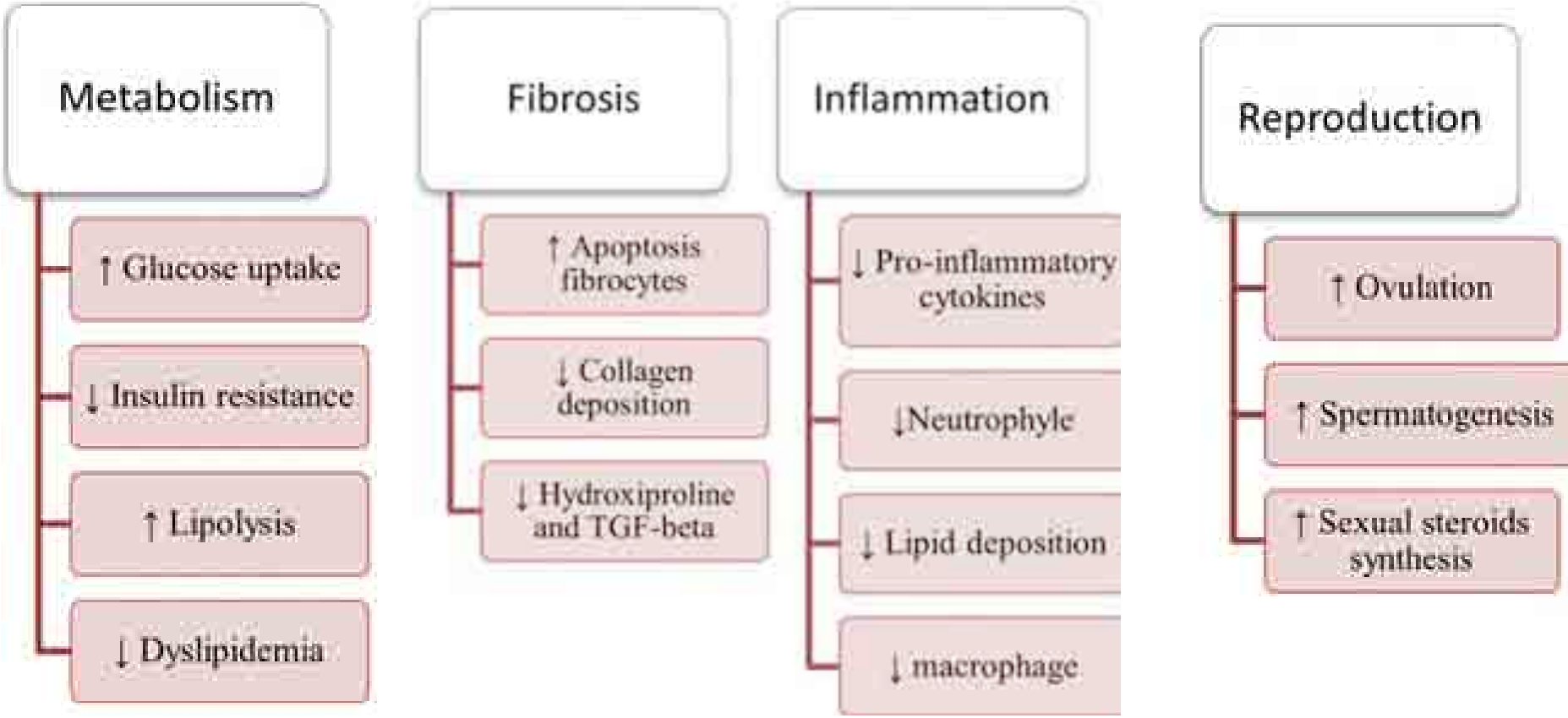
Fertility and Sterility® Vol. 105, No. 3, March 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.11.004



Ang 1-7 MAS may be altered when spermatogenesis is severely impaired

Reis, A. B., Araujo, F. C., Pereira, V. M., Dos Reis, A. M., Santos, R. A. and Reis, F. M. (2010) Angiotensin (1–7) and its receptor Mas are expressed in the human testis: implications for male infertility. J. Mol. Histol. **41**, 75–80



The tACE/Angiotensin (1–7)/Mas Axis Protects Against Testicular Ischemia Reperfusion Injury

May Al-Maghrebi and Waleed M. Renno

Urology 2016

OBJECTIVE To investigate whether exogenous angiotensin (Ang)-(1-7) administration can protect against the damaging consequences of testicular ischemia reperfusion (tIR) injury.

MATERIALS AND METHODS Eighteen male Sprague-Dawley rats were divided equally among the following 3 groups: sham, unilateral tIR injury (1 hour of ischemic treatment and 4 hours of reperfusion), and tIR + Ang-(1-7) (0.3 mg/kg). Testicular tissues obtained from the rats were evaluated for the expression of testicular angiotensin-converting enzyme (tACE), Ang-(1-7), and the Ang-(1-7)-specific receptor Mas by immunohistochemistry and enzyme-linked immunosorbent assay. Reduced spermatogenesis, induction of the caspase-8 pathway, and nitric oxide (NO) generation were assessed. The effects of tIR and Ang-(1-7) treatment on the PI3K/Akt antiapoptosis pathway were also investigated.

RESULTS Testicular morphological changes and reduced spermatogenesis associated with decreased expression of the tACE/Ang-(1-7)/Mas axis were observed during tIR. These effects were also accompanied by increased activity of caspase-3 and -8, downregulation of the survivin and BAD transcripts, and decreased NO formation. During tIR, PTEN expression was increased, leading to inactivation of the PI3K/Akt pathway. Acute treatment with Ang-(1-7) prior to reperfusion attenuated the tIR-induced damage described above.

CONCLUSION Expression of the tACE/Ang-(1-7)/Mas axis was downregulated during tIR. Administration of exogenous Ang-(1-7) prior to reperfusion rescued tACE and Mas expression and protected against germ cell apoptosis and oxidative stress. Increased NO generation and activation of the PI3K/Akt signaling pathway may have partially contributed to these effects. The tACE/Ang-(1-7)/Mas axis likely plays a role in the maintenance of normal testis physiology and spermatogenesis. UROLOGY ■■: 1.e1–1.e8, 2016.

SCIENTIFIC REPORTS

SCIENTIFIC REPORTS | 6:18896 | DOI: 10.1038/srep18896

OPEN

Sertoli cells have a functional NALP3 inflammasome that can modulate autophagy and cytokine production

Received: 15 September 2015

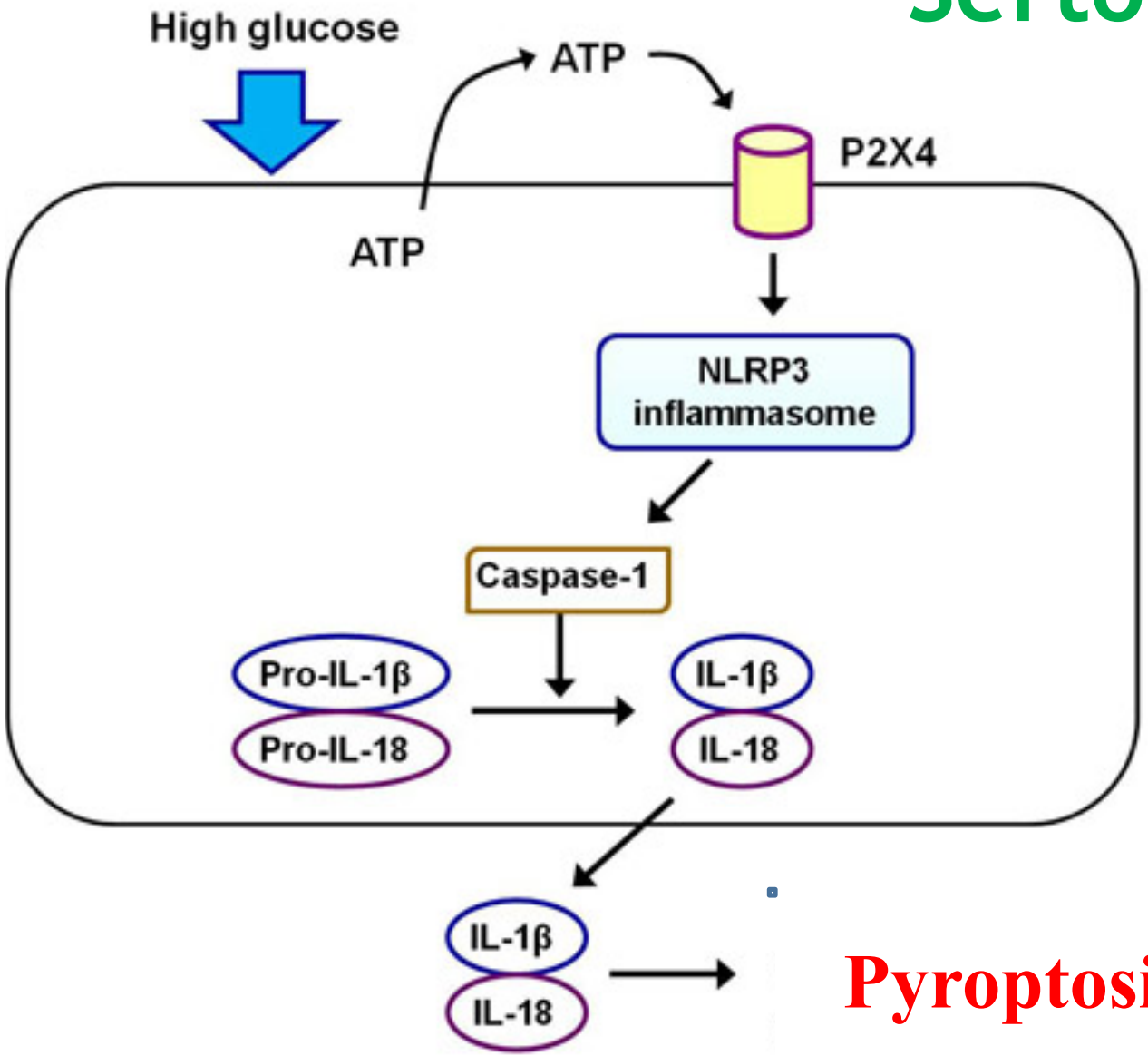
Accepted: 27 November 2015

Published: 08 January 2016

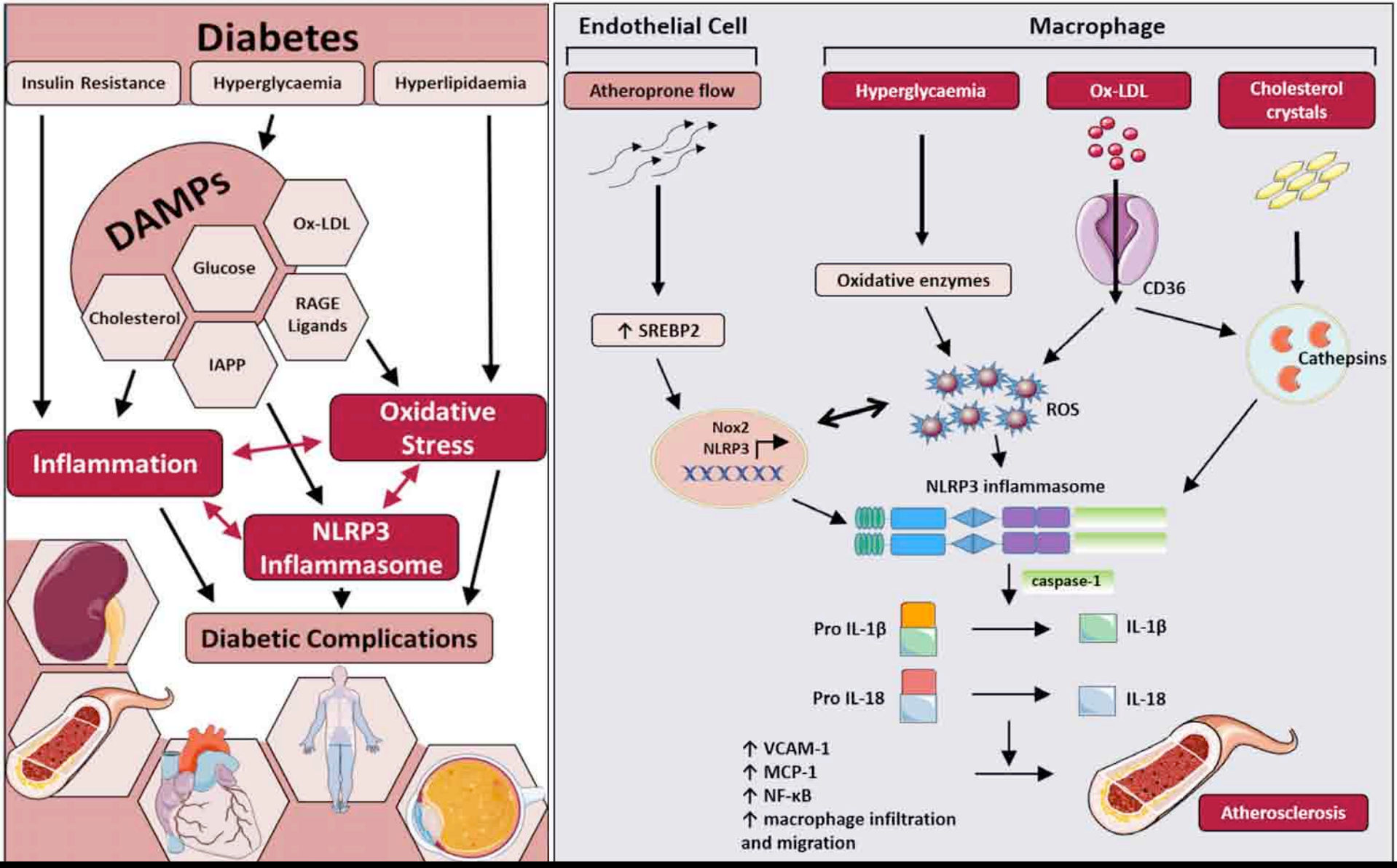
Soren Hayrabedyan[1], Krassimira Todorova[1], Asma Jabeen[2], Gergana Metodieva[2], Stavri Toshkov[3], Metodi V. Metodiev[2], Milcho Mincheff[3] & Nelson Fernández[2]

Sertoli cells, can function as non-professional tolerogenic antigen-presenting cells, and sustain the blood-testis barrier formed by their tight junctions. The NOD-like receptor family members and the NALP3 inflammasome play a key role in pro-inflammatory innate immunity signalling pathways. Limited data exist on NOD1 and NOD2 expression in human and mouse Sertoli cells. Currently, there is no data on inflammasome expression or function in Sertoli cells. We found that in primary pre-pubertal Sertoli cells and in adult Sertoli line, TLR4\NOD1 and NOD2 crosstalk converged in NFκB activation and elicited a NALP3 activation, leading to *de novo* synthesis and inflammasome priming. This led to caspase-1 activation and IL-1β secretion. We demonstrated this process was controlled by mechanisms linked to autophagy. NOD1 promoted pro-IL-1β restriction and autophagosome maturation arrest, while NOD2 promoted caspase-1 activation, IL-1β secretion and autophagy maturation. NALP3 modulated NOD1 and pro-IL-1β expression, while NOD2 inversely promoted IL-1β. This study is proof of concept that Sertoli cells, upon specific stimulation, could participate in male infertility pathogenesis via inflammatory cytokine induction.

Sertoli cell



Pyroptosis



The **inflammasome** is a multiprotein oligomer responsible for the activation of inflammatory responses. Inflammasome promotes the maturation and secretion of pro-inflammatory cytokines Interleukin 1β (IL-1β) and Interleukin 18 (IL18). The secretion of these cytokines results in pyroptosis, a form of programmed pro-inflammatory cell death distinct from apoptosis. In the case of dysregulation of the inflammasome, an assortment of major diseases may arise

SCIENTIFIC REPORTS

OPEN

Sertoli cells have a functional NALP3 inflammasome that can modulate autophagy and cytokine production

Received: 15 September 2015
Accepted: 27 November 2015

LPS
Mitochondrion organization
mTOR signaling pathway
Negative regulation of cell proliferation
NOD-like receptor signaling pathway
Regulation of tight junction assembly
RIG-I-like receptor signaling pathway
Regulation of I-kappaB kinase/NF-kappaB signaling
Tight junction

Common Pathways
Endocytosis
Adipocytokine signaling pathway
Bacterial invasion of epithelial cells
Fc epsilon RI signaling pathway
Fc gamma R-mediated phagocytosis
Lysosome organization
MAPK signaling pathway
Negative regulation of inflammatory response
Phagosome
Regulation of cell proliferation
Regulation of inflammatory response
Regulation of programmed cell death
Toll-like receptor signaling pathway

ie-DAP
Autophagy
Endosome to lysosome transport
Lysosomal transport
Negative regulation of cell proliferation
Positive regulation of epithelial cell migration
Positive regulation of macroautophagy
Positive regulation of leukocyte cell-cell adhesion

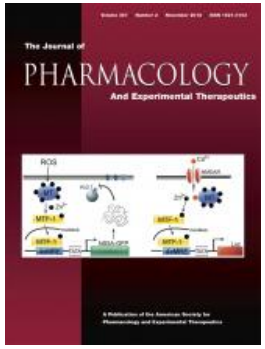
1521-0103/355/3/370–380$25.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

http://dx.doi.org/10.1124/jpet.115.226936
J Pharmacol Exp Ther 355:370–380, December 2015

NLRP3 Inflammasome Involvement in the Organ Damage and Impaired Spermatogenesis Induced by Testicular Ischemia and Reperfusion in Mice

Letteria Minutoli, Pietro Antonuccio, Natasha Irrera, Mariagrazia Rinaldi, Alessandra Bitto, Herbert Marini, Gabriele Pizzino, Carmelo Romeo, Antonina Pisani, Giuseppe Santoro, Domenico Puzzolo, Carlo Magno, Francesco Squadrito, Antonio Micali, and Domenica Altavilla

Department of Clinical and Experimental Medicine, University of Messina, Azienda Ospedaliera Universitaria Policlinico "G. Martino", Messina, Italy (L.M., N.I., M.R., A.B., H.M., G.P., F.S.); Department of Paediatric, Gynaecological, Microbiological, and Biomedical Sciences, University of Messina, Azienda Ospedaliera Universitaria Policlinico "G. Martino", Messina, Italy (P.A., C.R., D.A.); Department of Biomedical Sciences and Morphofunctional Imaging, University of Messina, Azienda Ospedaliera Universitaria Policlinico "G. Martino", Messina, Italy (A.P., G.S., D.P., A.M.); and Department of Human Pathology, University of Messina, Azienda Ospedaliera Universitaria Policlinico "G. Martino", Messina, Italy (C.M.)



ASPET | THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

J Pharmacol Exp Ther 355:370–380, December 2015

IJAE
Vol. 119, n. 1 (Supplement): 131, 2014
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Italian Journal of Anatomy and Embryology

Role of NLRP3 in an experimental model of testicular ischemia and reperfusion in mice

Antonio Micali[1], Antonina Pisani [1], Alba Maria Arco [1], Letteria Minutoli[2], Pietro Antonuccio[3], Carmelo Romeo[3], Gabriele Pizzino[2], Francesco Squadrito[2], Domenica Altavilla[2], Domenico Puzzolo[1]

[1] Department of Biomedical Sciences and Morphofunctional Imaging,, University of Messina, Italy
[2] Department of Clinical and Experimental Medicine, University of Messina, Italy
[3] Department of Paediatric, Gynaecological, Microbiological and Biomedical Sciences, University of Messina, Italy

NLRP3 inhibition might have a protective role on spermatogenesis

Cardiovascular Drugs and Therapy
April 2018, Volume 32, Issue 2, pp 135–145 | Cite as

Combined SGLT2 and DPP4 Inhibition Reduces the Activation of the Nlrp3/ASC Inflammasome and Attenuates the Development of Diabetic Nephropathy in Mice with Type 2 Diabetes

Authors Authors and affiliations

Yochai Birnbaum, Mandeep Bajaj, Hsiu-Chiung Yang, Yumei Ye

CONCLUSION:

Dapa attenuates the inflammasome activation and progression of DN in T2DM mice and whether these effects can be augmented by adding DPP4I saxagliptin.

Cardiovascular Drugs and Therapy
April 2017, Volume 31, Issue 2, pp 119–132 | Cite as

SGLT-2 Inhibition with Dapagliflozin Reduces the Activation of the Nlrp3/ASC Inflammasome and Attenuates the Development of Diabetic Cardiomyopathy in Mice with Type 2 Diabetes. Further Augmentation of the Effects with Saxagliptin, a DPP4 Inhibitor

Conclusions

Dapa attenuated the activation of the inflammasome, fibrosis, and deterioration of LVEF in BTBR mice. The anti-inflammatory, anti-fibrotic effects are likely SGLT2- and glucose-lowering-independent, as they were replicated in the in vitro model.

ACC.17

752
JACC March 21, 2017
Volume 69, Issue 11

Heart Failure and Cardiomyopathies

DAPAGLIFLOZIN ATTENUATES DIABETIC CARDIOMYOPATHY AND THE ACTIVATION OF THE NLRP3/ASC INFLAMMASOME IN MICE WITH TYPE-2 DIABETES: A GLUCOSE-LOWERING AND SGLT-2 INDEPENDENT EFFECT

Poster Contributions
Poster Hall, Hall C
Friday, March 17, 2017, 3:45 p.m.-4:30 p.m.

Session Title: Diabetes and Endothelial Dysfucntion in Heart Failure
Abstract Category: 12. Heart Failure and Cardiomyopathies: Basic
Presentation Number: 1162-244

Authors: *Yumei Ye, Mandeep Bajaj, Yochai Birnbaum, UTMB, Galveston, TX, USA, Baylor College of Medicine, Houston, TX, USA*

Background: SGLT2 inhibition with empagliflozin reduced the primary composite outcome (cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke) in patients with type-2 diabetes (T2D).

Purpose: To assess whether Dapagliflozin (Dapa) attenuates the deterioration of left ventricular (LV) function and the activation of the inflammasome in T2D mice.

Conclusions: Dapa attenuates T2D-induced activation of the inflammasome, increased expression of collagen and the adverse cardiac remodeling. As SGLT-2 is not expressed in the heart and similar effects were seen in vitro, a direct SGLT-2-independent and glucose lowering-independent effect is present.

CLINICAL RESEARCH STUDY

The American Journal of Medicine, Vol 130, No 6S, June 2017

THE AMERICAN JOURNAL of MEDICINE®

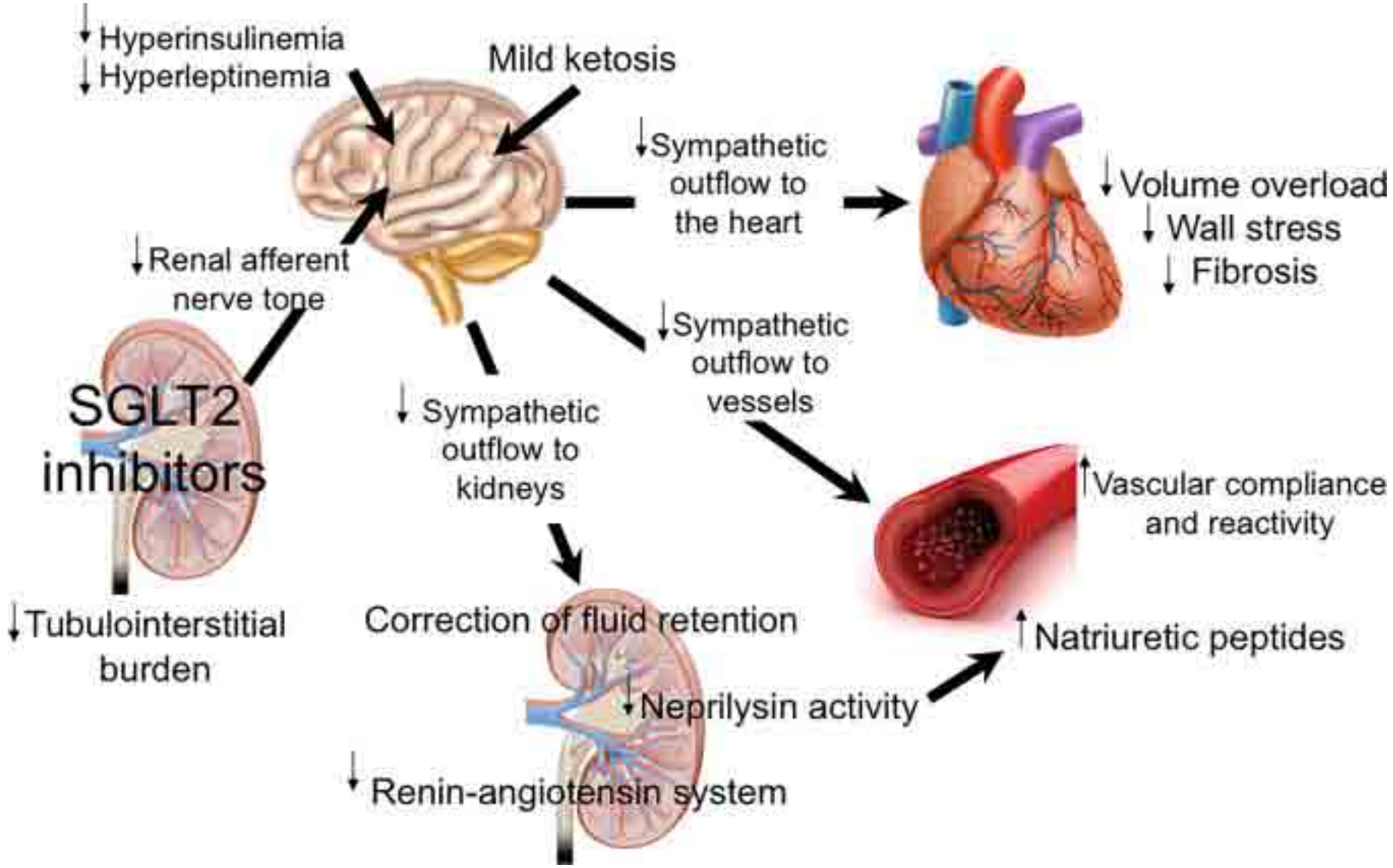
EMPA-REG OUTCOME: The Endocrinologist's Point of View

Leigh Perreault, MD

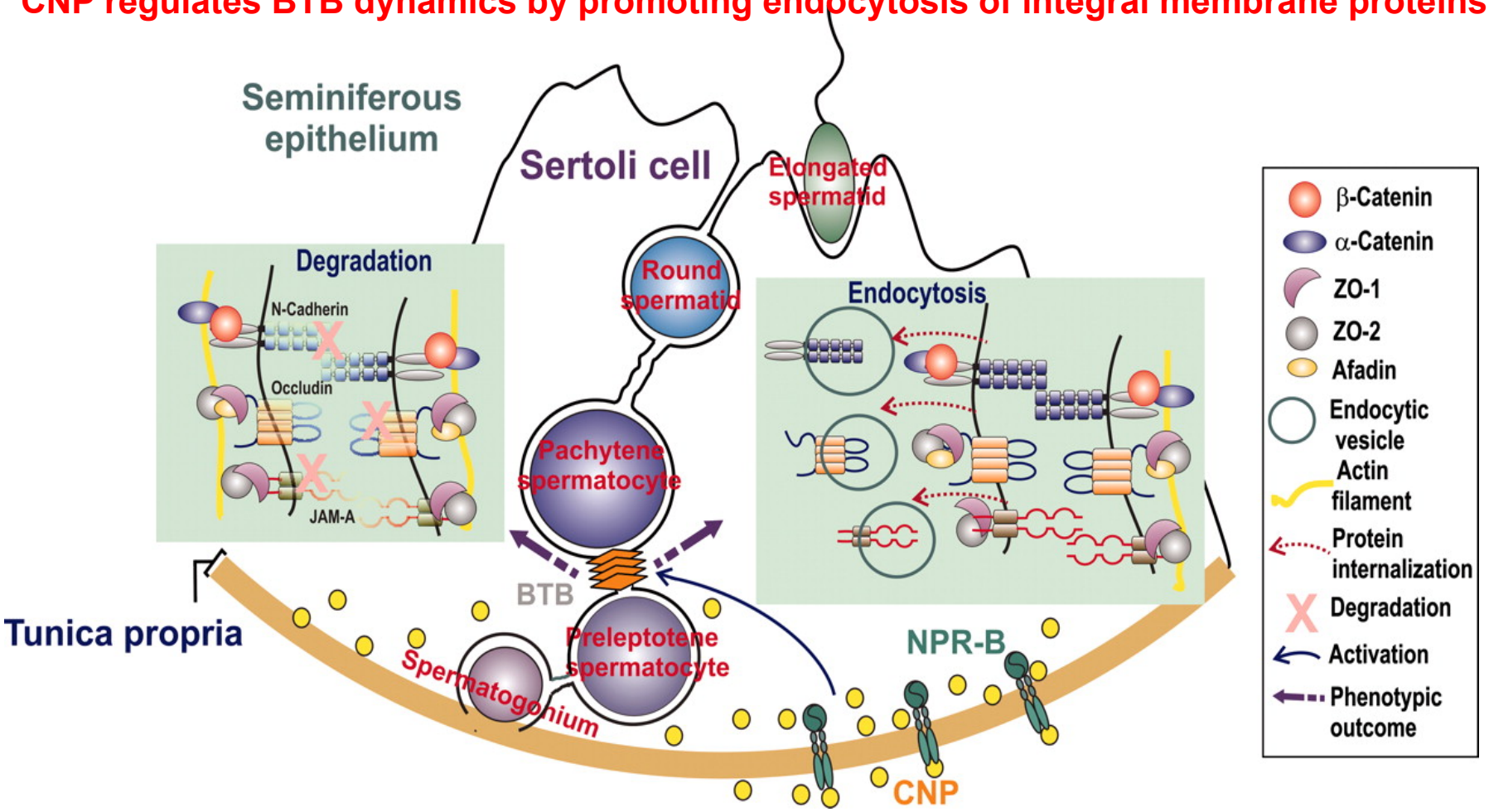
University of Colorado Anschutz Medical Campus, Aurora.

For many years, it was widely accepted that control of plasma lipids and blood pressure could lower macrovascular risk in patients with type 2 diabetes mellitus (T2DM), whereas the benefits of lowering plasma glucose were largely limited to improvements in microvascular complications. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) study demonstrated for the first time that a glucose-lowering agent, the sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin, could reduce major adverse cardiovascular events, cardiovascular mortality, hospitalization for heart failure, and overall mortality when given in addition to standard care in patients with T2DM at high cardiovascular risk. These results were entirely unexpected and have led to much speculation regarding the potential mechanisms underlying cardiovascular benefits. In this review, the results of EMPA-REG OUTCOME are summarized and put into perspective for the endocrinologist who is treating patients with T2DM and cardiovascular disease.

 • *The American Journal of Medicine (2017) 130, S51-S56*


↓Hyperinsulinemia
↓Hyperleptinemia
Mild ketosis
↓Sympathetic outflow to the heart
↓Volume overload
↓Wall stress
↓Fibrosis
↓Renal afferent nerve tone
SGLT2 inhibitors
↓Sympathetic outflow to vessels
↓Sympathetic outflow to kidneys
↑Vascular compliance and reactivity
↓Tubulointerstitial burden
Correction of fluid retention
↑Natriuretic peptides
↓Neprilysin activity
↓Renin-angiotensin system

CNP regulates BTB dynamics by promoting endocytosis of integral membrane proteins



CNP regulates BTB dynamics by promoting endocytosis of integral membrane proteins. This effect, coupled with degradation of proteins at the BTB possibly via the ubiquitination/lysosomal pathway under the influence of other molecules, in turn reduces the steady-state levels of integral membrane proteins at the BTB. The net result opens the BTB to facilitate preleptotene spermatocyte migration that occurs at stage VIII of the epithelial cycle. It is likely that CNP is working in concert with other molecules in the microenvironment of the seminiferous epithelium, such as TGF-β3 and TNFα, to regulate BTB dynamics.

PNAS Weiliang Xia et al. PNAS 2007;104:10:3841-3846

THE C-TYPE NATRIURETIC PEPTIDE SYSTEM IN THE TESTIS

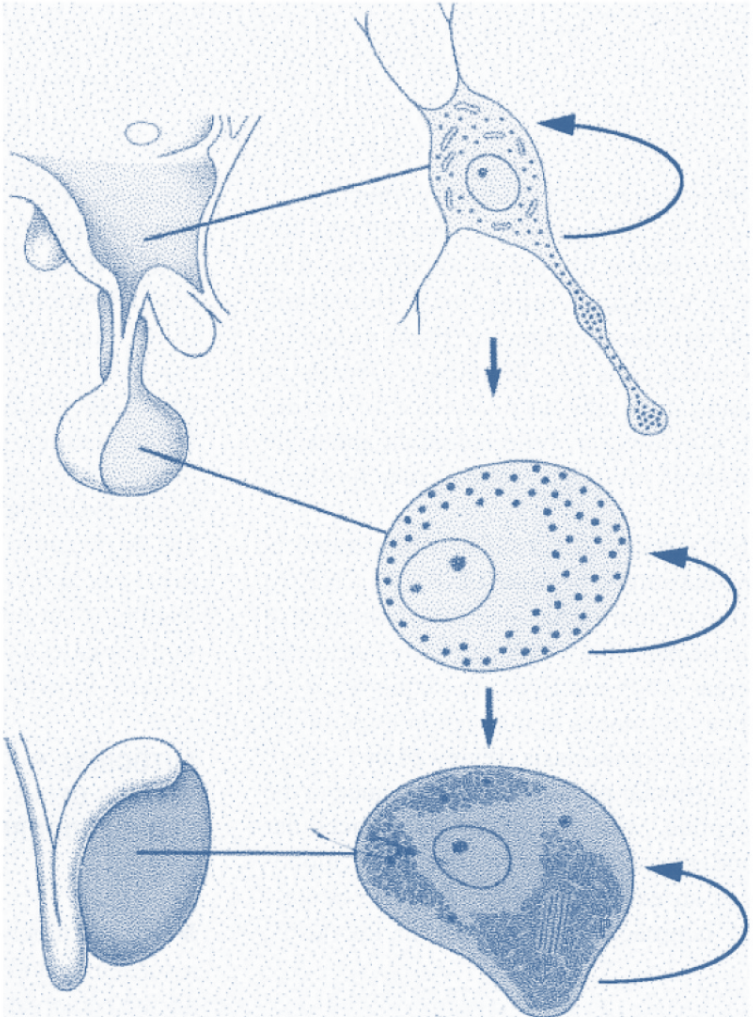
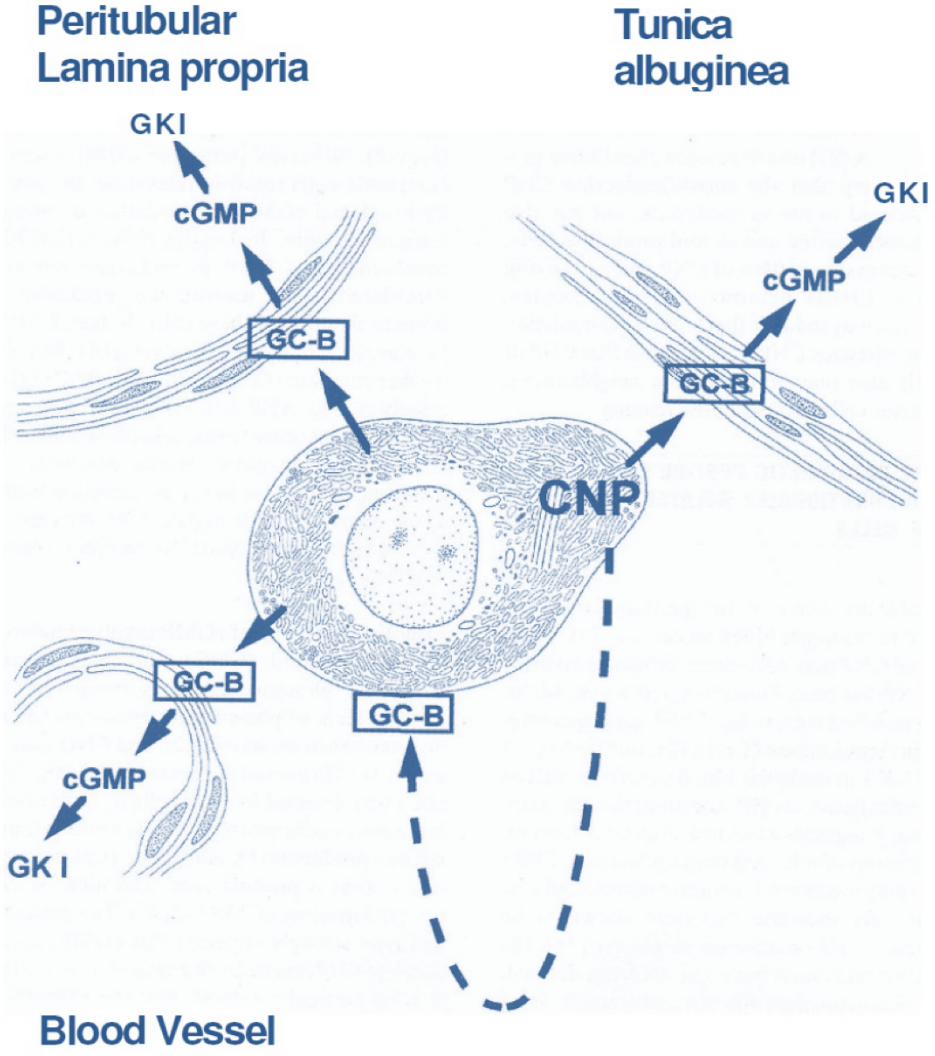


Fig. 1. Autocrine effects of CNP in Leydig cells, gonadotropes, and LHRH neurons. In these cell types CNP is produced and leads to an accumulation of the second messenger cGMP mediated by guanylate cyclase B, the receptor for CNP (5,14,17-20). Moreover, CNP induces an increase of testosterone release by Leydig cells (14), and an increase of LHRH secretion by LHRH neurons (20).

BMR Biomedical Reviews

Biomedical Reviews 1997; 8: 111-117

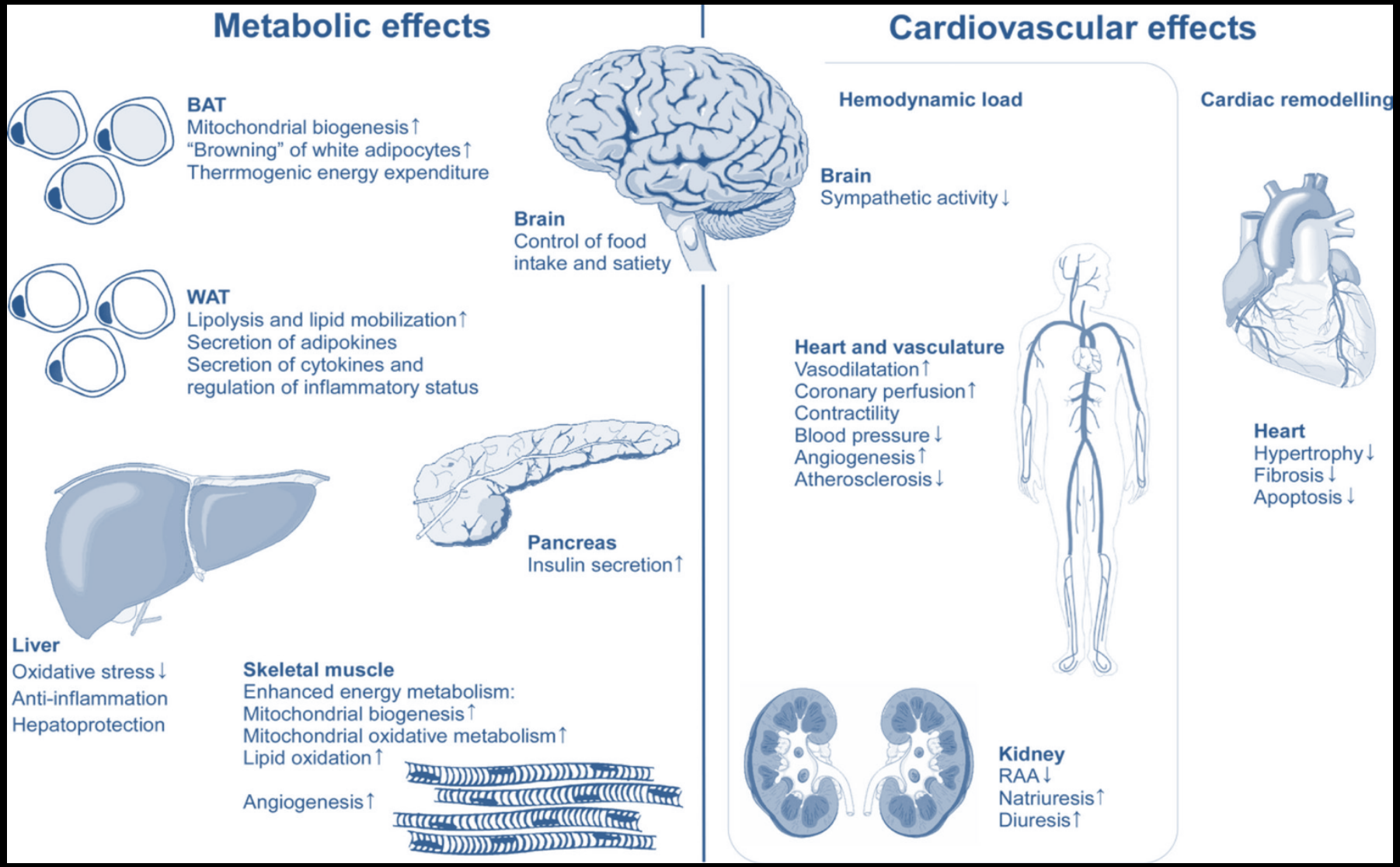
THE C-TYPE NATRIURETIC PEPTIDE SYSTEM IN THE TESTIS



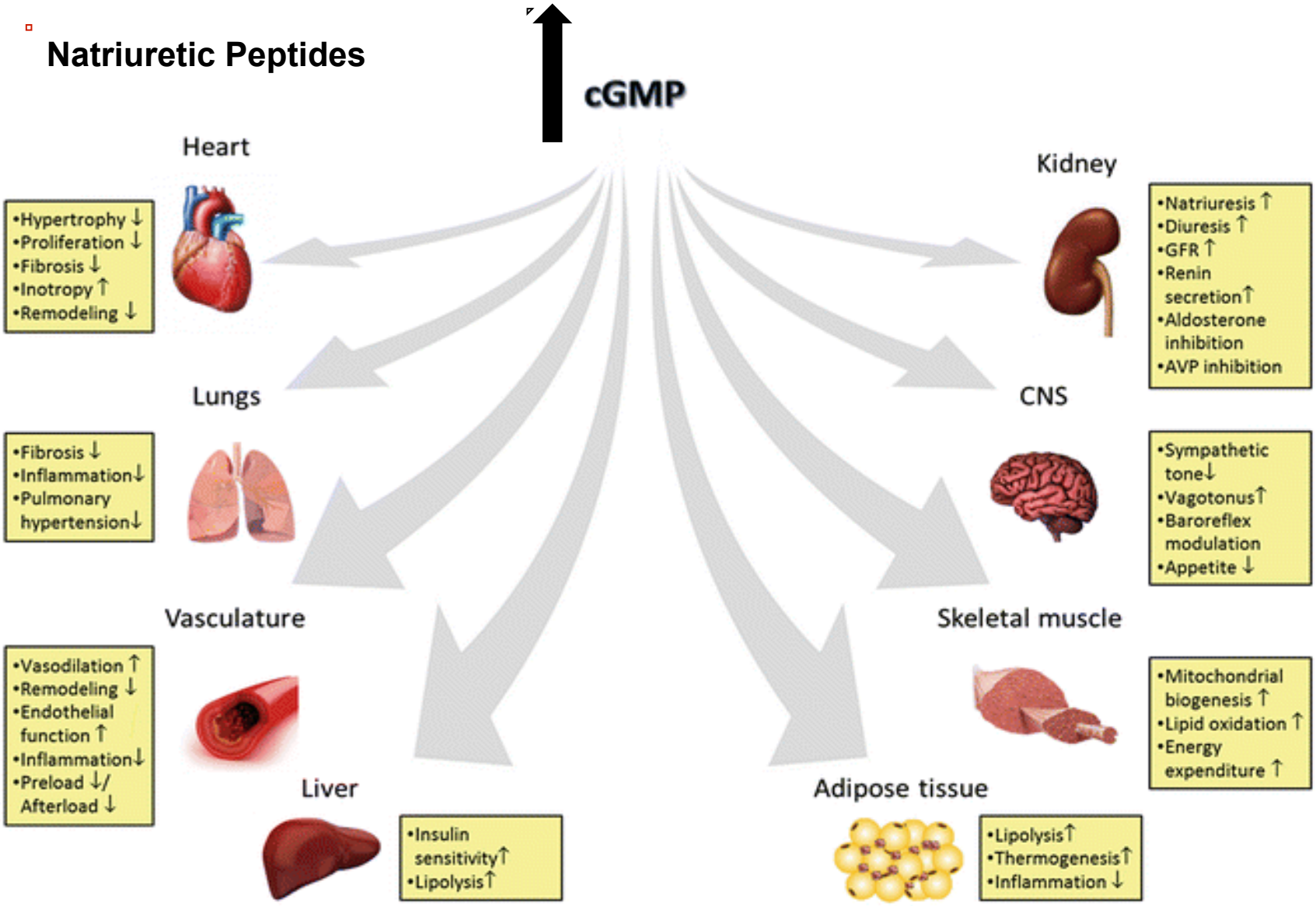
Biomedical Reviews 1997; 8: 111-117

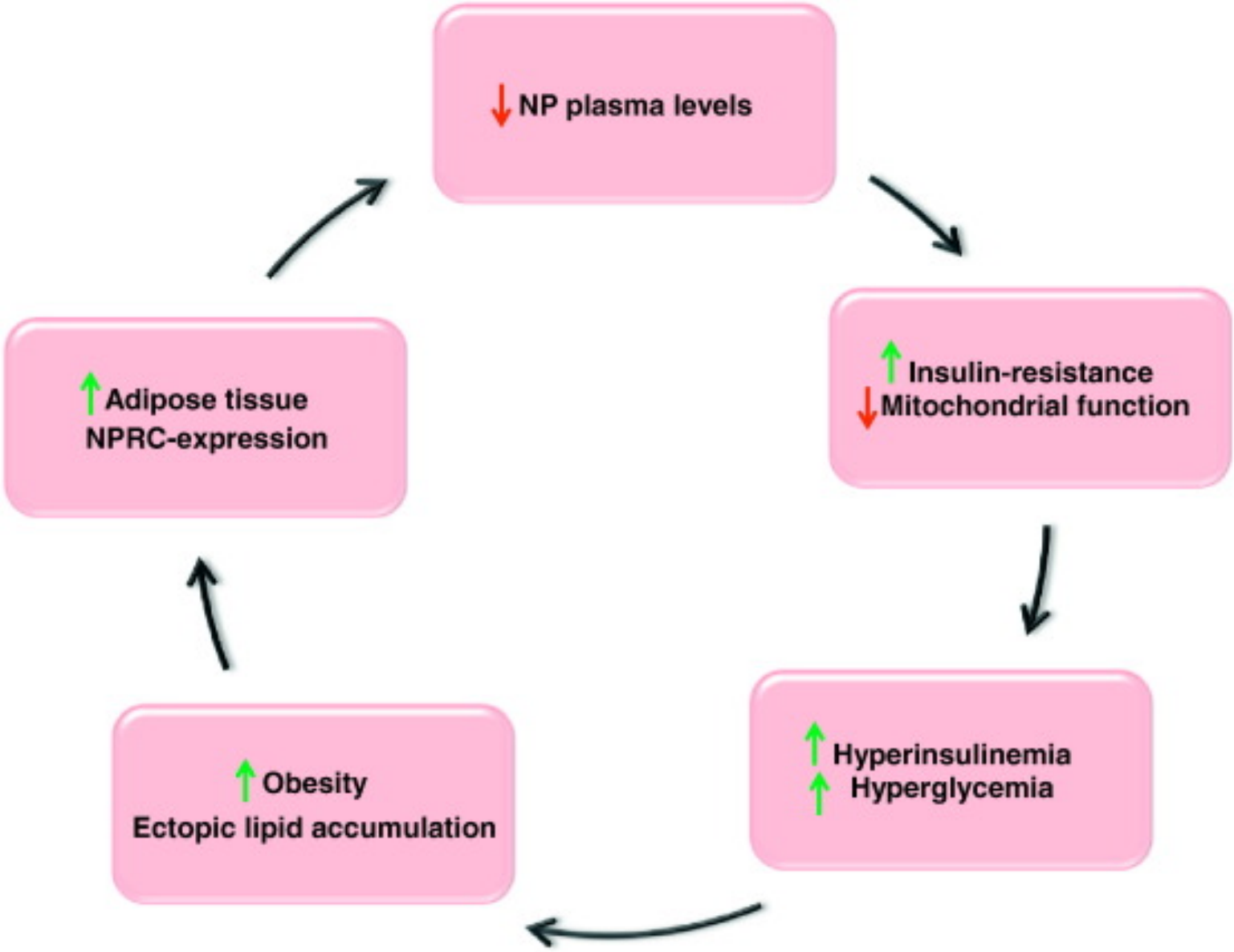
Fig. 2. Schematic presentation of presumed testicular actions of CNP. CNP is produced in human Leydig cells. Based on the presence of specific receptors for CNP, Leydig cells, myofibroblasts of the tunica albuginea, myofibroblasts of the peritubular lamina propria and, vascular smooth muscle cells represent potential sites of CNP activity. This may result in relaxation of contractile cells, presumably mediated by cGMP and GKI (37). In Leydig cells, autocrine actions of CNP may influence testosterone production (14) via a promiscuous activation of' cAMP-dependent protein kinase by cGMP (42, 45).

NPs regulate key functions of the cardiovascular system



Natriuretic Peptides

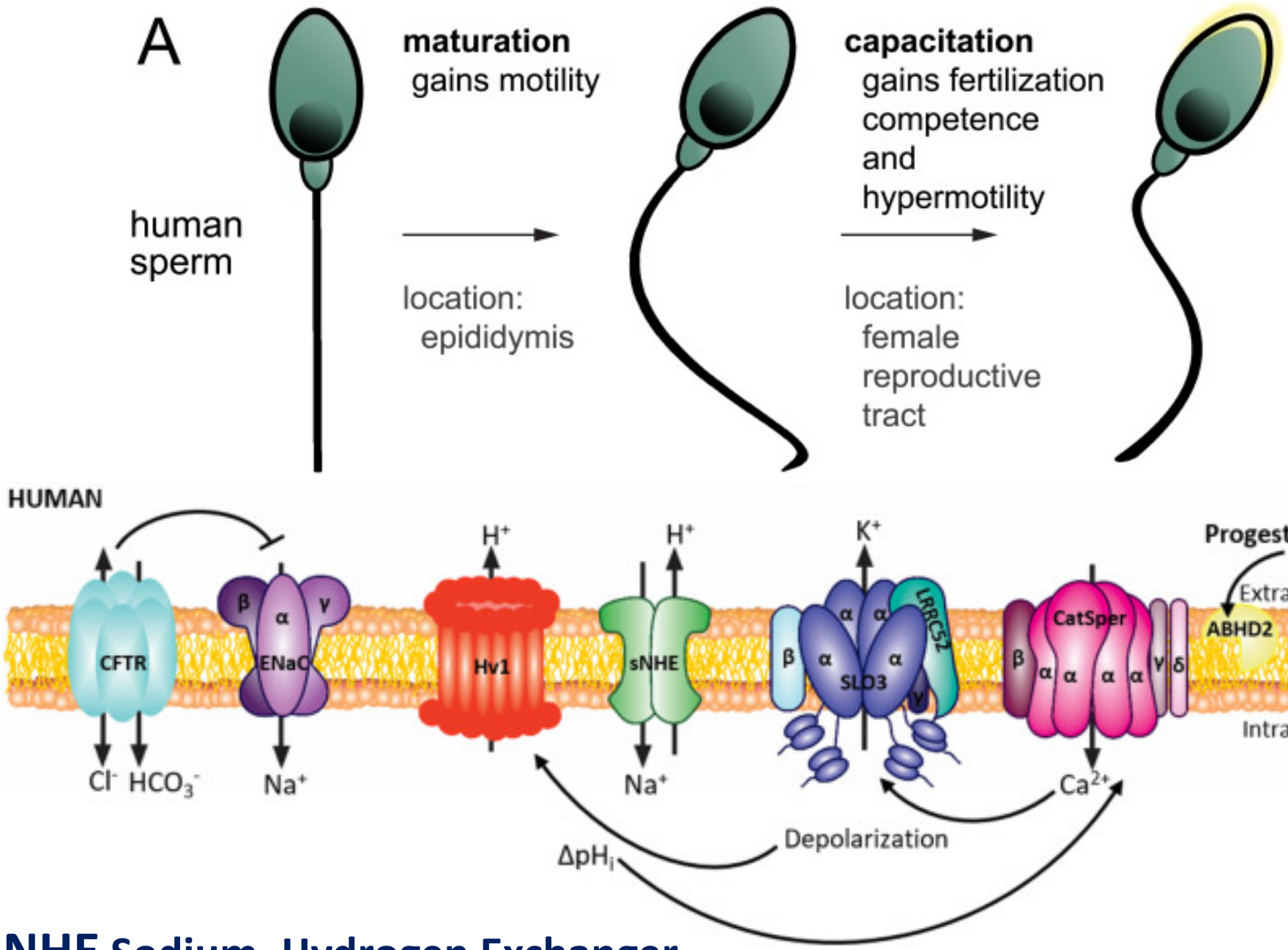



↓NP plasma levels
↑Insulin-resistance
↓Mitochondrial function
↑Hyperinsulinemia
↑Hyperglycemia
↑Obesity
Ectopic lipid accumulation
↑Adipose tissue
NPRC-expression

Proposed effect of SGLT2 inhibition	Effect on biomarkers
• Diuresis, natriuresis • Blood pressure lowering • Loss of body weight • Reduced inflammation/oxidative stress • Improved vascular compliance • Long-term preservation of renal function • Metabolic effects on myocardium, improving energetics • Inhibition of Na/H co-transporter • Improvement in myocardial remodeling	↓ NT-proBNP ↓ hsTnI
• Transient decrease in eGFR	↑ Galectin-3

Januzzi, Jr., J.L. et al. J Am Coll Cardiol. 2017;70(6):704-12.

Through its beneficial effects on the heart, canagliflozin prevented a rise in N-terminal pro–B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin I (hsTnI). Possibly through transient reduction in estimated glomerular filtration rate (eGFR), galectin-3 increased modestly. Na/H = sodium/proton; SGLT2 = sodium glucose co-transporter 2.



NHE Sodium–Hydrogen Exchanger

Algorithm for Adding/Intensifying Insulin

START BASAL (Long-Acting Insulin)

A1C < 8% — **TDD 0.1–0.2 U/kg**

A1C > 8% — **TDD 0.2–0.3 U/kg**

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - BG < 70 mg/dL: 10% – 20%
  - BG < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

***Glycemic Goal:**

- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

Glycemic Control Not at Goal*

INTENSIFY (Prandial Control)

Add GLP-1 RA

Or SGLT-2i
Or DPP-4i

Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3

- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals
- **Start: 10% of basal dose or 5 units**

Basal Bolus

- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
- **Start: 50% of TDD in three doses before meals**

Insulin titration every 2–3 days to reach glycemic goal:

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%

 DOI 10.4158/CS-2017-0153

Int. J. Dev. Biol. 43: 343-347 (1999)

Original Article

IGF-I, IGF-II and insulin promote differentiation of spermatogonia to primary spermatocytes in organ culture of newt testes

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THE INTERNATIONAL JOURNAL OF DEVELOPMENTAL BIOLOGY

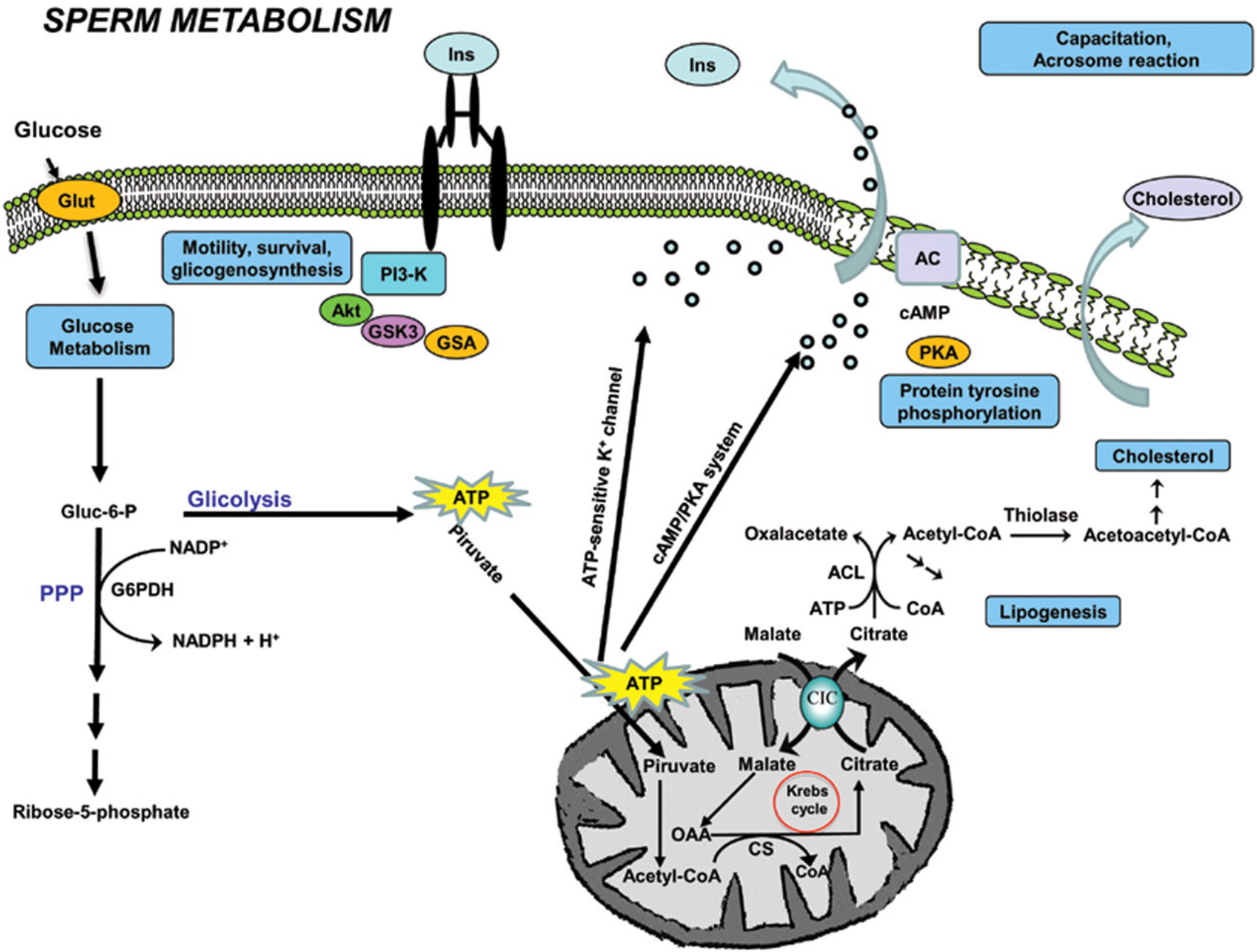
Physiology & Behavior

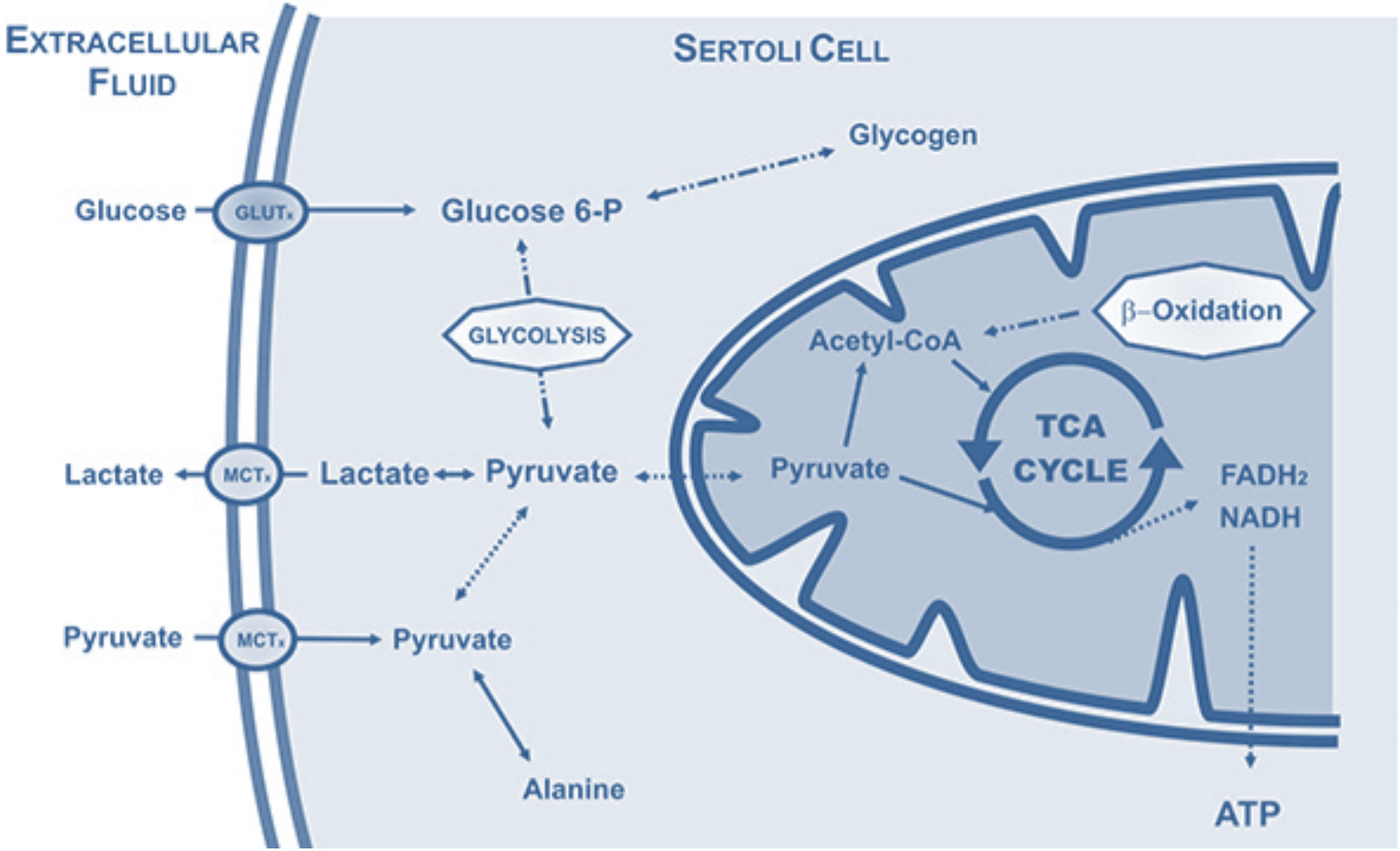
Insulin: its Role in the Central Control of Reproduction

Physiol Behav. 2014 June 22; 0: 197–206.

Highlights

- Insulin plays a key role in the regulation of reproduction in addition to metabolism
- Insulin regulates both pulsatile and surge secretion of GnRH/LH
- Insulin may be a signal in prenatal programming of adult reproductive function
- Insulin targets in the brain include kisspeptin, AgRP and POMC neurons
- Insulin resistance in human disease is associated with reproductive dysfunction


SPERM METABOLISM
Ins
Ins
Capacitation,
Acrosome reaction
Glucose
Glut
Motility, survival,
glicogenosynthesis
PI3-K
Akt
GSK3
GSA
Cholesterol
AC
cAMP
PKA
Protein tyrosine
phosphorylation
Glucose
Metabolism
Gluc-6-P
Glicolysis
ATP
Piruvate
ATP-sensitive K+ channel
cAMP/PKA system
Cholesterol
Thiolase
Oxalacetate
Acetyl-CoA
Acetoacetyl-CoA
ACL
ATP
CoA
Lipogenesis
Malate
Citrate
NADP+
PPP
G6PDH
NADPH + H+
ATP
CIC
Piruvate
Malate
Citrate
Krebs
cycle
OAA
CS
Acetyl-CoA
CoA
Ribose-5-phosphate



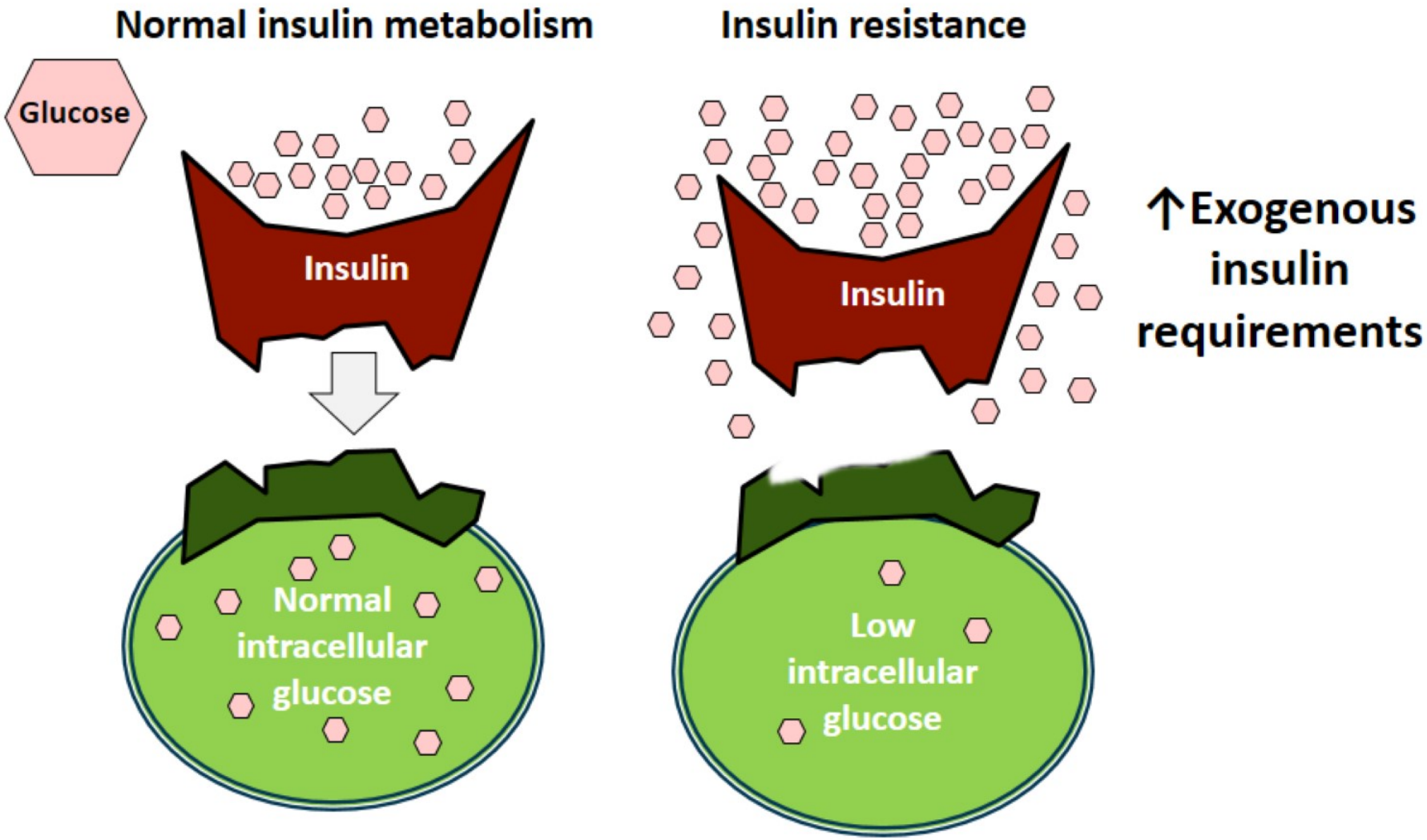
Highlights

- The first hours of insulin deprivation are critical in hSCs in vitro.
- Insulin deprivation affects glucose uptake and lactate production/export.
- Insulin-deprived hSCs present altered expression of metabolism-associated genes.
- GLUT1 and GLUT3 expression levels are modulated by insulin-deprivation in hSCs.

Cell types affected by
Lack of functional insulin

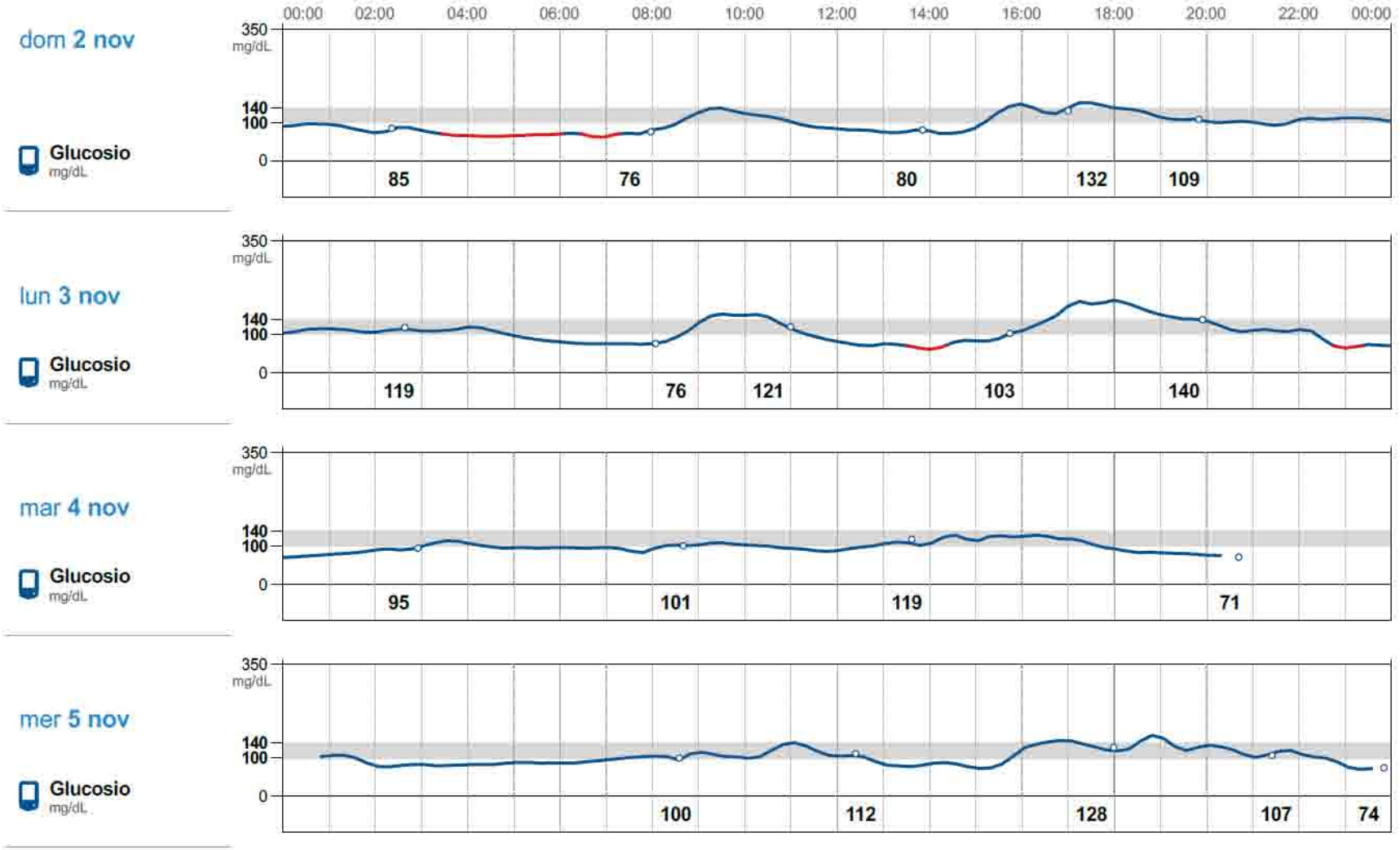
Exogenous insulin treatment rescues testicular phenotype

Insulin Resistance, Overinsulinization, and T2DM



Rizza RA, et al. *Diabetologia*. 1985;28(2):70-75.

Diario giornaliero



Legenda Glucosio alto (>240) Glucosio basso (<70) Test con striscia Scansione sensore Registrato Picco postprandiale Nuovo sensore Modifica ora

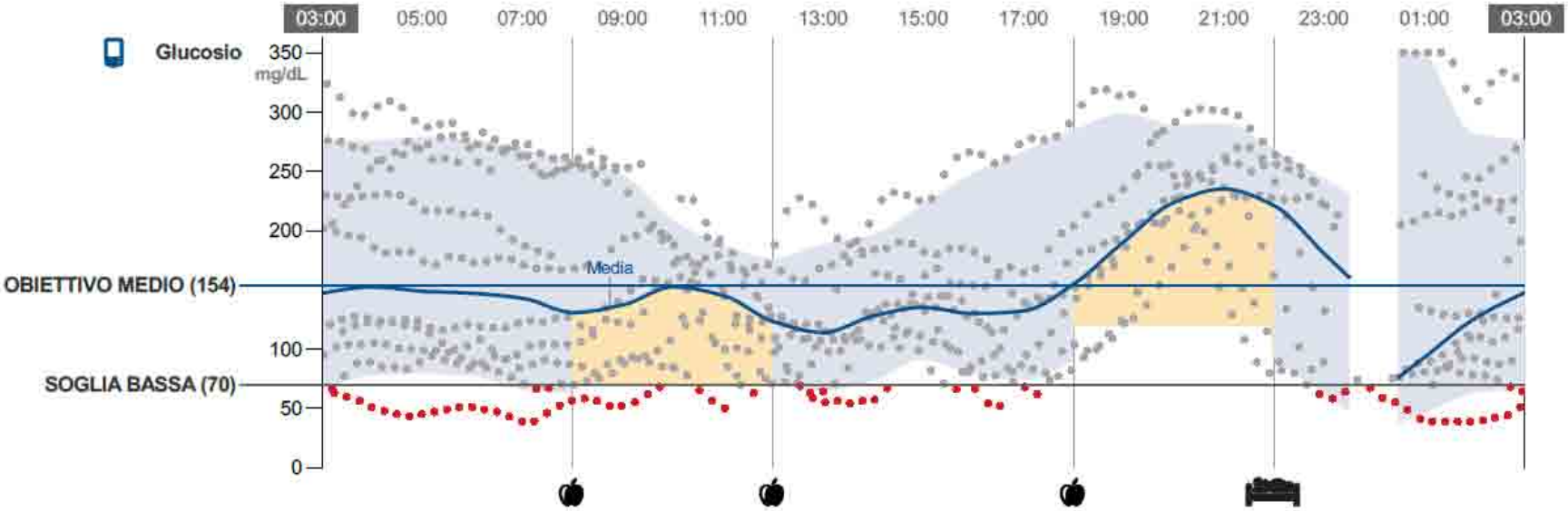
Indicatori di profilo del glucosio (con valori del glucosio)

25 ottobre 2018 - 7 novembre 2018 (14 giorni)

IMPOSTAZIONE GLUCOSIO BASSO CONSENTITO: Medio

IMPOSTAZIONI OBIETTIVO MEDIO: 154 mg/dL (A1c: 7,0% o 53 mmol/mol)

A1c stimata 7,2% o 55 mmol/mol



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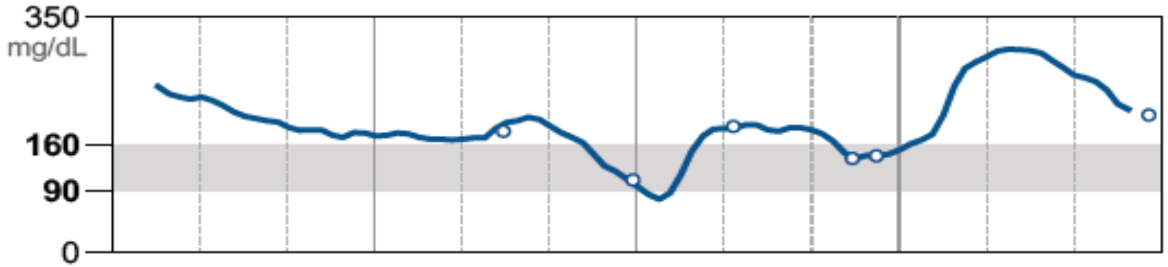
5 nov



192
mg/dL

Rationale for Combination of Basal Insulin plus a GLP-1 Agonist

Basal insulin analogues

- Suppress hepatic glucose production
- Control nocturnal and FPG
- Improve β-cell function
- Weight *re*-gain ~1–3 kg
- Less hypoglycemia risk vs NPH
- Simple titration algorithms available
- Avoid clinical inertia

GLP-1 receptor agonists

- Differential impacts on both FPG,PPG
- Improve insulin release and sensitivity to insulin
- Decrease gastric emptying
- No independent increase in hypoglycaemia
- Weight loss ~1–3 kg
- Simple to use

Complementary and potentially synergistic effects

Optimise HbA_{1c} control, safely

Glycemic Control Algorithm

INDIVIDUALIZE GOALS

- **A1C ≤ 6.5%** — For patients without concurrent serious illness and at low hypoglycemic risk
- **A1C > 6.5%** — For patients with concurrent serious illness and at risk for hypoglycemia

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ⚠ TZD
- ⚠ Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ⚠ Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

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Grazie per l’attenzione!