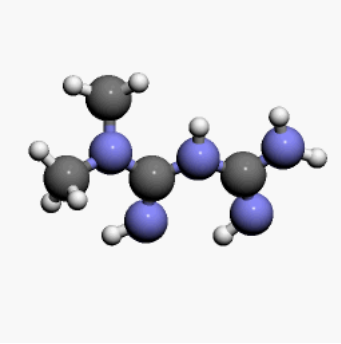
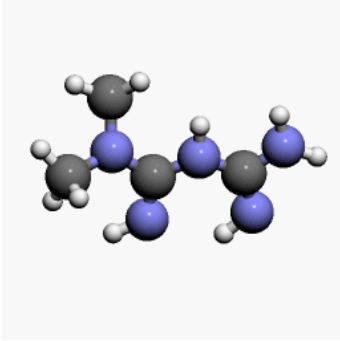
"Metformin: A drug for all reasons?"

Professor Chris R. Triggle, PhD, FBPhS.

Weill Cornell Medicine - Qatar





DISCLOSURE STATEMENT

Speaker:

Christopher R. Triggle, Phd, FBPhS

- Has no relevant financial relationship to disclose
- and WILL BE DISCUSSING off-label or investigational use of products or services…Metformin

As faculty members of Weill Cornell Medicine - Qatar we are committed to providing transparency for any and all external relationships prior to giving an academic relationship.

I, *Chris Triggle (Professor of Pharmacology),* declare that I do **NOT** have a financial interest in commercial products or services or any conflicts of interest related to this lecture entitled:

"Metformin: A drug for all reasons?"

Lecture Objectives

- **Summarize the basic pharmacology of metformin – particularly with reference to its use in the treatment of T2DM and its vasculoprotective effects.**
- **Evaluate the evidence of putative anti-cancer effects of metformin.**
- **Identify other potential indications for metformin.**

ALSO:

Some Shakespeare

A little bit of history.

A little bit of German Renaissance art.

A little bit of controversy – why concentration matters.

And something for fans of Star Trek

PERSONALISED / PRECISION / TARGETED THERAPY

METFORMIN – a Drug for All Reasons?

IF The Bard Of Avon was giving this talk today he might well re-phrase a well known speech from Julius Caesar, Act 3 Scene 2 and say:

"I COME TO PRAISE METFORMIN AND NOT TO BURY IT"

BUT ------

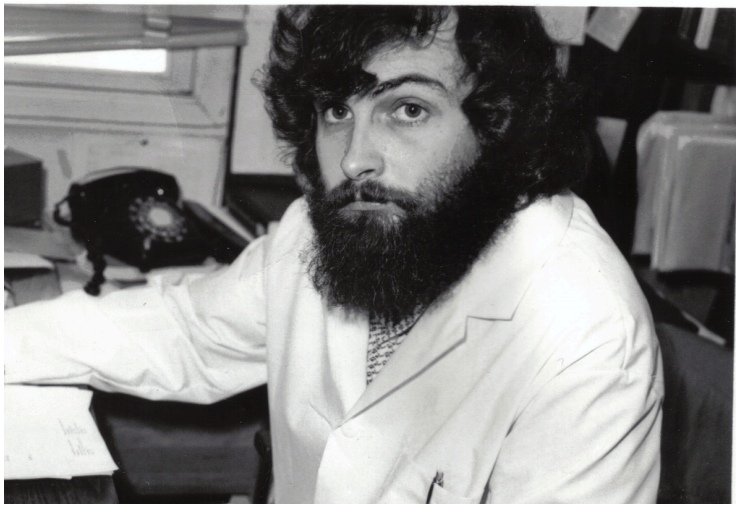
If Mary Poppins hadn't supplied the spoonful of sugar, maybe her charges wouldn't have needed metformin in the first place!

50+ years ago:
Pharmacotherapy for diabetes 1966

- **INSULINS** – animal origins (beef and or pork).
- **ORAL HYPOGLYCAEMICS:**

a. **Sulfonylureas:** tolbutamide & chlorpropamide

a. **Biguanides:** phenformin – FDA withdraws late 1978 (metformin used in UK)



Source: Third edition ***"The Pharmacological Basis of Therapeutics"*** – Goodman & Gilman, 1966.

Class	Example	Mechanism	I^{O} action	Advantages	Disadvantages	$
Biguanide	metformin	Activates AMPK; microbiome?	↓Hepatic glucose production	Experience; No hypoglycaemia; no weight gain; ↓CVD	GI SE; lactic acidosis (v.rare); VitB12 deficiency; CIs: CKD	$
Sulfonylureas	glyberide	Closes K_{ATP}	↑ insulin secretion	Extensive experience	Hypoglycaemia; weight gain =3-4 Kg; CV events?	$
Meglitinidines "prandins"	repaglinide	Closes K_{ATP}	↑ insulin secretion	↓ Postprandial excursions	Hypoglycaemia; weight gain; CV events?	$$
Thiazolidinediones (Glitazones)	pioglitazone	PPARγ activation	↑ insulin sensitivity	No hypoglycaemia; Good lipid profile	Weight gain 4-5 Kg; edema/CHF; bone fractures; bladder cancer?	$$
α-glucosidase inhibitors	acarbose	Inhibits intestinal α-glucosidase	Slows intestinal absorption	No hypoglycaemia; ↓Postprandial excursions	Only modest efficacy; GI issues; compliance?	SS
GLP-1 analogues	Exenatide	GLP-1 receptor agonists	↑Insulin secretion/ satiety; ↓glucagon secretion	No hypoglycaemia; weight reduction; improved β-cell function; CV benefits?	GI SEs; injections acute pancreatitis - controversial?	SSS
DPP-4 inhibitors	sitagliptin	Enhances GLP-1	As for GLP-1	Oral; No hypoglycaemia and well tolerated	Modest efficacy HbA1c; angioedema Acute pancreatitis?	$$$
SGLT-2 inhibitors	FLOZINS dapaglifozin	↓glucose	kidney	Weight reduction; no hypoglycaemia? CV PROTECTION?	NEW; dehydration; UTI. Ketoacidosis?	SSS

HISTORY

REVIEW ARTICLE

Traditional Plant Medicines as Treatments for Diabetes

Clifford J. Bailey, PhD
Caroline Day, PhD

Diabetes Care. 12: 553-562. 1989.

Plants	Location of use
Aconitum carmichaeli	Orient
Allium cepa	Asia, Europe, Middle East
Allium sativum	Asia, Europe, Middle East
Amorphophallus konjac	Orient
Anemarrhena asphodeloides	Orient
Atractylodes japonica	Orient
Blighia sapida	Africa, Central America
Catharanthus roseus	Africa, Asia, Europe, Australasia
Coccinia indica	Asia
Cyamopsis tetragonolobus	Asia
Dioscorea japonica	Orient
Eleutherococcus senticosus	Orient
Emericella quadrilineata	Asia
Ephedra distachya	Orient
Ficus bengalensis	Asia
Galega officinalis	Europe
Ganoderma lucidum	Orient
Gymnema sylvestre	Asia, South Africa
Lithospermum erythrorhizon	Orient
Lupinus termis	Middle East
Momordica charantia	Asia, Australasia, Central America, West Africa
Momordica foetida	West Africa
Oryza sativa	Orient
Panax ginseng	Orient
Panax quinquefolium	Orient
Saccharum officinarum	Orient
Tecoma stans	Central and South America, Middle East, West Africa
Trigonella foenumgraecum	Asia, Europe
Vaccinium myrtillus	Europe, North America

Guanidine - - galegine

⬇

Synthalin A & B, polyethylene biguanides 1926-1940, liver & kidney problems

⬇

Pentamidine

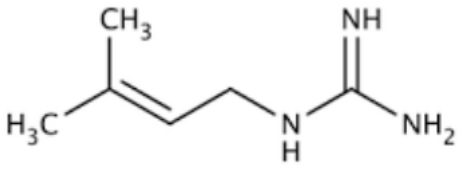
⬇

Trypanosomiasis & Chagas Disease

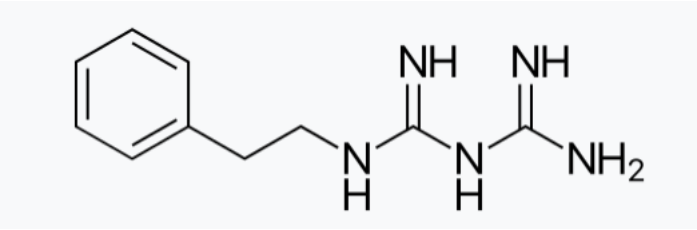
Goat's Rue / French Lilac

Galega officinalis, French lilac, which in Germany was called "plague herb", contain numerous guanidine derivatives, including galegine which cause hypoglycaemia. Goat's rue is widely used internationally as a galactogogue.

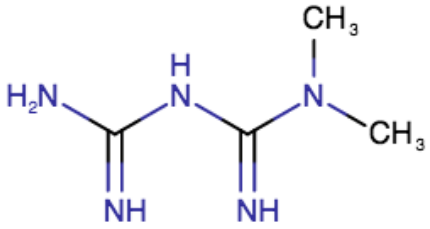
Galegine was, unsuccessfully, evaluated as an anti-hyperglycaemic drug in the 1920/30s. Synthetic biguanides phenformin & metformin were evaluated in 1950s



Galegine



phenformin (phen-ethyl; Ciba Geigy)



metformin (dimethyl)

Metformin: 10 out of 10

1. Introduced in UK in 1958 with ~ 60 years of clinical knowledge.
2. Still the "FIRST CHOICE" drug for the treatment of type 2 diabetes.
3. Estimated 150 million patients currently use metformin worldwide.
4. Cardiovascular (microvascular) protective (UKPDS data).
5. Low risk of hypoglycaemia.
6. No weight gain; modest weight loss.
7. Orally effective, safe and relatively free of side effects.
8. Generic and therefore comparatively inexpensive.
9. Meta analysis suggests protective role in cancer.
10. Studies as an anti-ageing drug?

Want it or not - metformin in the drinking water?

Estimated urinary excretion ~250,000 Kg/day

Chemosphere 93 (2013) 2116–2123

Contents lists available at ScienceDirect

Chemosphere

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

Pharmaceuticals and personal care products found in the Great Lakes above concentrations of environmental concern

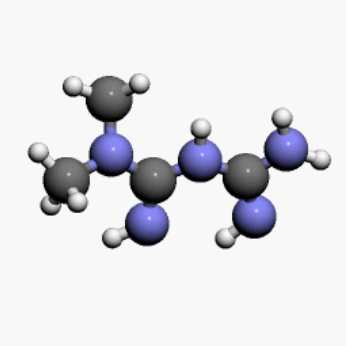
Benjamin D. Blair [a], Jordan P. Crago [a], Curtis J. Hedman [b], Rebecca D. Klaper [a,*]

[a] School of Freshwater Sciences, University of Wisconsin-Milwaukee, 600 E. Greenfield Ave, Milwaukee, WI 53204, United States
[b] State Laboratory of Hygiene, University of Wisconsin-Madison, 2601 Agriculture Drive, Madison, WI 53718, United States

HIGHLIGHTS

- Pharmaceuticals and personal care products (PPCPs) were monitored in Lake Michigan.
- Fifty-four PPCPs were assessed in surface water and sediment on six dates.
- Many PPCPs, such as metformin, were detected 3.2 km away from the shore.
- Hydrophobic compounds were detected in sediment at concentrations up to 510 ng g^{-1}.
- Using a risk quotient, the ecosystem risk was found to be high for many PPCPs.

Metformin – A drug for ALL reasons?



DIABETES
OBESITY
>3.5 million

CARDIOVASCULAR
DISEASE
>17 million

metformin?

CANCER
>8 million

AGEING
>8%
population
over 65

MILES – Metformin In Longevity Study

TAME – Targeting Ageing with Metformin

First clinical use in France & United Kingdom in 1957/8, but not until 1995 in USA and now >150 million people prescriptions/year.

Stem Cell Reports
Report
OPEN ACCESS

Metformin Acts on Two Different Molecular Pathways to Enhance Adult Neural Precursor Proliferation/Self-Renewal and Differentiation

Michael Fatt,[1,3,10] Karolynn Hsu,[2,10] Ling He,[8] Fredric Wondisford,[9] Freda D. Miller,[1,3,4,5] David R. Kaplan,[1,3,4] and Jing Wang[2,6,7,*]

[1]Program in Neurosciences and Mental Health, Hospital for Sick Children, Toronto, ON M5G 1X8, Canada
[2]Regenerative Medicine Program, Ottawa Hospital Research Institute, Ottawa, ON K1H 8L6, Canada
[3]Institute of Medical Science
[4]Department of Molecular Genetics
[5]Department of Physiology
University of Toronto, Toronto, ON M5G 1X5, Canada
[6]Department of Cellular and Molecular Medicine
[7]Brain and Mind Research Institute
University of Ottawa, Ottawa, ON K1H 8M5, Canada
[8]Department of Pediatrics and Medicine, Johns Hopkins Medical School, Baltimore, MD 21287, USA
[9]Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ 08901, USA
[10]Co-first author
*Correspondence: jiwang@ohri.ca
http://dx.doi.org/10.1016/j.stemcr.2015.10.014
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)

The Lancet September 12 1998.

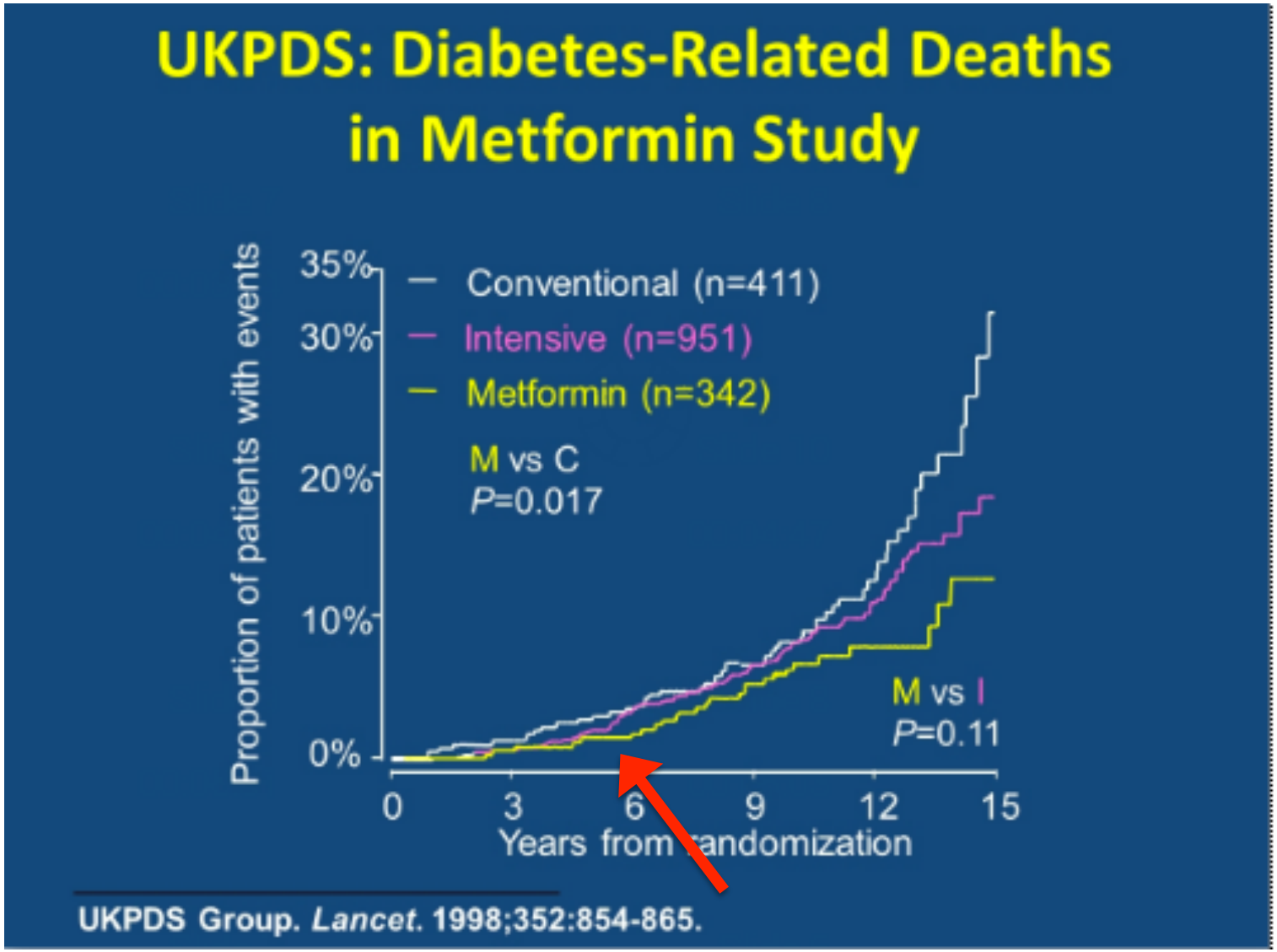
*UK Prospective Diabetes Study (UKPDS) Group**

RISK REDUCTION WITH METFORMIN: Based on data from a randomised control trial over a period of 10.7 years of 1704 overweight newly diagnosed T2DM patients. Diet vs. metformin vs. intensive blood-glucose control with chlorpropamide, glibenclamide or insulin. The metformin (alone) treated group showed decreased diabetes-related endpoints, diabetes-related death and all cause mortality.

CONCLUSION: On balance, treatment (of T2DM) with metformin appears to be advantageous as a first-line pharmacological therapy in diet-treated overweight patients with T2DM.

From Professor Lebovitz
2014 EASD Virtual Meeting:

http://www.easdvirtualmeeting.org/resources/18622



Improved Endothelial Function With Metformin in Type 2 Diabetes Mellitus

Kieren J. Mather, MD,* Subodh Verma, MD, PHD,† Todd J. Anderson, MD‡
Indianapolis, Indiana; and Toronto and Calgary, Canada

Endothelial – Vasculo-Protective

OBJECTIVES This study was designed to assess the effect of metformin on impaired endothelial function in type 2 diabetes mellitus.

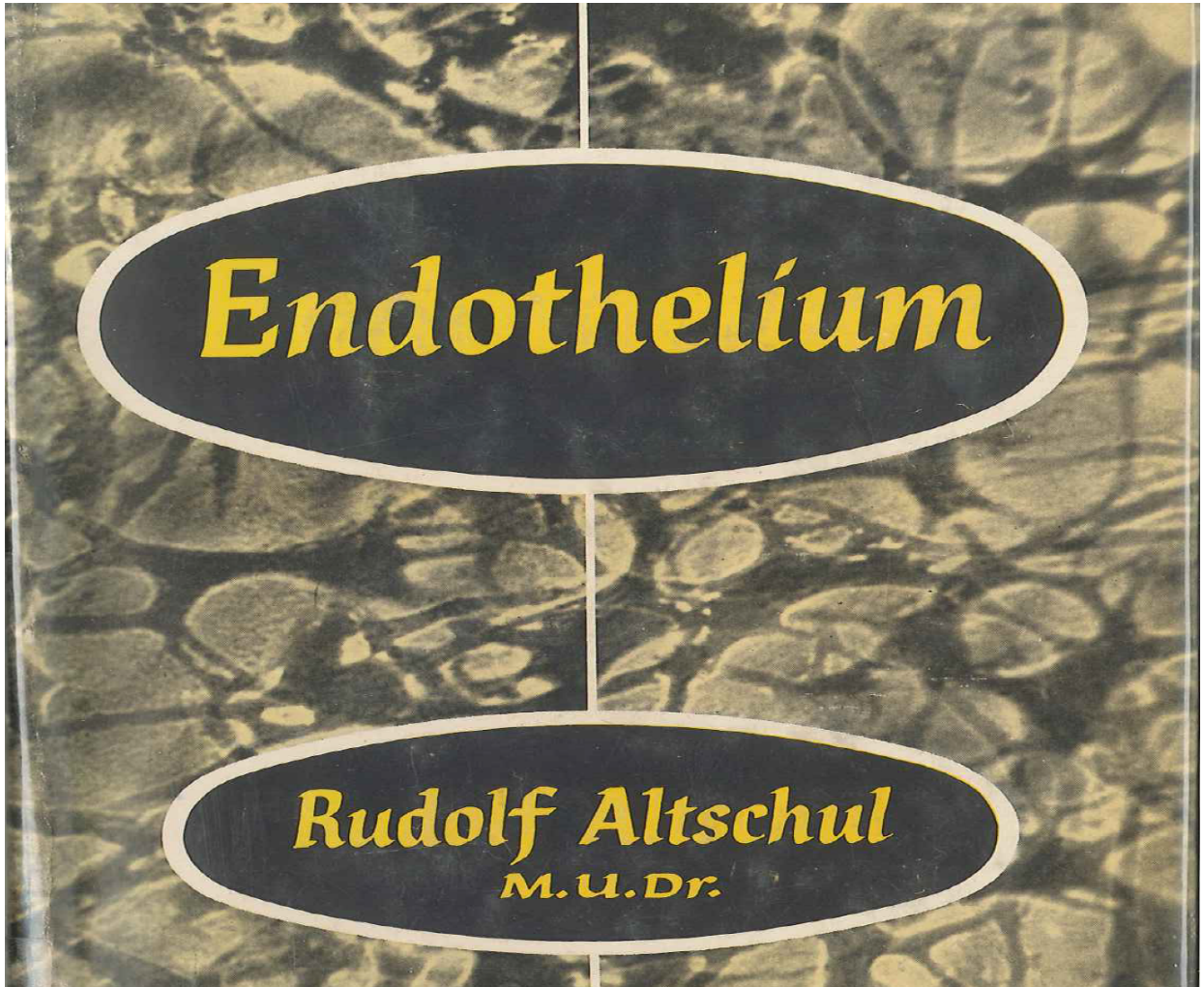
BACKGROUND Abnormalities in vascular endothelial function are well recognized among patients with type 2 (insulin-resistant) diabetes mellitus. Insulin resistance itself may be central to the pathogenesis of endothelial dysfunction. The effects of metformin, an antidiabetic agent that improves insulin sensitivity, on endothelial function have not been reported.

METHODS Subjects with diet-treated type 2 diabetes but without the confounding collection of cardiovascular risk factors seen in the metabolic syndrome were treated with metformin 500 mg twice daily (n = 29) or placebo (n = 15) for 12 weeks. Before and after treatment, blood flow responses to intraarterial administration of endothelium-dependent (acetylcholine), endothelium-independent (sodium nitroprusside) and nitrate-independent (verapamil) vasodilators were measured using forearm plethysmography. Whole-body insulin resistance was assessed on both occasions using the homeostasis model (HOMA-IR).

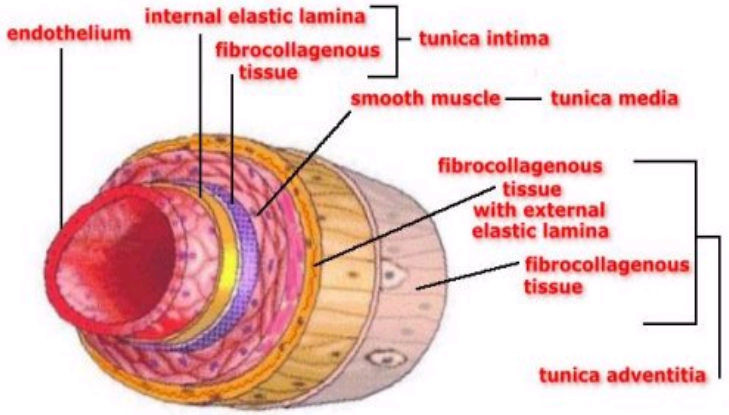
RESULTS Subjects who received metformin demonstrated statistically significant improvement in acetylcholine-stimulated flows compared with those treated with placebo ($p = 0.0027$ by 2-way analysis of variance), whereas no significant effect was seen on nitroprusside-stimulated ($p = 0.27$) or verapamil-stimulated ($p = 0.40$) flows. There was a significant improvement in insulin resistance with metformin (32.5% reduction in HOMA-IR, $p = 0.01$), and by stepwise multivariate analysis insulin resistance was the sole predictor of endothelium-dependent blood flow following treatment ($r = -0.659$, $p = 0.0012$).

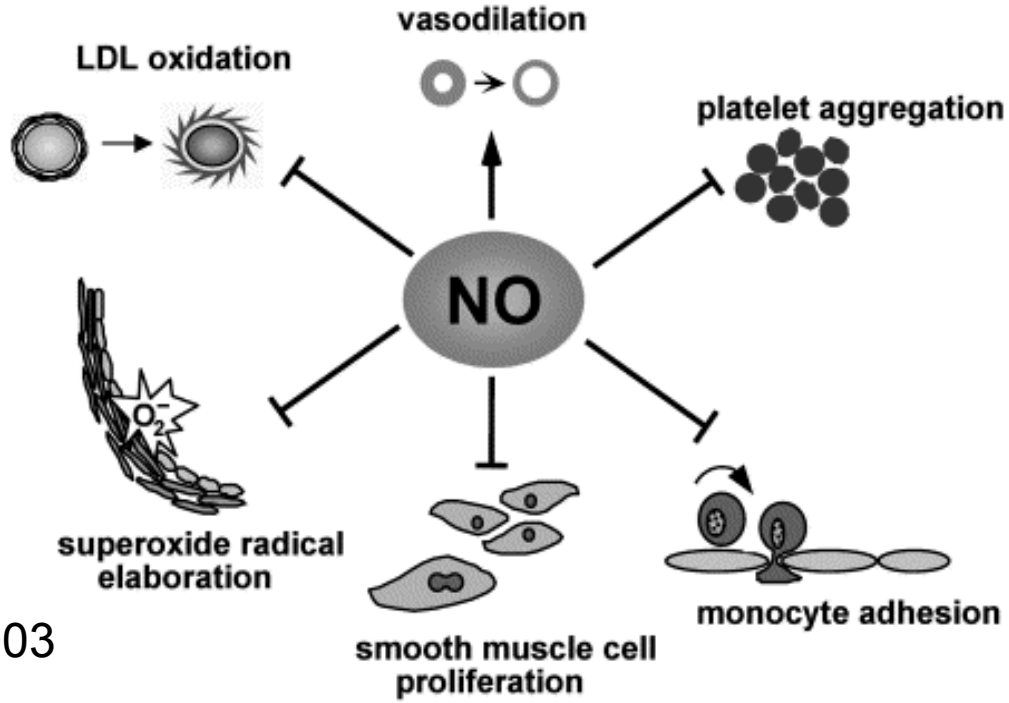
CONCLUSIONS Metformin treatment improved both insulin resistance and endothelial function, with a strong statistical link between these variables. This supports the concept of the central role of insulin resistance in the pathogenesis of endothelial dysfunction in type 2 diabetes mellitus. This has important implications for the investigation and treatment of vascular disease in patients with type 2 diabetes mellitus. (J Am Coll Cardiol 2001;37:1344–50) © 2001 by the American College of Cardiology

"You are only as old as your endothelium"- Rudolf Altschul, 1954



The Endothelium – structure/function.
~2.0 Kg endothelial cells in 70Kg person





From Boger Cardiovasc Res 59: 824, 2003

Endothelial dysfunction - Defined as an impaired vascular relaxation to endothelium-dependent vasodilators such as acetylcholine & bradykinin or an impaired flow-mediated vasodilatation response. It is an early (earliest) indicator of arterio- and atherosclerosis.

Q. Can a short exposure of endothelial cells to metformin improve endothelial function and enhance eNOS-P?

Protocol:

Mouse ECs cultured in either normal or high glucose and effects of 50μM metformin on ser1177eNOS and sirtuin 1 (SIRT1) determined.

Answer:

Yes.

Ghosh, Triggle & Ding et al. Biochemical Pharmacology 2015.

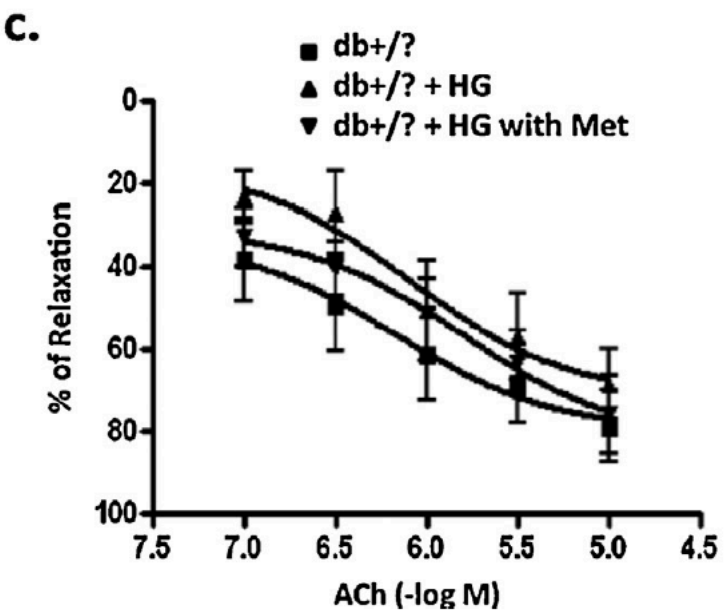
Metformin improves endothelial function in aortic tissue and microvascular endothelial cells subjected to diabetic hyperglycaemic conditions

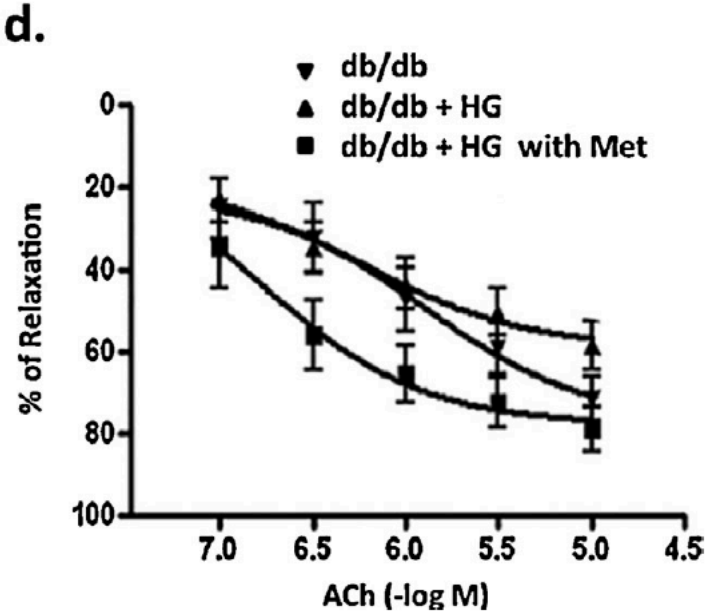
Biochemical Pharmacology 2015

Suparna Ghosh[a,1], Arun P. Lakshmanan[a,1], Mu Ji Hwang[b], Haidar Kubba[b], Ahmed Mushannen[b], Chris R. Triggle[a,b], Hong Ding[a,b,*]

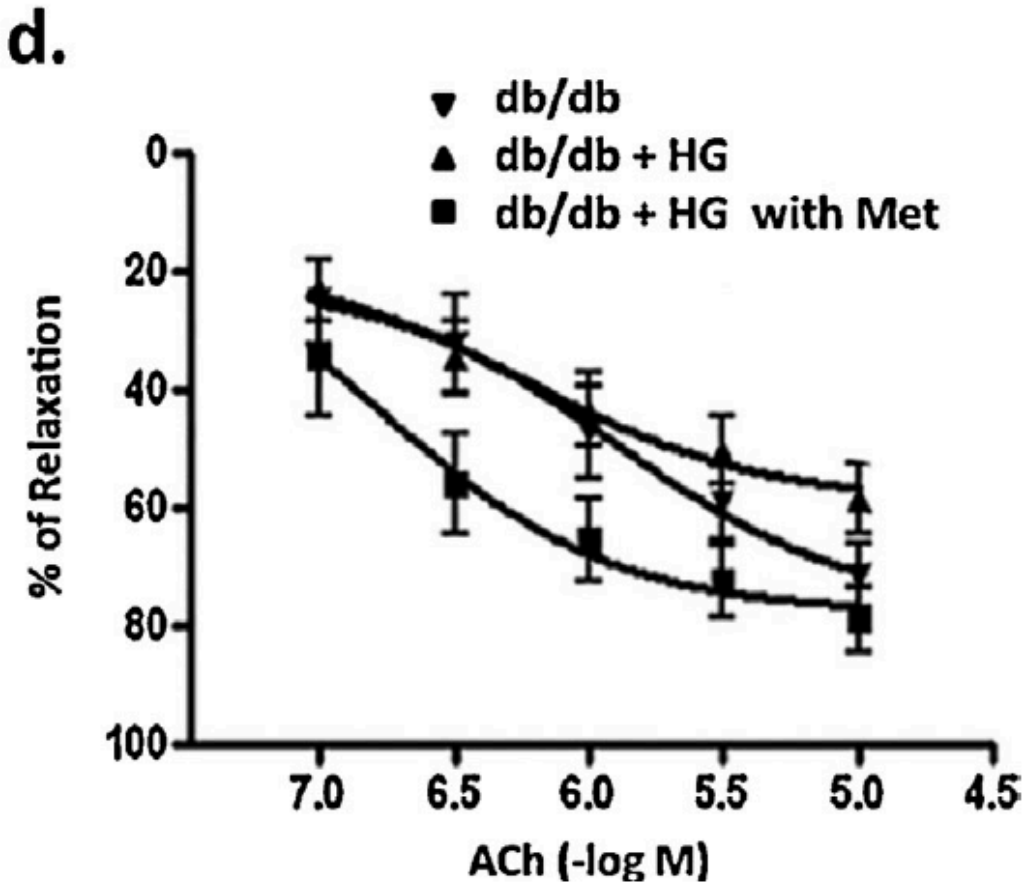
[a] *Department of Pharmacology, Weill Cornell Medical College in Qatar, P.O. Box 24144, Education City, Doha, Qatar*
[b] *Medical Education, Weill Cornell Medical College in Qatar, P.O. Box 24144, Education City, Doha, Qatar*

50µM metformin not only improves endothelial function in blood vessels from diabetic mice but this can also be correlated with protection of eNOS function.





50µM metformin not only improves endothelial function in blood vessels from diabetic mice but this can also be correlated with protection of eNOS function.

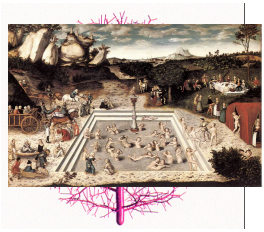


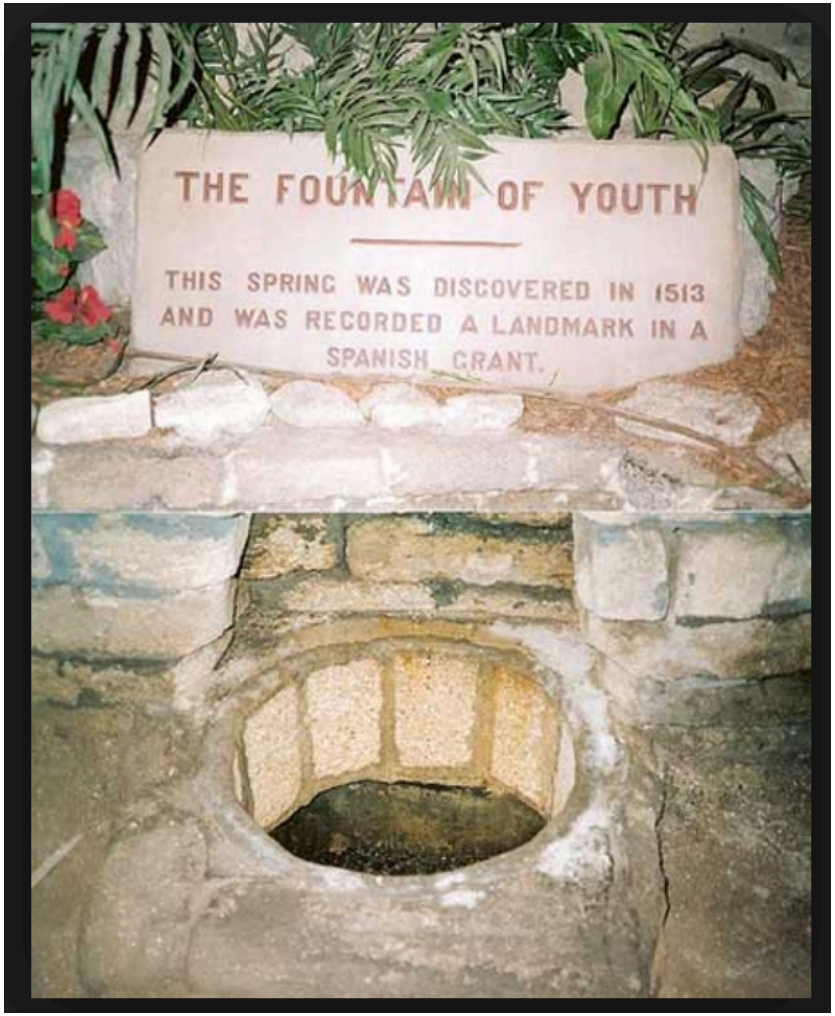
SIRTUINS are the "*Seven Samurai*" in the regulation of metabolism & ageing

The sirtuins 1-7 are histone deacetylases (HDACs) that require NAD+ as a co-factor. They were named after their homology to the Saccharomyces cerevisiae gene silent information regulator 2 (Sir2). In yeast and the nematode, C. elegans, Sir2 mediates the effects of calorie restriction to extend life span.

The Fountain of Youth by Lucas Cranach – Berlin National Museum

1546 - FIRST DEMONSTRATION OF EFFECTIVENESS OF GENE THERAPY WITH SIRT1





Inspired by Lucas Cranach's art we demonstrated that metformin prevents high glucose-induced endothelial cell senescence via a SIRT1-dependent mechanism.

BJP BRITISH JOURNAL OF PHARMACOLOGY
BPS BRITISH PHARMACOLOGICAL SOCIETY

Br J Pharmacol. 2014 Jan; 171(2): 523–535.
Published online 2013 Dec 23. doi: 10.1111/bph.12496
PMCID: PMC3904269

Metformin modulates hyperglycaemia-induced endothelial senescence and apoptosis through SIRT1

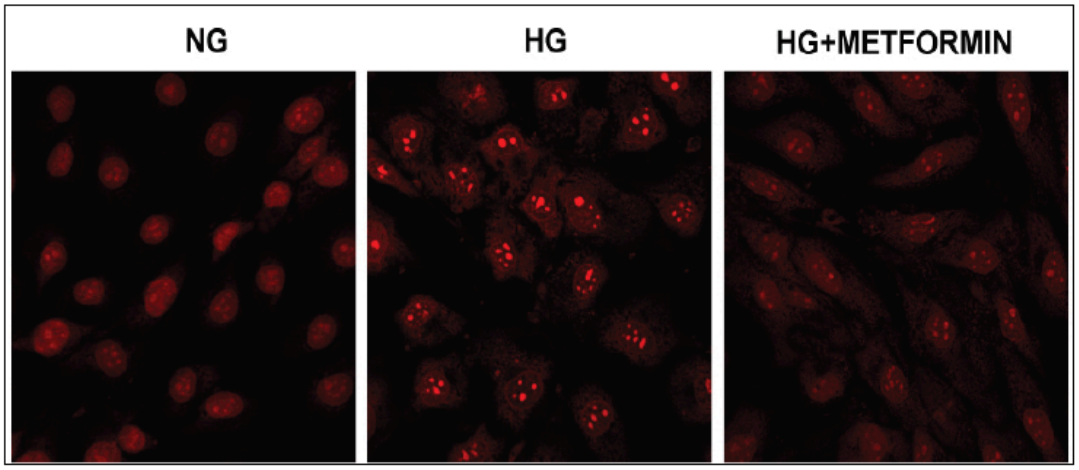
Gnanapragasam Arunachalam,[1] Samson Mathews Samuel,[1] Isra Marei,[1] Hong Ding,[1,2] and Chris R Triggle[1,2]

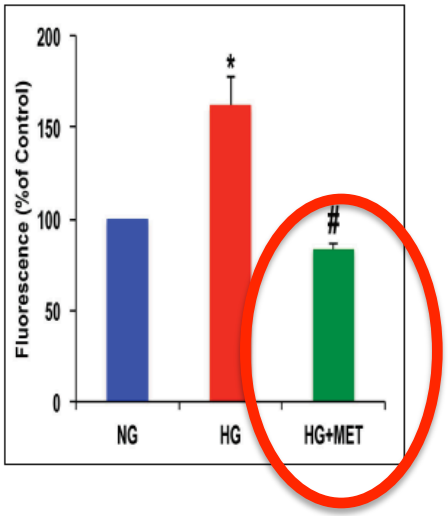
SUMMARY: Pretreatment of mouse microvascular endothelial cells maintained in high glucose [HG] with 50μM metformin prevents HG-induced endothelial cell senescence. siRNA-knockdown of the NAD-dependent deacetylase – sirtuin-1 and metformin promotes deacetylation of eNOS and pro-angiogenic activity.

NOTE: Sirtuin-1 has been previously shown to be downregulated in cells that have high insulin resistance and inducing sirtuin-1 expression increases insulin sensitivity.

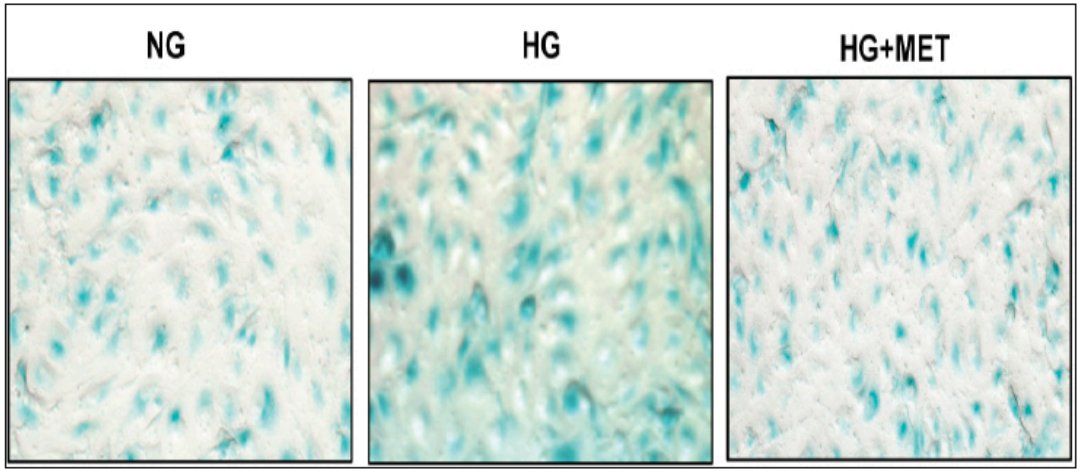
Metformin protects endothelial cells against high glucose-induced senescence

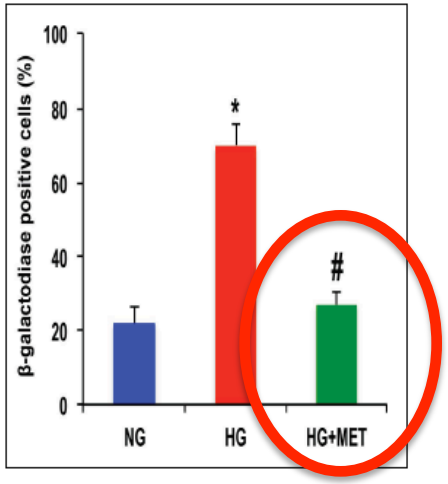
1. DHE Staining





2. β-galactosidase activity

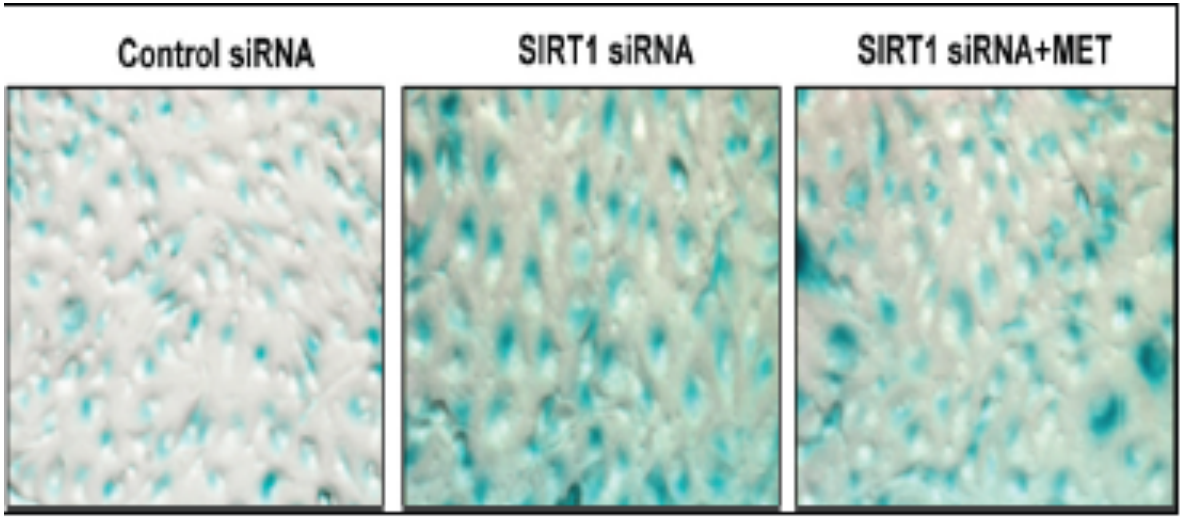


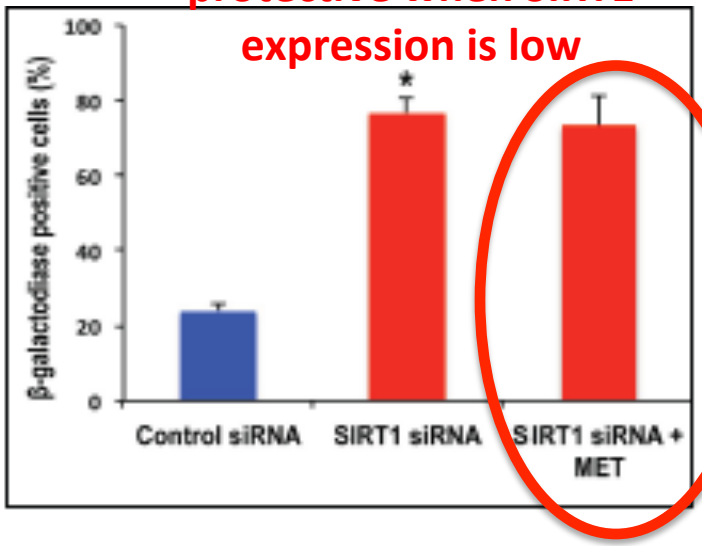


MMECs treated with NG (11mM) and HG (40mM) along with metformin (50μM) for 72 hr. 1. DHE staining showing the ROS levels, 2. β-galactosidase activity as a measure of senescence.

In absence of SIRT1 metformin no longer reduces effects of HG on β-galactosidase activity

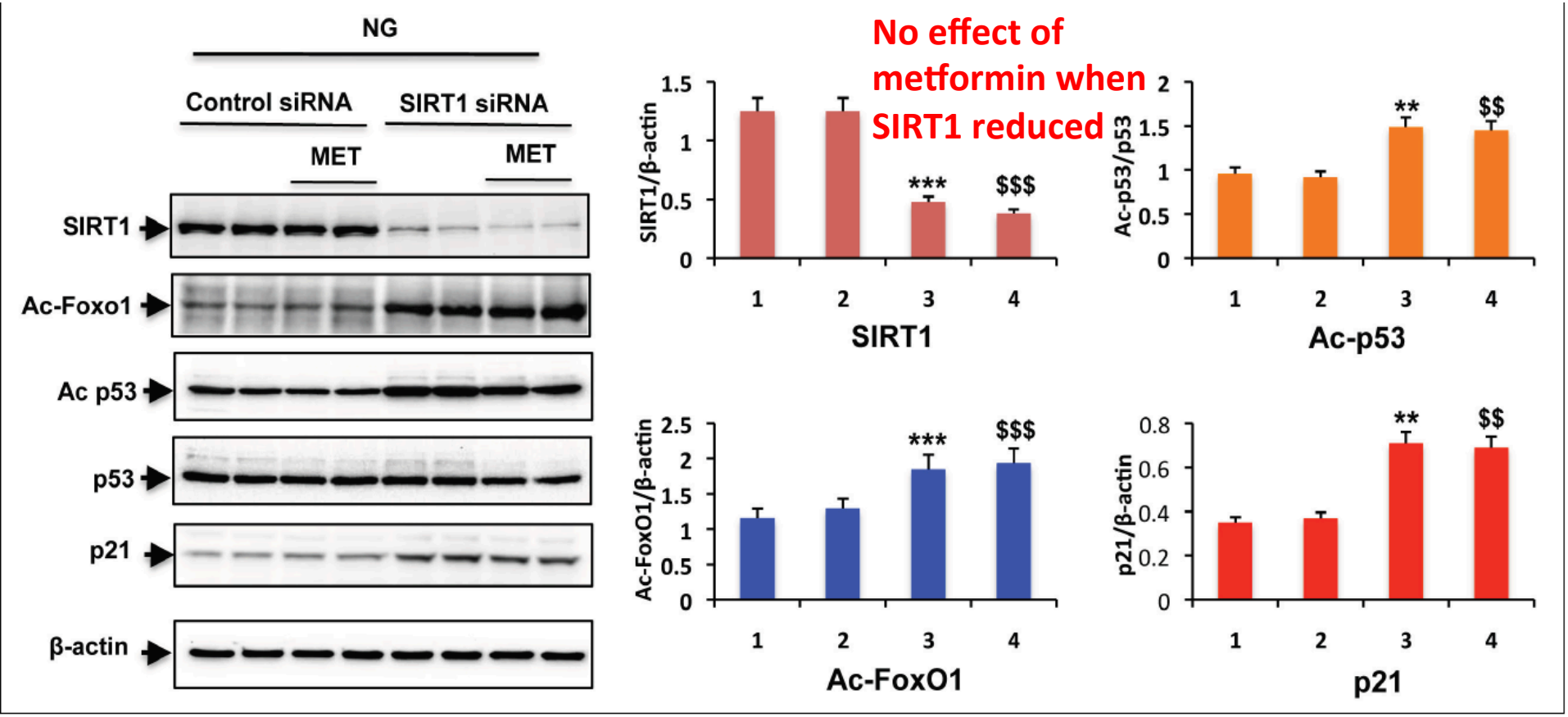
Metformin is no longer protective when SIRT1 expression is low





MMECs transfected with control and SIRT1 siRNAs and then treated NG (11 mM) along with metformin (50μM). SIRT1 knockdown showed increased β-galactosidase activity as a measure of senescence. Metfromin treatment does not show any effect in reducing the β-galactosidase activity.

Knockdown of SIRT1 mimics effects of HG on protein expression/acetylation



MMECs transfected with control and SIRT1 siRNAs and then treated NG (11 mM) along with metformin (50μM). SIRT1 knockdown showed increased Ac-Foxo1, Ac-p53 and p21 levels.

In absence of SIRT1 metformin now has no "rescue effect" on protein expression/acetylation.

microRNAs – small non-coding molecules with RNA-silencing actions: Role in regulation of vascular function:

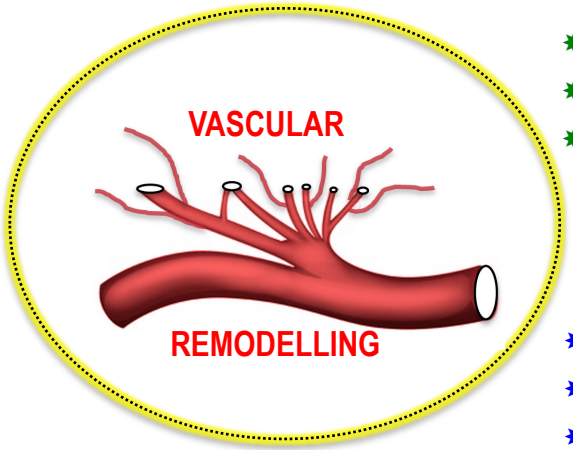
Angiogenesis

- miR-126,miR221/222
- miR-17-92,miR-23-24
- miR-16, miR-424
- miR-130, miR-132
- miR-101, miR-200b

miR221 & 222

Inflammation

- miR-126, miR-21, miR-181b
- miR-10a, miR-31, miR-17
- miR155, miR-150, miR-17-92
- miR-424, miR-17-5b, miR-20a
- miR-106a, miR-146



Diabetic Nephropathy

- miR-192, miR-377,
- miR-93, miR-29c,
- miR-21 and miR-25

Diabetic Retinopathy

- miR-146, miR-155
- miR-132, miR-21
- miR-34, miR-220b, miR-29

EC senescence

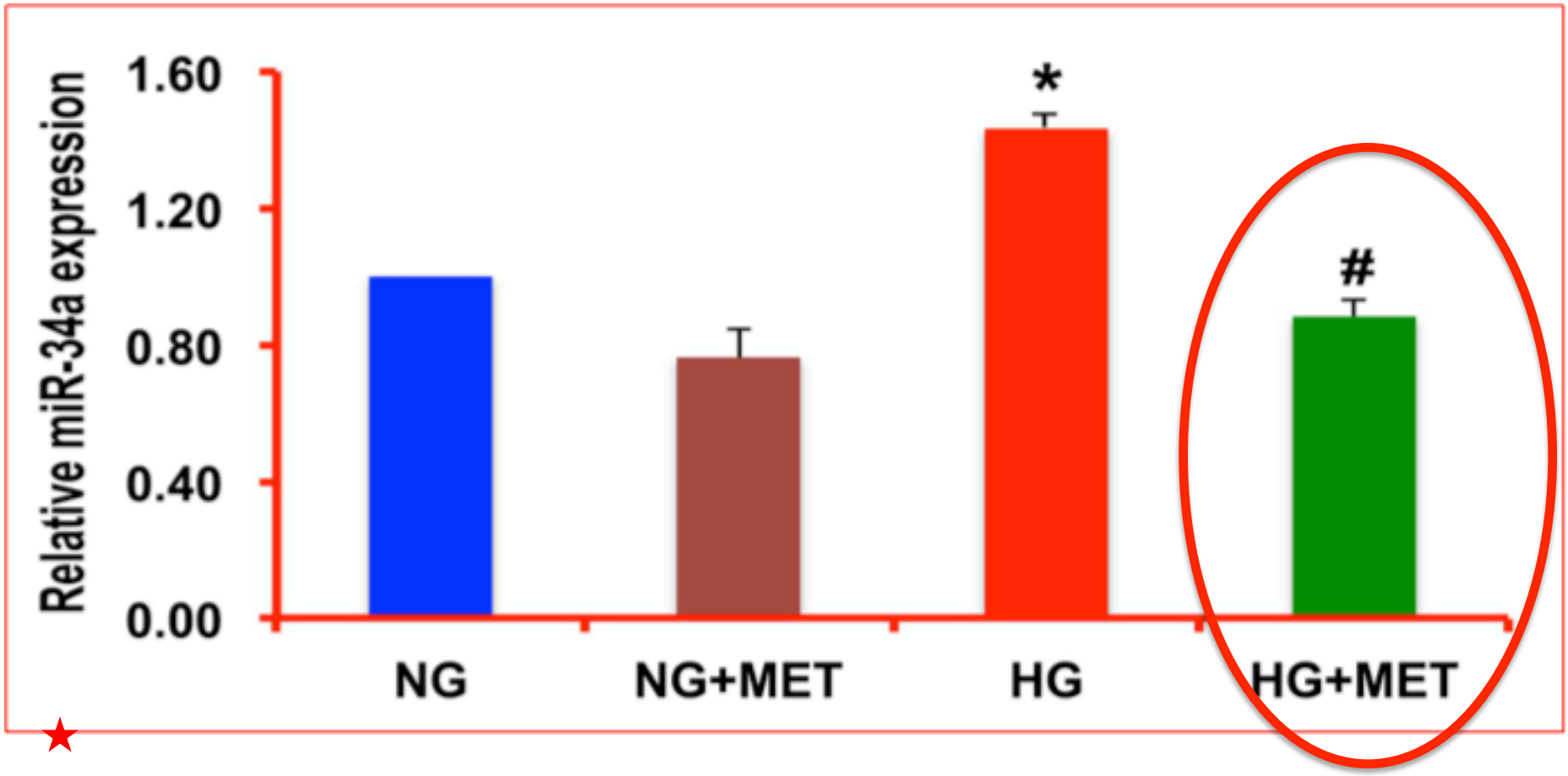
- miR-34a, miR-217
- miR-200, miR-146a

miR-34a – tumour suppressor & via binding within 3' UTR of SIRT1 reduces sirtuin 1 expression

Diabetic Heart /ECs

- miR-320, miR-221/222
- miR-133, miR-1
- miR-206, miR-125b, miR-503

miR34a increased in HG but reduced by metformin

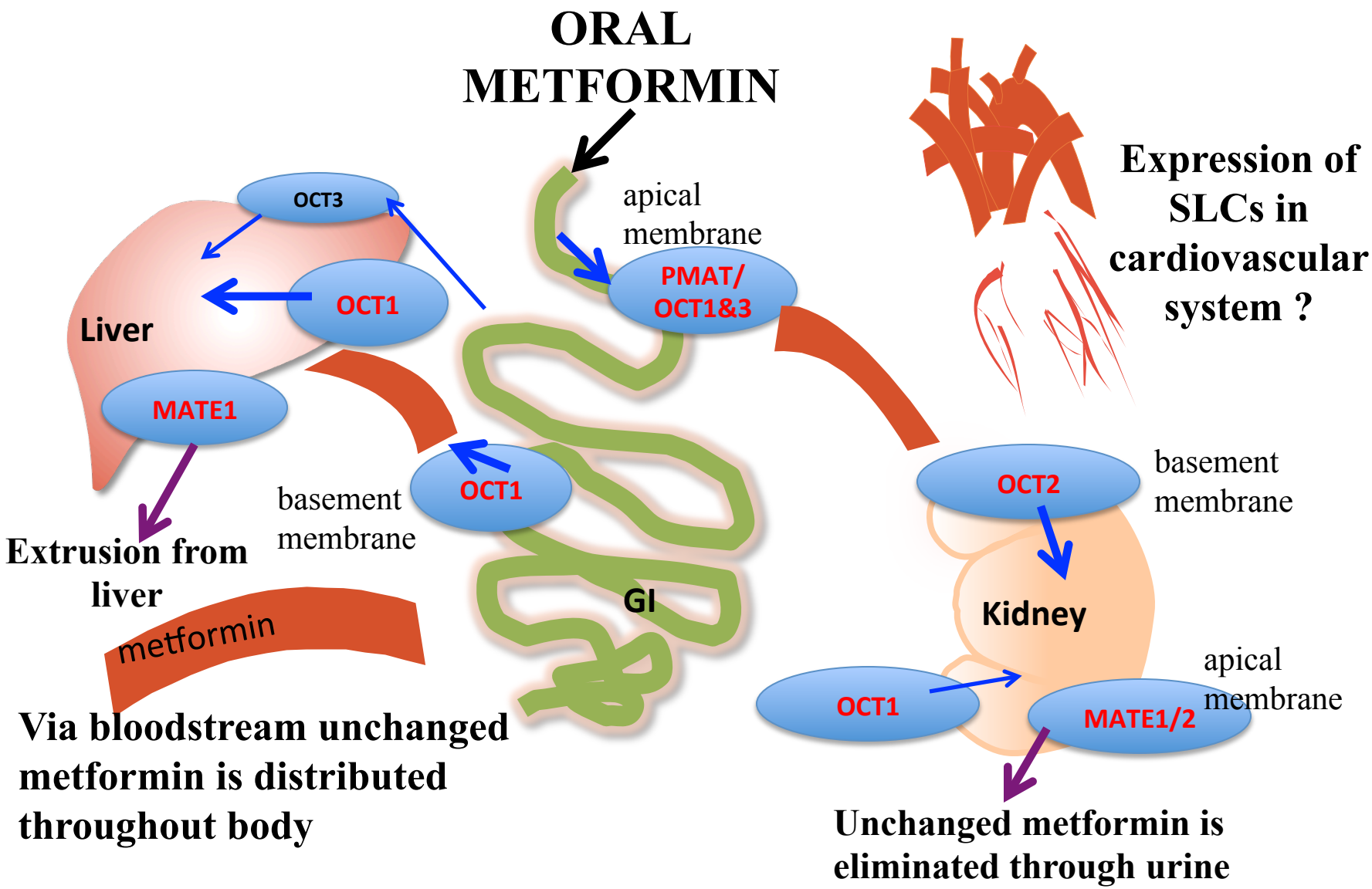


★ Mean ± S.E.M of miR-34a expression normalized to U6 small nuclear RNA as an endogenous control

Arunachalam, et al & Triggle & Ding: J Pharmacol exp Ther: 2016.

SO HOW DOES METFORMIN MEDIATE ITS EFFECTS?

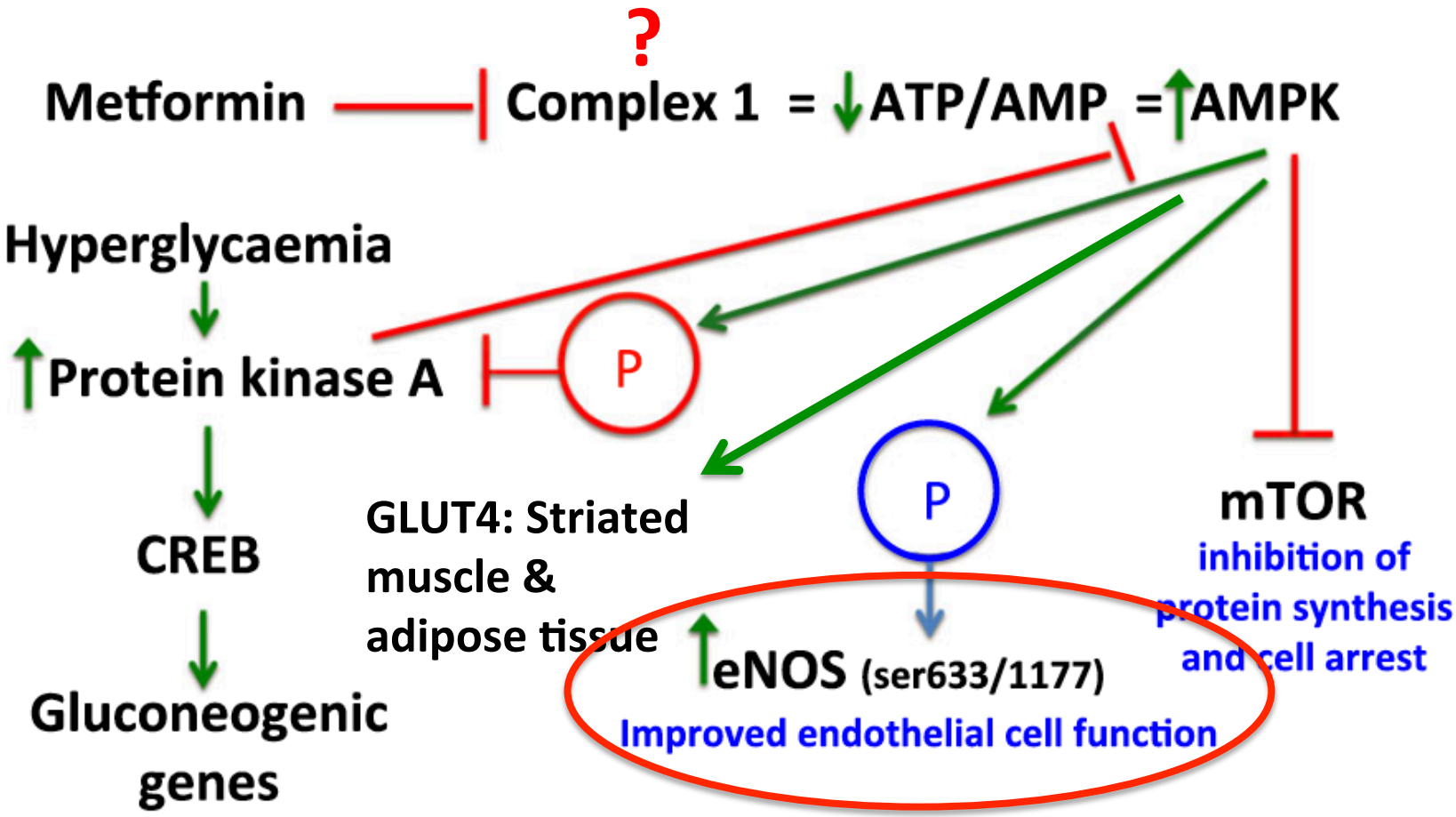
Distribution of SLC transporters for metformin



Metformin inhibits mitochondrial Complex 1?

THE ZOMBIE LITERATURE

Metformin: Reduces hyperglycaemia; protects endothelium; reduces cell growth.



Adapted from: Triggle & Ding: Acta Physiologica 2017

MY GUT FEELING IS?

In 1984 Bonora et al reported that IV administered metformin has no effect on plasma glucose in non-diabetic patients.

1) *"Novel Gut-Based Pharmacology of Metformin in Patients with Type 2 Diabetes Mellitus"* **Antonella Napolitano, GSK, PLOS ONE** July 2014 | Volume 9 | Issue 7 | e100778

Metformin affects gut microbiome and enhances entero-hepatic recirculation of bile acids, modulation of gut microbiota and changes in gut hormones, especially GLP-1.

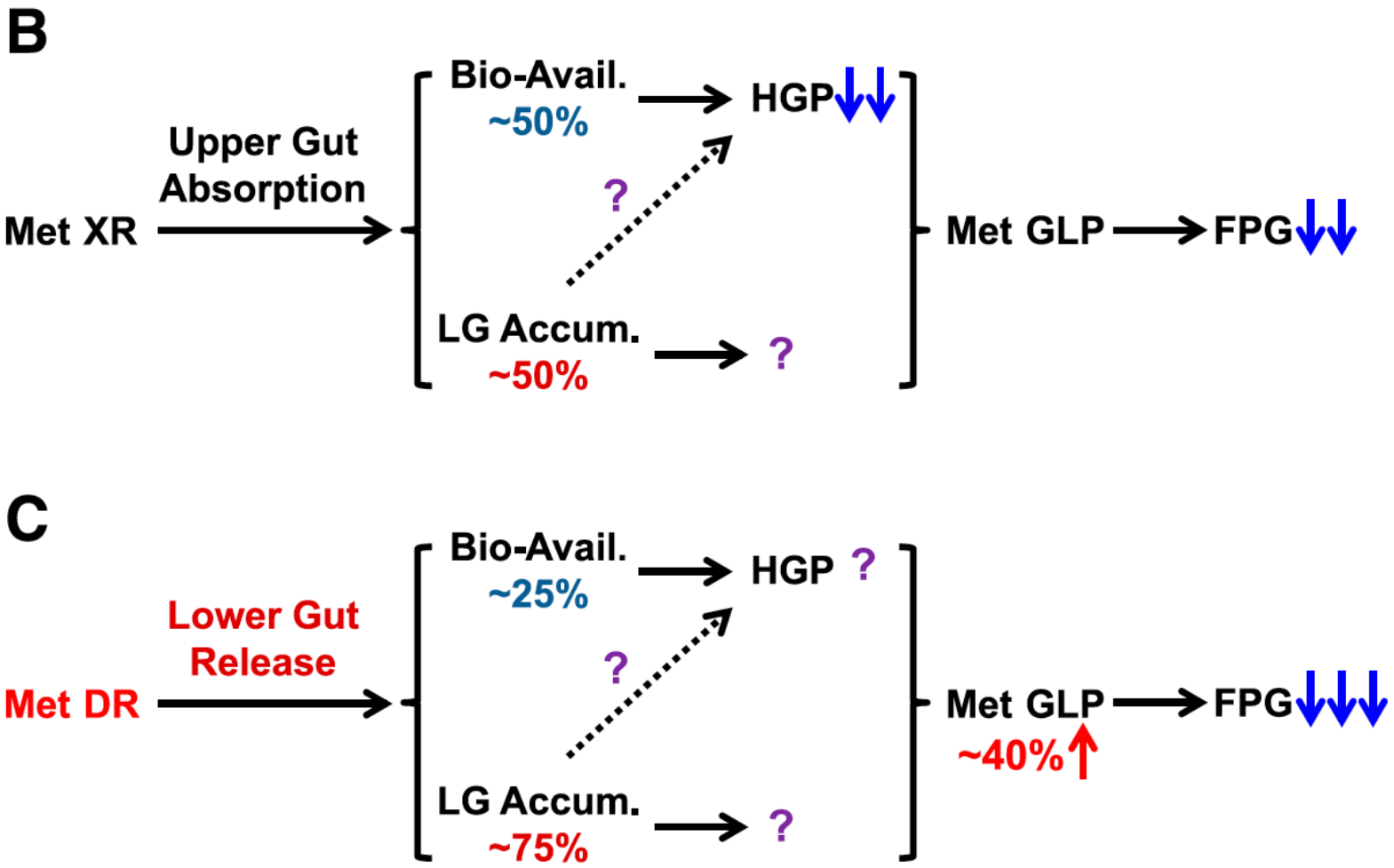
2) *"The Primary Glucose-Lowering Effect of Metformin Resides in the Gut, Not the Circulation: Results From Short-term Pharmacokinetic and 12-Week Dose-Ranging Studies"*. John B. Busse. Diabetes Care 2016;39:198–205.

NOTE: the metformin concentration in the jejunum peaks at 500 µg/g, 30–300 times greater than plasma concentrations.

Mechanism of Metformin: A Tale of Two Sites

Ruisheng Song

Diabetes Care 2016;39:187–189 | DOI: 10.2337/dci15-0013



Yes, concentration does matter!

CellMetabolism
Essay

2015

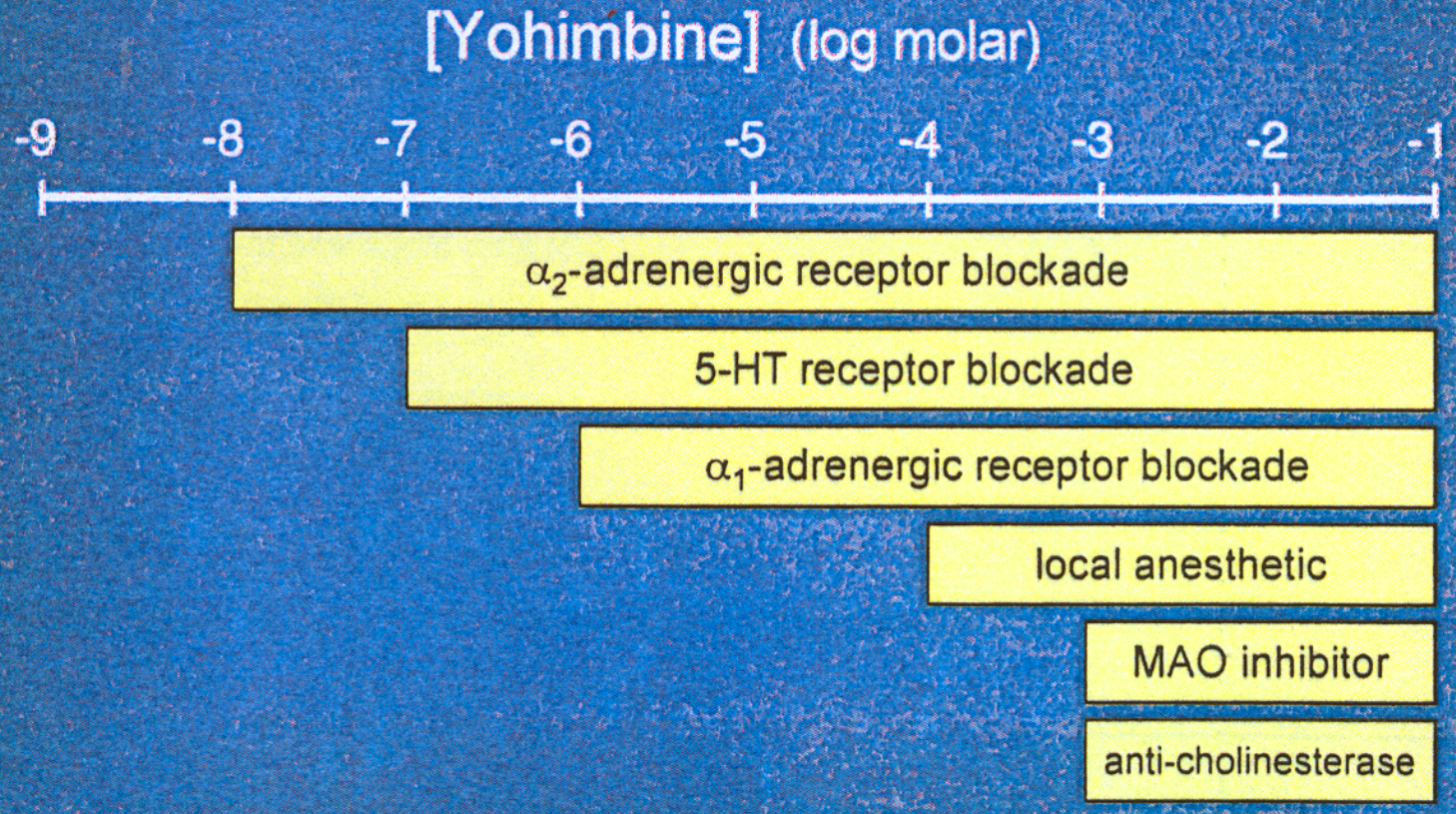
CellPress

MetforminAction:ConcentrationsMatter

LingHe[1]andFredricE.Wondisford[1,*]
[1]DivisionofMetabolism,DepartmentsofPediatrics,PhysiologyandMedicine,JohnsHopkinsUniversitySchoolofMedicine,Baltimore,MD21287,USA*Correspondence:
fwondis1@jhmi.eduhttp://dx.doi.org/10.1016/j.cmet.2015.01.003

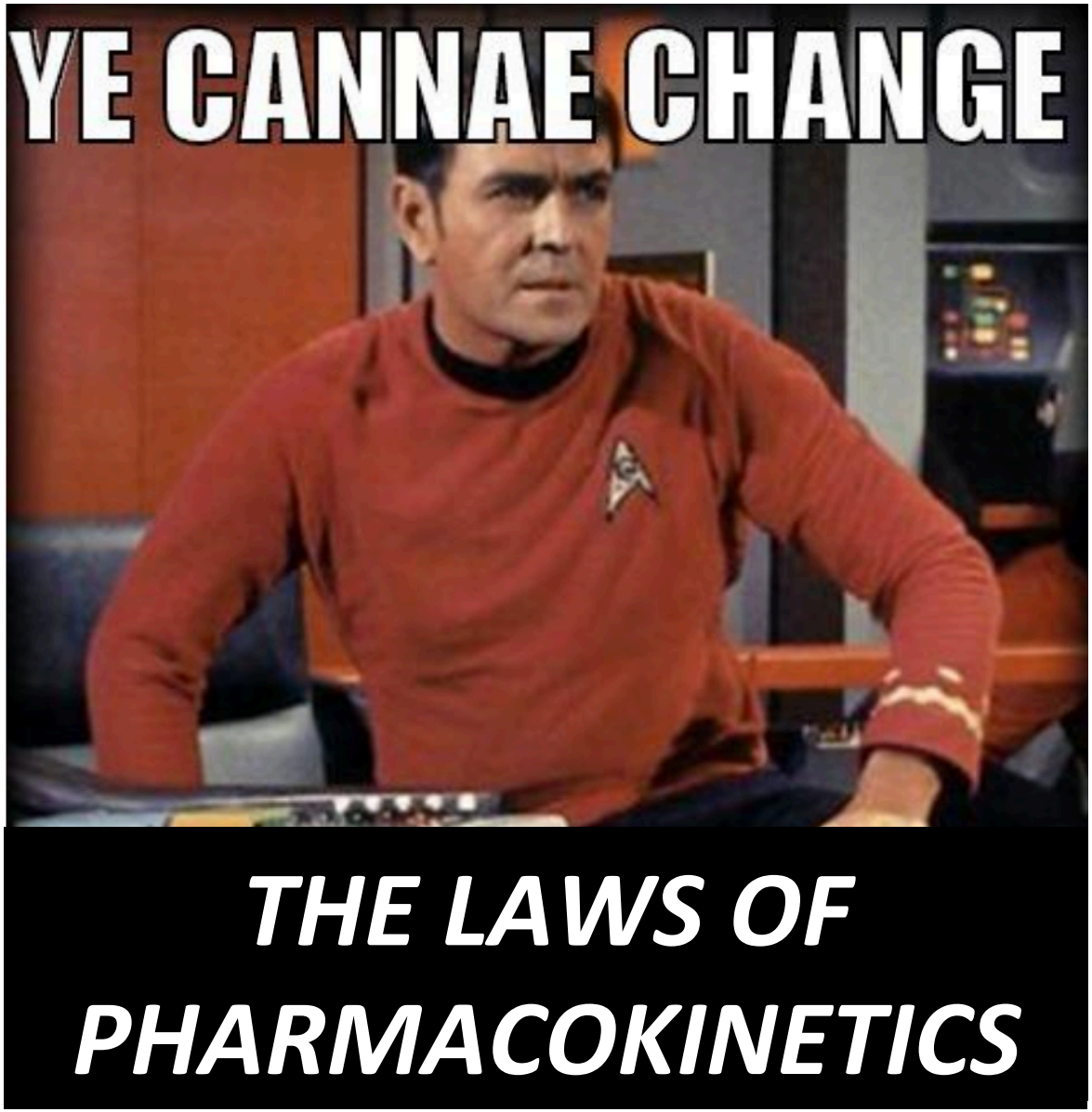
Metforminhasbeenusedfornearlyacenturyandisnowthemostwidelyprescribedoralanti-diabeticagentworldwide.Yethow metforminactsremainsonlypartiallyunderstoodandcontroversial.Onekeyreasonmaybethatalmostallpreviousstudieswere conductedwithsupra-pharmacologicalconcentrations(doses)ofmetformin,10–100timeshigherthanmaximallyachievable therapeuticconcentrationsfoundinpatientswithtype2diabetesmellitus.

Drug Selectivity Depends on Concentration




REALITY CHECK

“Ye cannae change the Laws of Pharmacokinetics”

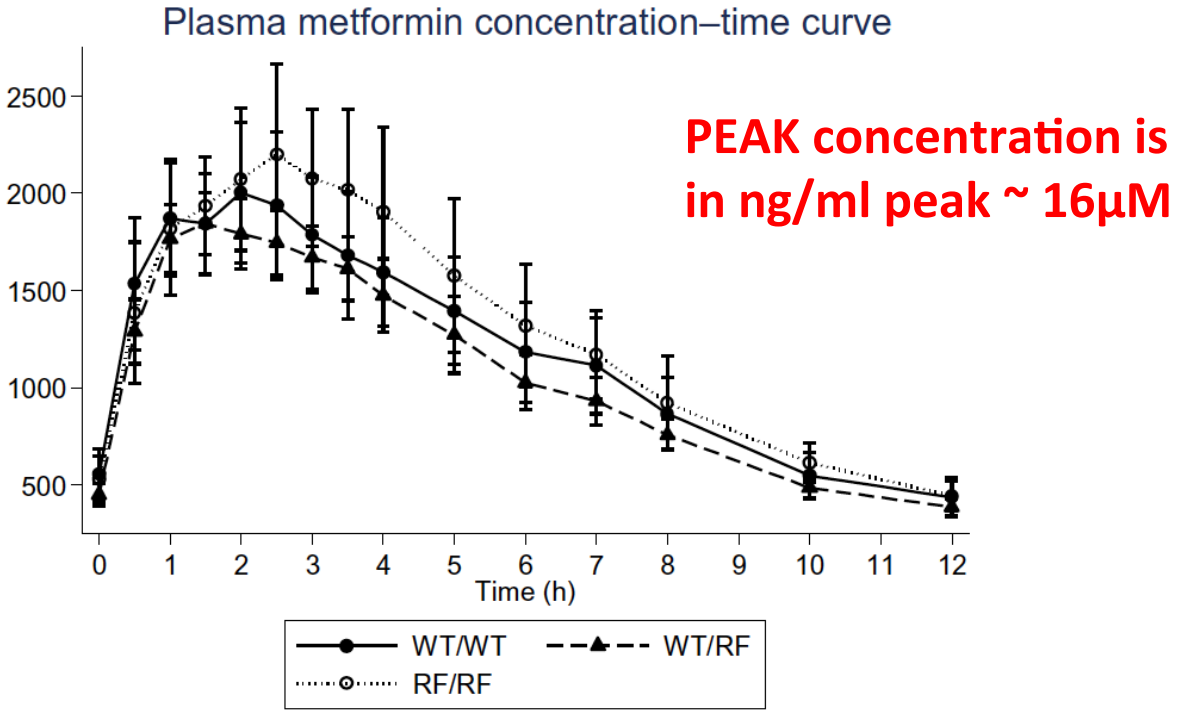


Eur J Clin Pharmacol
DOI 10.1007/s00228-015-1853-8

PHARMACOGENETICS

Steady-state pharmacokinetics of metformin is independent of the *OCT1* genotype in healthy volunteers

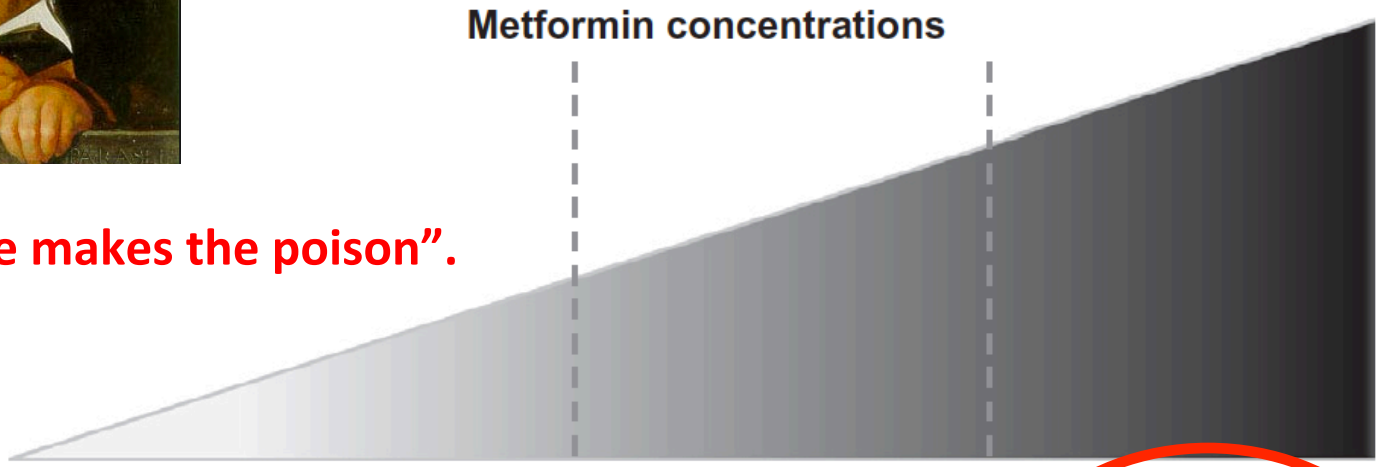
Mette Marie Hougaard Christensen[1] · Kurt Højlund[2] · Ole Hother-Nielsen[2] · Tore Bjerregaard Stage[1] · Per Damkier[1,3] · Henning Beck-Nielsen[2] · Kim Brøsen[1]



PEAK concentration is in ng/ml peak ~ 16µM

Metformin & Cancer: Is it a Paracelsus effect, or selective toxicity?

"The dose makes the poison".



	Standard clinical use	In vivo preclinical studies	In vitro laboratrory studies
Dose	250 to 2250 mg/day	750 mg/kg per day	2 to 50 mM
Relative Dose*	0.15 to 1.0	2 to 45	25 to 1000

From Baldrick & Renehan: European J Cancer 2014; 50: 2119-2125.

Cell

An Ancient, Unified Mechanism for Metformin Growth Inhibition in *C. elegans* and Cancer

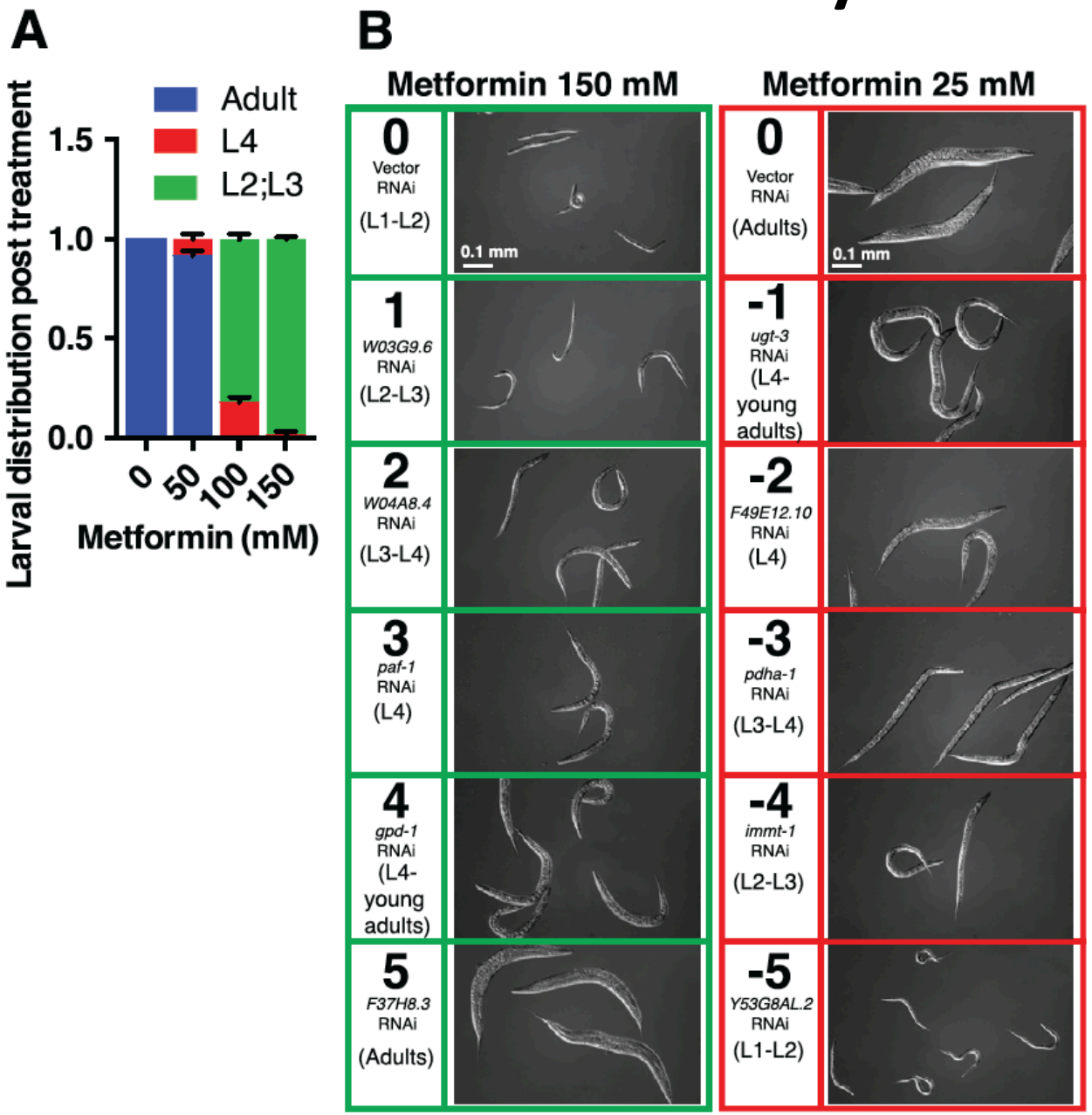
IMPACT FACTOR >28

Lianfeng Wu,[1,2,3,4] Ben Zhou,[1,2,3,4] Noriko Oshiro-Rapley,[5] Man Li,[6] Joao A. Paulo,[7] Christopher M. Webster,[1,2,3,4] Fan Mou,[6] Michael C. Kacergis,[1,2] Michael E. Talkowski,[2,8] Christopher E. Carr,[5,9] Steven P. Gygi,[7] Bin Zheng,[6] and Alexander A. Soukas[1,2,3,4,10,*]

[1]Department of Medicine, Diabetes Unit, Massachusetts General Hospital, Boston, MA 02114, USA
[2]Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA 02114, USA
[3]Department of Medicine, Harvard Medical School, Boston, MA 02115, USA
[4]Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA
[5]Department of Molecular Biology, Massachusetts General Hospital, Boston, MA 02114, USA
[6]Cutaneous Biology Research Center, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA
[7]Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA
[8]Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
[9]Department of Earth, Atmospheric and Planetary Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[10]Lead Contact
*Correspondence: asoukas@mgh.harvard.edu
http://dx.doi.org/10.1016/j.cell.2016.11.055

CONCENTRATIONS MATTER! In this study the investigators used metformin concentrations 8.0mM, 25mM, 50mM & 150mM.

Concentration really does matter!



To achieve a plasma concentration of **100mM** in man you would need to give an oral dose of

>5Kg!

Does metformin protect against cancer?

BMJ 2005

RESEARCH POINTERS

Metformin and reduced risk of cancer in diabetic patients

Josie M M Evans, Louise A Donnelly, Alistair M Emslie-Smith, Dario R Alessi, Andrew D Morris

Division of Community Health Sciences, Section of Public Health, University of Dundee, Dundee DD2 4BF
Josie M M Evans *lecturer in epidemiology*
Louise A Donnelly *statistician*

Mill Practice, Dundee

Metformin, widely given to patients with type 2 diabetes, works by targeting the enzyme AMPK (AMP activated protein kinase), which induces muscles to take up glucose from the blood. A recent breakthrough has found the upstream regulator of AMPK to be a protein kinase known as LKB1.[1 2] LKB1 is a well recognised tumour suppressor. Activation of AMPK by metformin and exercise requires LKB1, and this would also explain why exercise is beneficial in the primary and secondary prevention of certain cancers. We hypothesise that metformin use in patients with type 2 diabetes may reduce their risk of cancer.

What this paper suggests

Metformin may reduce the risk of cancer in patients with type 2 diabetes

What research is needed now

A more rigorous cohort study, before experimental work is initiated

We collated information about use of metformin for

HOWEVER, rather than a direct anti-proliferative effect:
1/ Suppression of gluconeogenesis (G-6-P, PEPCK) and hyperinsulinemia would reduce tumour growth – particularly when insulin sensitive.
2/ Tumour cells highly dependent on glycolysis (Warburg effect) that would be inhibited by metformin (HKI & HKII).

review

Annals of Oncology 00: 1–12, 2016
doi:10.1093/annonc/mdw410

Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis

C. Coyle*, F. H. Cafferty, C. Vale & R. E. Langley

MRC Clinical Trials Unit at University College London, London, UK

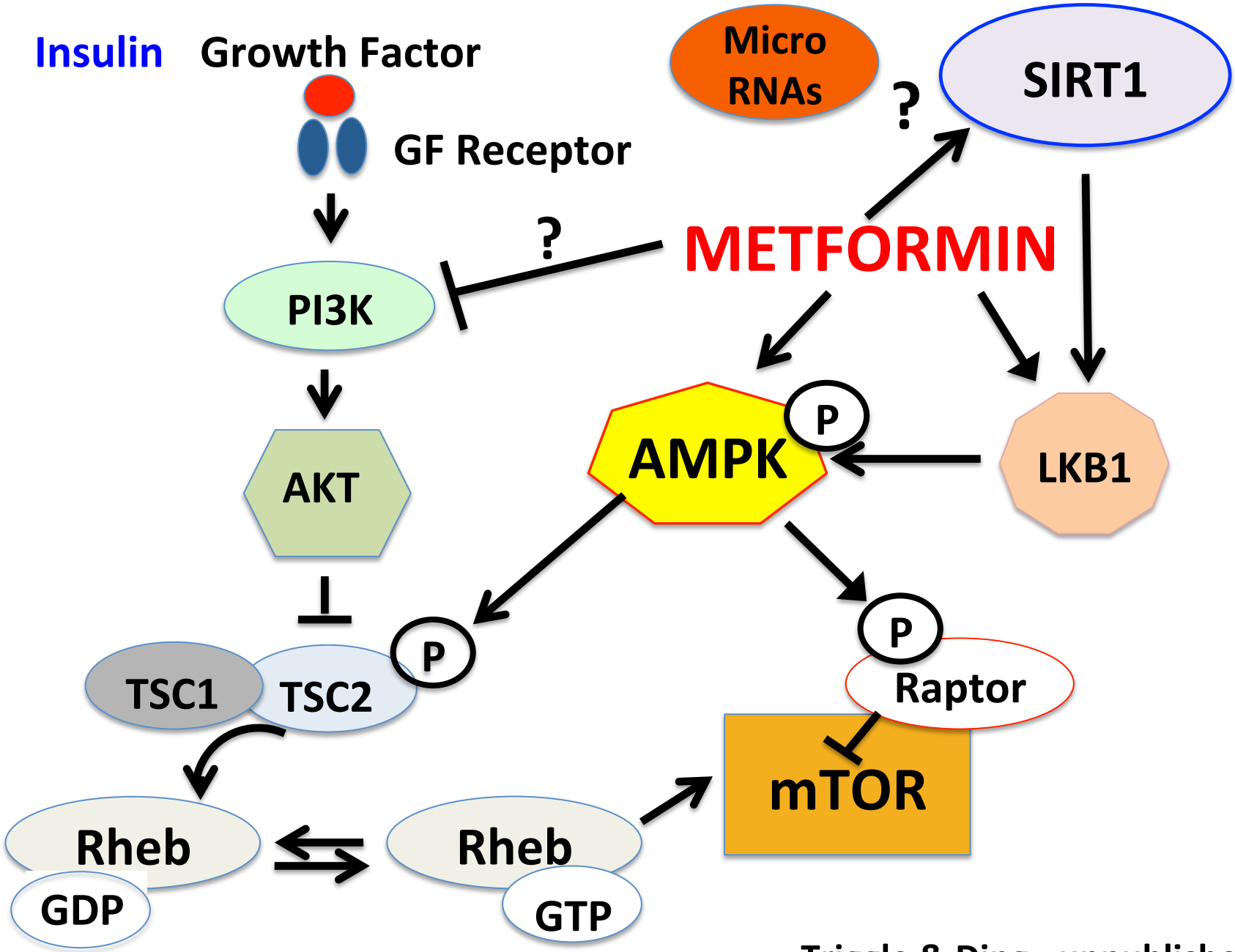
This 2016 review by Coyle *et al* concludes that is there a particular benefit for metformin in colorectal and prostate cancer.

ACTIVE TRIALS:

1. The Metformin Active Surveillance Trial – a Phase III trial of metformin vs. placebo given before primary therapy in assessing time to progression in low-risk **prostate cancer**.

2. The STAMPEDE Trial – a randomised phase III trial of metformin vs. placebo. Aims to evaluate whether the addition of metformin improves survival in the treatment of hormonenaïve, **high-risk, localised and metastatic prostate cancer**.

3. In colorectal cancer, a phase III trial of metformin versus standard care assessing recurrence and survival in stage III disease is now in set-up phase in South Korea.



Triggle & Ding - unpublished

Biochemical Pharmacology xxx (2017) xxx-xxx

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com

Metformin represses glucose starvation induced autophagic response in microvascular endothelial cells and promotes cell death

Samson Mathews Samuel [a], Suparna Ghosh [a], Yasser Majeed [a], Gnanapragasam Arunachalam [a], Mohamed M. Emara [c], Hong Ding [a, b], Chris R. Triggle [a, b, *]

PROOF

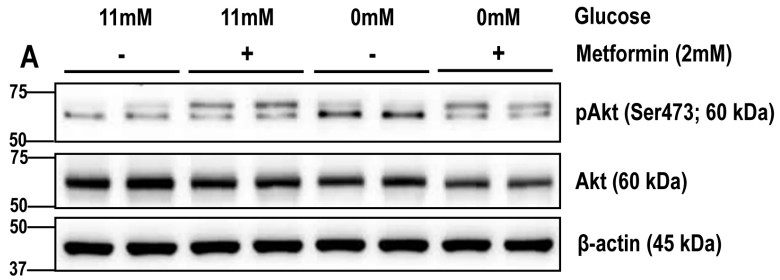
Autophagy, a catabolic process involving protein/organelle degradation and autophagosomes / lysosomes, serves a dual role in cancer:

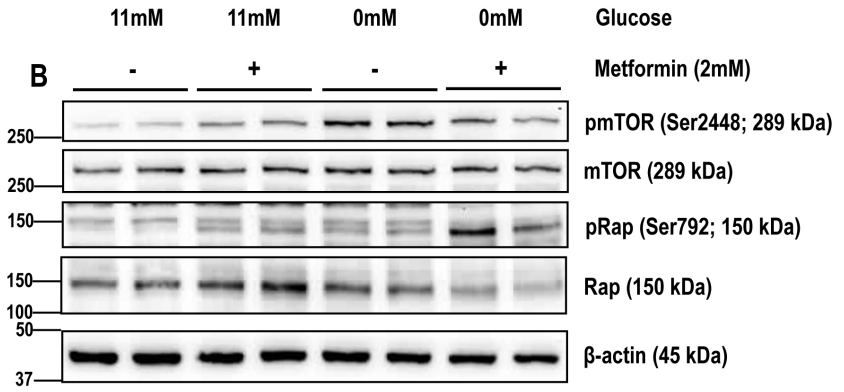
1. a tumour suppressor mechanism that prevents the accumulation of damaged proteins and organelles.

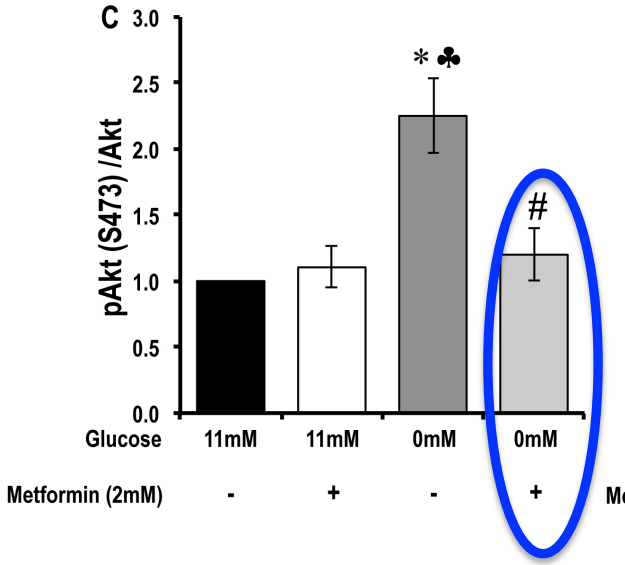
2. a mechanism of cell survival that promotes the growth of established tumors - tumour cells activate autophagy in response to cellular stress and/or increased metabolic demands and enable cell survival.

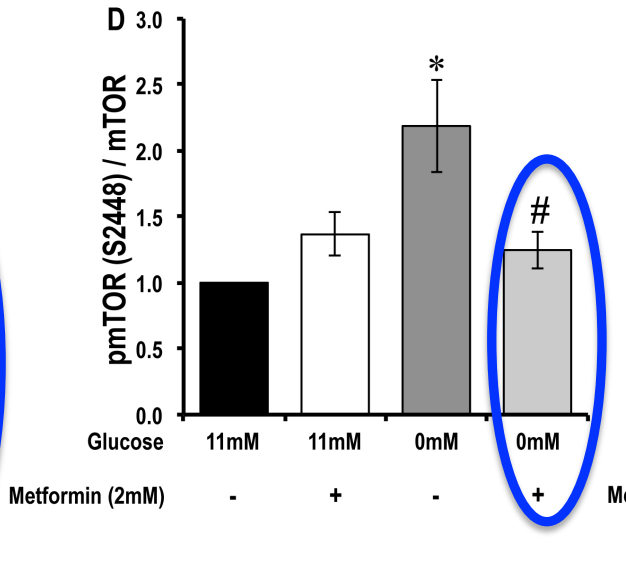
3. Metformin has been reported to both promote and inhibit autophagy via AMPK-dependent and –independent mechanisms.

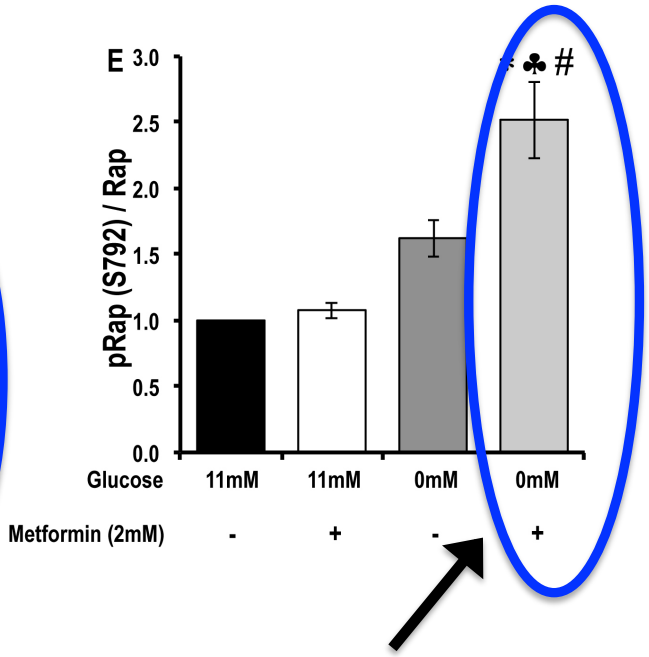
Glucose starvation initiates ER Stress & activates the Akt/mTOR pathway, BUT inhibited by metformin





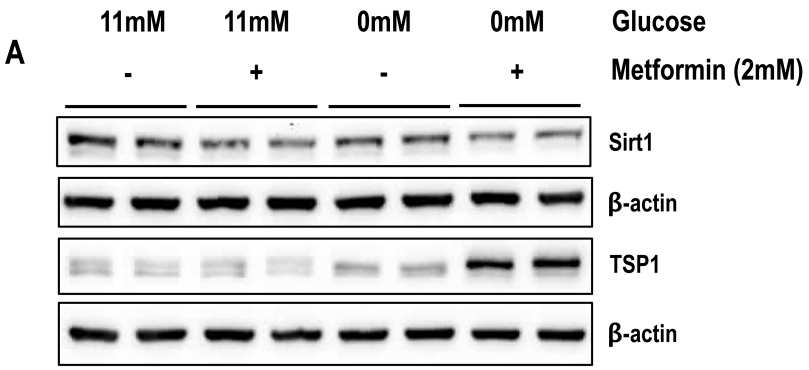






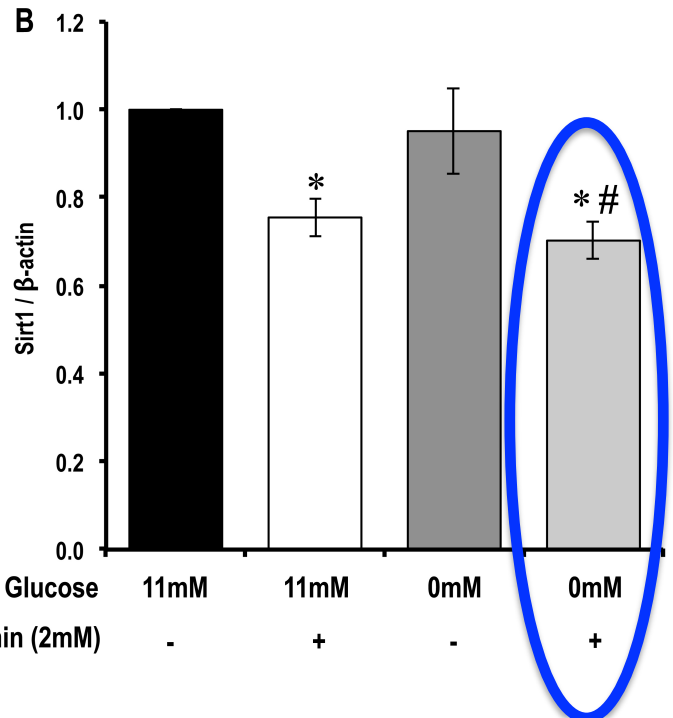
NOTE: significant increase in the mTOR inhibitory Raptor phosphorylation (pRap; S792)

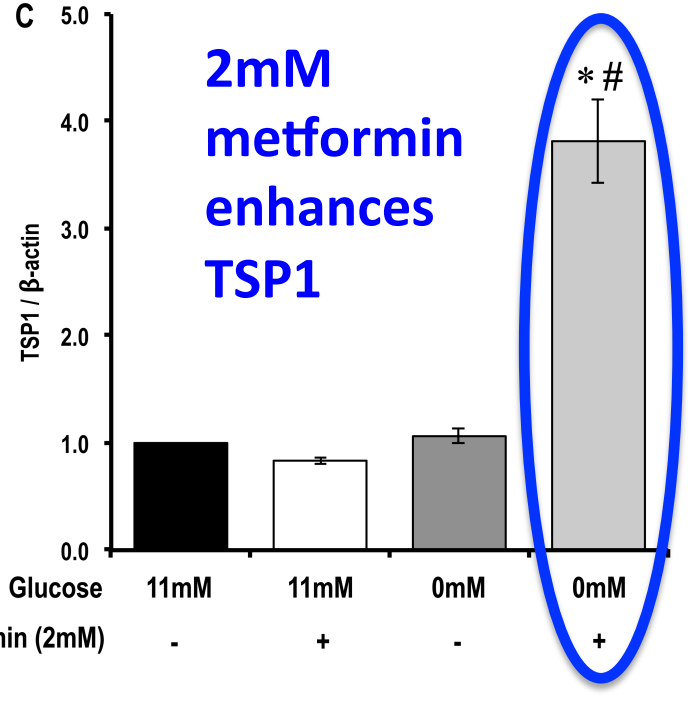
Glucose starvation & metformin is anti-angiogenic



2mM metformin decreases SIRT1

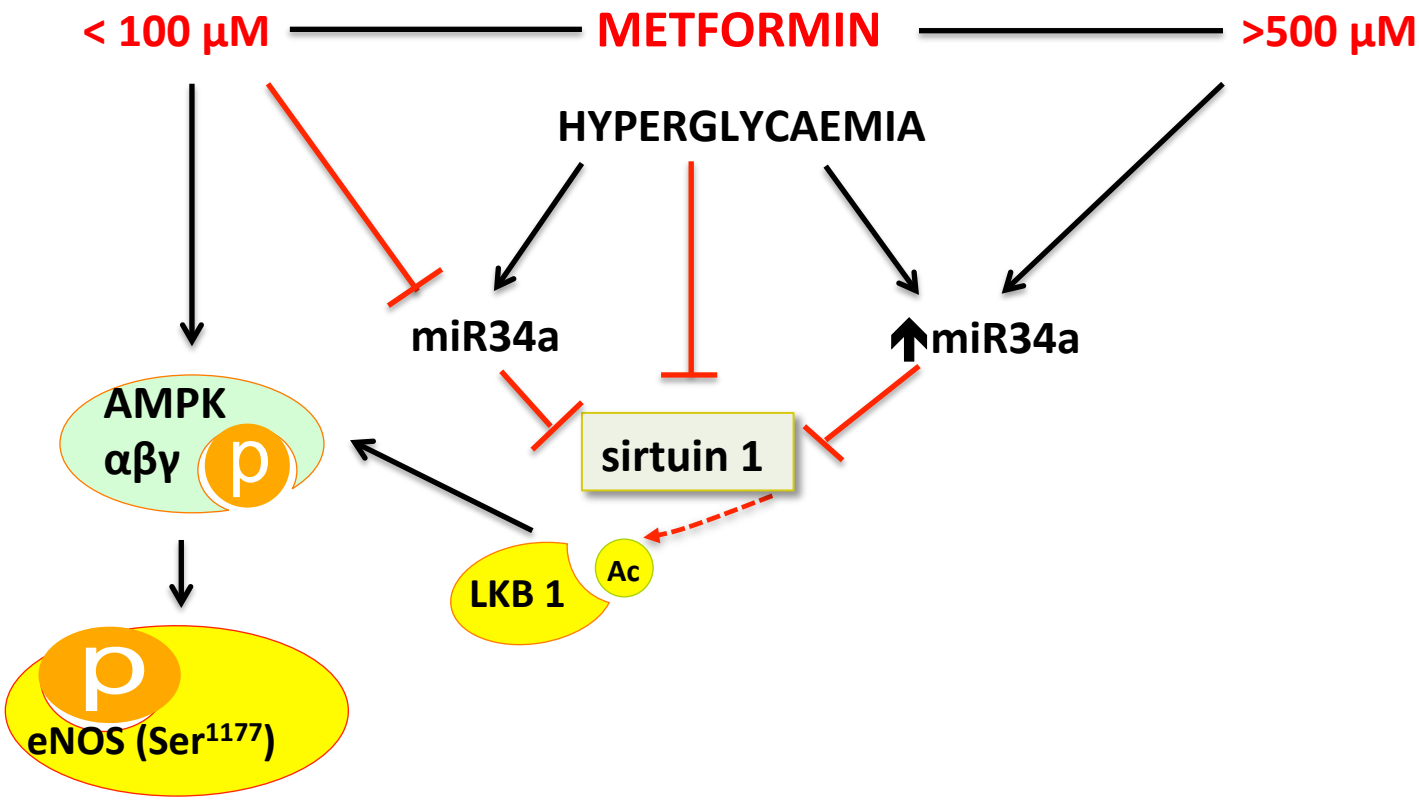
Samuel & Triggle unpublished





2mM metformin enhances TSP1

Concentration-Dependent Effects of Metformin



< 100 µM metformin is "endothelial protective" – protects against HG-induced senescence, enhances eNOS activity, enhances angiogenesis: AMPK-dependent?

>500 µM metformin has anti-angiogenic actions, inhibits autophagy, reduces cell survival: AMPK independent?

Conclusions

- **Multiple targets for metformin, but note concentration dependence.**
- **Therapeutic levels modulate eNOS and SIRT1 function in endothelial cells = endothelial / vascular protective.**
- **Effects of metformin on endothelium linked to SIRT1/ microRNA34a & AMPK (?)**
- **"Paracelsus levels" of metformin have anti-angiogenic action and promote apoptosis (data not shown) – and might explain anti-cancer effects of metformin. BUT can such high levels be reached in cancer cells with therapeutic doses (as for diabetes) of metformin? Possibly IF there is an imbalance in the expression of inward versus extrusion transporters for the drug.**

Acknowledgements

الصندوق القطري لرعاية البحث العلمي
Qatar National Research Fund
Member of Qatar Foundation

الصندوق القطري لرعاية البحث العلمي
Qatar National Research Fund
Member of Qatar Foundation

Dr. Triggle Lab:
Postdocs: Dr. Gnanapragasam Arunachalam
Dr. Samson M. Samuel
Ms Suparna Ghosh – Research Specialist
Mr. Mu Ji Hwang, Mr. Haidar Kubba, Mr. Ahmed Mushannen – Medical students
Ms. Tina Bharani, Merna Hussein &
Mr. Tarek Taha –Medical students

Collaborators WCMC-Q Doha
Dr. Hong Ding's Lab:
Postdocs: Dr. Gnanapragasam Arunachalam
Dr. Rohit Upadhyay
Dr. Arun P. Lakhsmanan
Dr. Yasser Majeed

- **Grants, BMRP**
  NPRP, UREP
  CIHR (Canada)

- Collaborators via NPRP
  - **Profs. Morley Hollenberg, Todd Anderson - University of Calgary**
  - **Prof. Chris Garland/Kim Dora - University of Oxford**
  - **Profs. Aimin Xu/Paul Vanhoutte - University of Hong Kong**