GUT-renal Axis In Diabetic Nephropathy

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Tabriz university of medical science

The Gut-Kidney Axis: Putative Interconnections Between Gastrointestinal and Renal Disorders

Markku Lehto [1,2]* and Per-Henrik Groop [1,3,4]

Frontiers in endocrinology: September2018,volum 9,article 557

Potential regulatory links

between

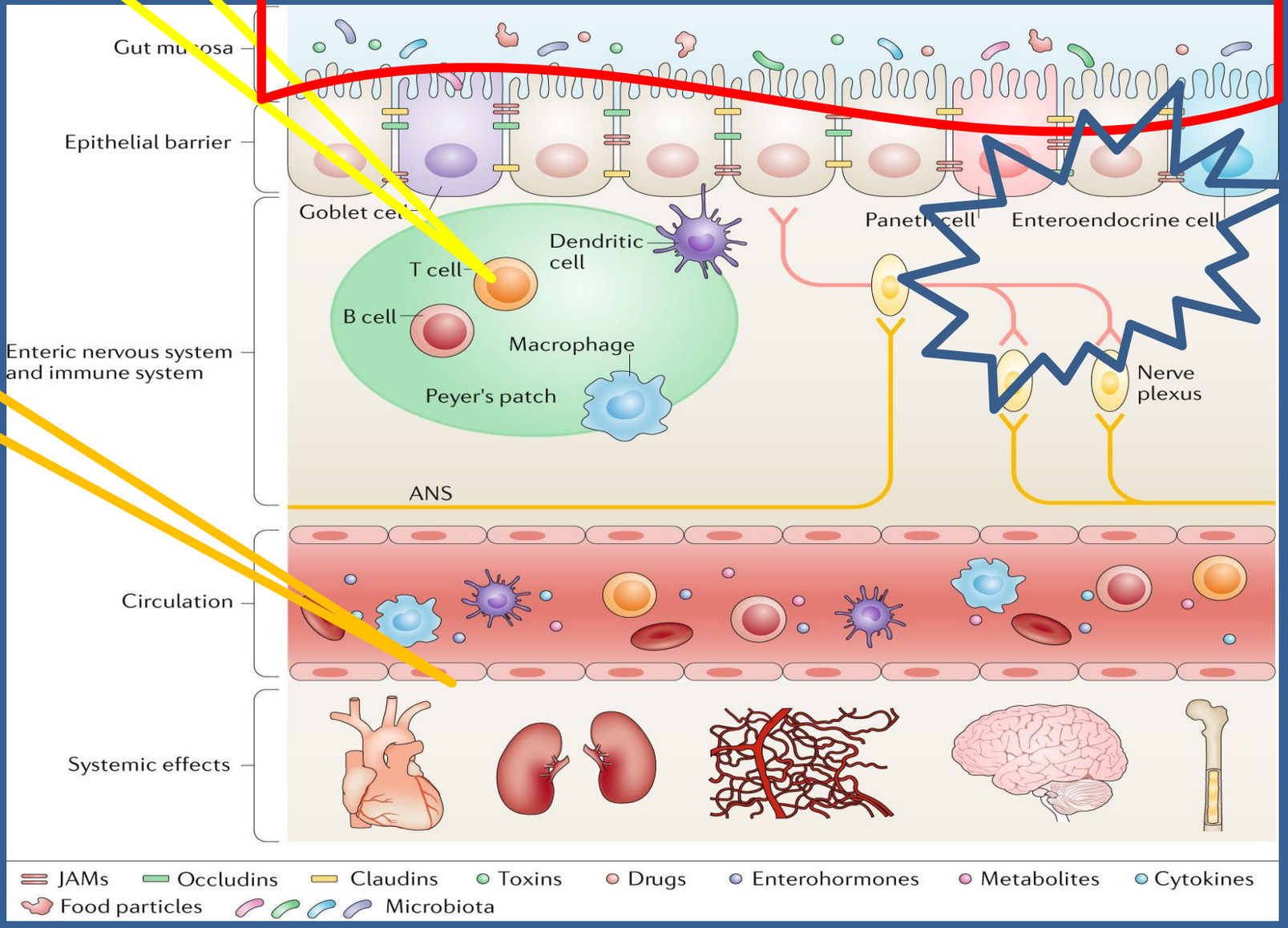
Gastrointestinal tract and the kidney

Gut- Renal Axis involves

Immunologic al issues

Microbial Intractions

Imflamm ation



Effect of GUT MICROBIOTA Axisis on renal function

Review Article

Complications

The gut-kidney axis in chronic renal failure: A new potential target for therapy

Tawfik KHOURY,[1] Keren TZUKERT,[2] Roy ABEL,[2] Ayman ABU RMEILEH,[1] Ronen LEVI,[2] Yaron ILAN[1]

Gut microbiome is a central player in the gut-kidney axis.

Microbiome products, such as advanced glycation end products, phenols, and indoles, are absorbed into the circulation but are cleared by normal-functioning kidneys.

Hemodialysis International 2017; **21**:323–334

GUT MICROBIOTA

- Human gut hosts 100 trillion microorganisms!
- Thousands of species!!
- Weighing an average around 1.5 kg!!!
- Microbiota changes from infancy to adulthood
- Bacteria from 3 major groups represent

- ~95% of the total microbiota

1. Firmicutes
2. Bacteroidetes
3. Actinobacteria

Hemodialysis International 2017; 21:323–334

Review Article

Complications

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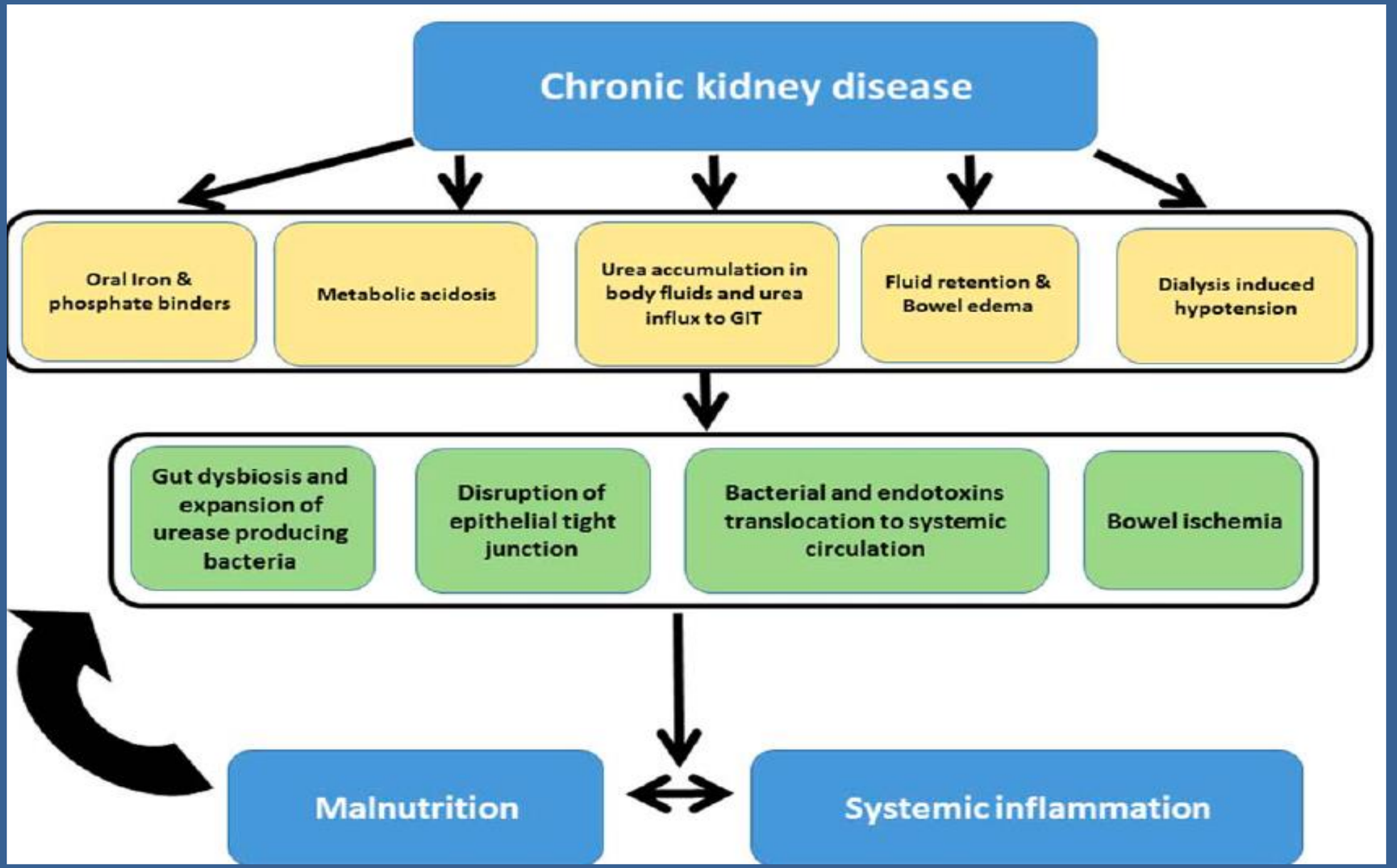
Tawfik KHOURY,[1] Keren TZUKERT,[2] Roy ABEL,[2] Ayman ABU RMEILEH,[1] Ronen LEVI,[2] Yaron ILAN[1]

Potential mechanisms for the interplay between the gut microbiome and CKD

Maintaining an intestinal epithelial barrier by

1. Restoration of protein tight junction structure,
2. Upregulation of mucin genes
3. Suppressing intestinal inflammation that involves toll-like receptor (TLR) signaling.
4. Certain bacteria produce molecules that serve to direct proper T cell population balance.

In CKD: Damage to the gut barrier and bacterial translocation



Hemodialysis International 2017; 21:323–334

Effect of GUT MICROBIOTA Axis on Renal function

Damage to the gut barrier and bacterial translocation

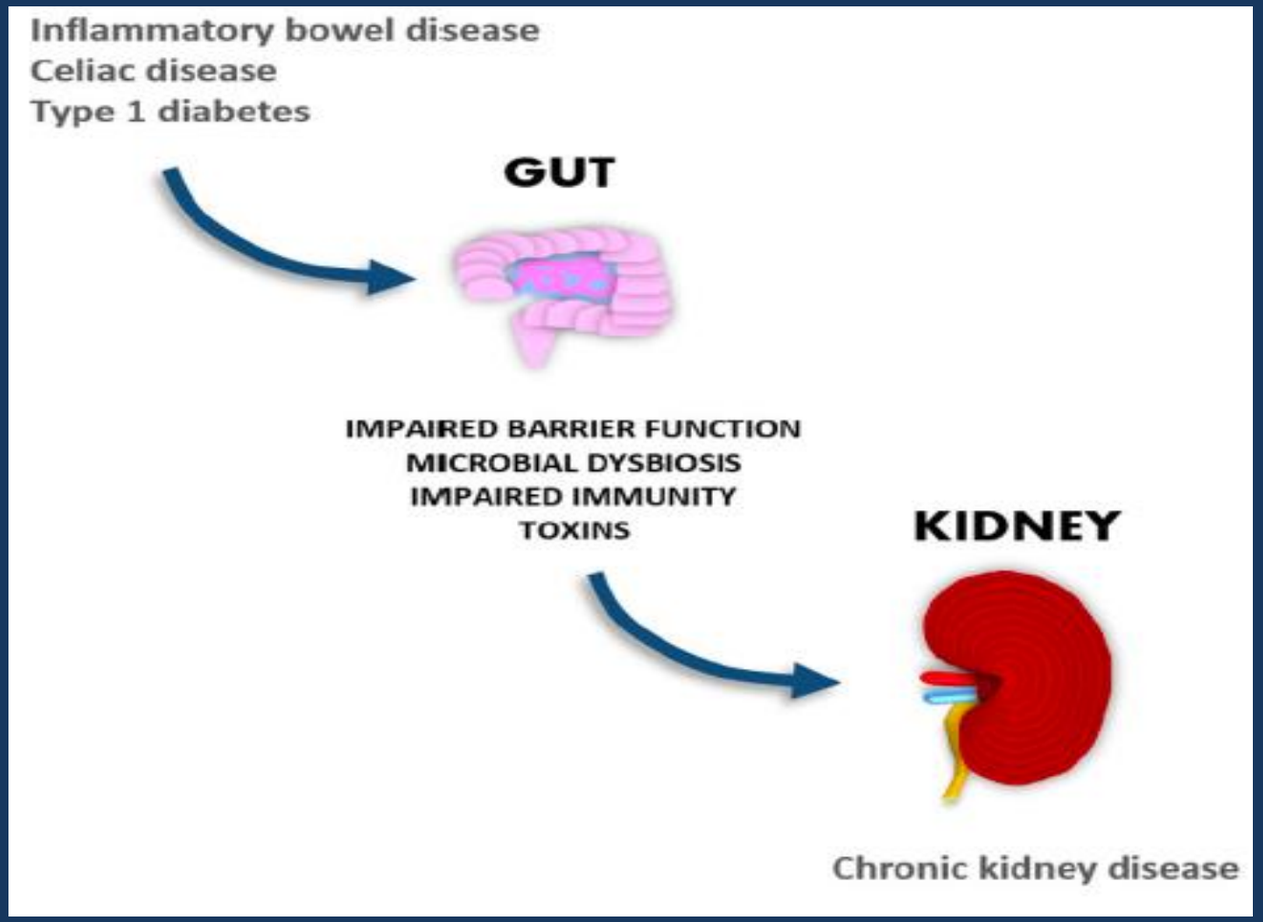
Quantitative/qualitative alterations of the intestinal microbiota :

Altered composition of the gut microbiome

Termed gut dysbiosis

Frontiers in endocrinology: September2018.volum 9 article 557

The gut–renal axis



Frontiers in endocrinology: September2018.volum 9 .article 557

Effect of GUT MICROBIOTA Axis on

Diabetic Nephropathy

OPEN ACCESS Freely available online PLOS one

Gut Microbiota in Human Adults with Type 2 Diabetes Differs from Non-Diabetic Adults

Nadja Larsen[1]*, Finn K. Vogensen[1], Frans W. J. van den Berg[1], Dennis Sandris Nielsen[1], Anne Sofie Andreasen[2], Bente K. Pedersen[2], Waleed Abu Al-Soud[3], Søren J. Sørensen[3], Lars H. Hansen[3], Mogens Jakobsen[1]

The study included male Swedish adults

1. Phylum Firmicutes and class Clostridia were significantly reduced in the diabetic group compared to the control group

2. the ratios of Bacteroidetes to Firmicutes AND the *Bacteroides-Prevotella group to Clostridium coccoides - Eubacteria* rectale group correlated positively and significantly with plasma glucose concentrations.

3. class Lactobacilli species was highly enriched in diabetic compared to non-diabetic persons and positively correlated with plasma glucose.

TYPE 2 DIABETES GUT MICROBIOME ANALYSES

Chinese patients with type 2 diabetes were characterized

1. **Moderate degree of gut microbial dysbiosis,**
2. **Decrease in the abundance of butyrate-producing bacteria and**
3. ***Increase in Clostridium.***

Qin et al. Nature. 2012

TYPE 2 DIABETES GUT MICROBIOME ANALYSES

Consistency

1. Based metagenomic clusters both studies reported : type 2 diabetes patients and controls can be distinguished with high accuracy although with very different microbial entities
2. Depletion of butyrate producing bacteria in type 2 diabetes.

Divergence

1. Chinese study reported an enrichment of several Clostridium species in type 2 diabetes
2. Swedish study reported an enrichment of several Lactobacilli species in type 2 diabetes.

Qin et al. Nature. 2012

MicroDiab - Studies of interactions between the gut Microbiome and the human host biology to elucidate novel aspects of the pathophysiology And pathogenesis of type 2 Diabetes

Indo-Danish Collaborative Research Grant

Supported by DBT

COLLABORATORS

Madras Diabetes Research Foundation, Chennai

Translational Health Science and Technological Institute, Delhi

TCS Innovation Labs, Tata Consultancy Services, Pune

The Novo Nordisk Foundation Center for Basic Metabolic Research, Copenhagen

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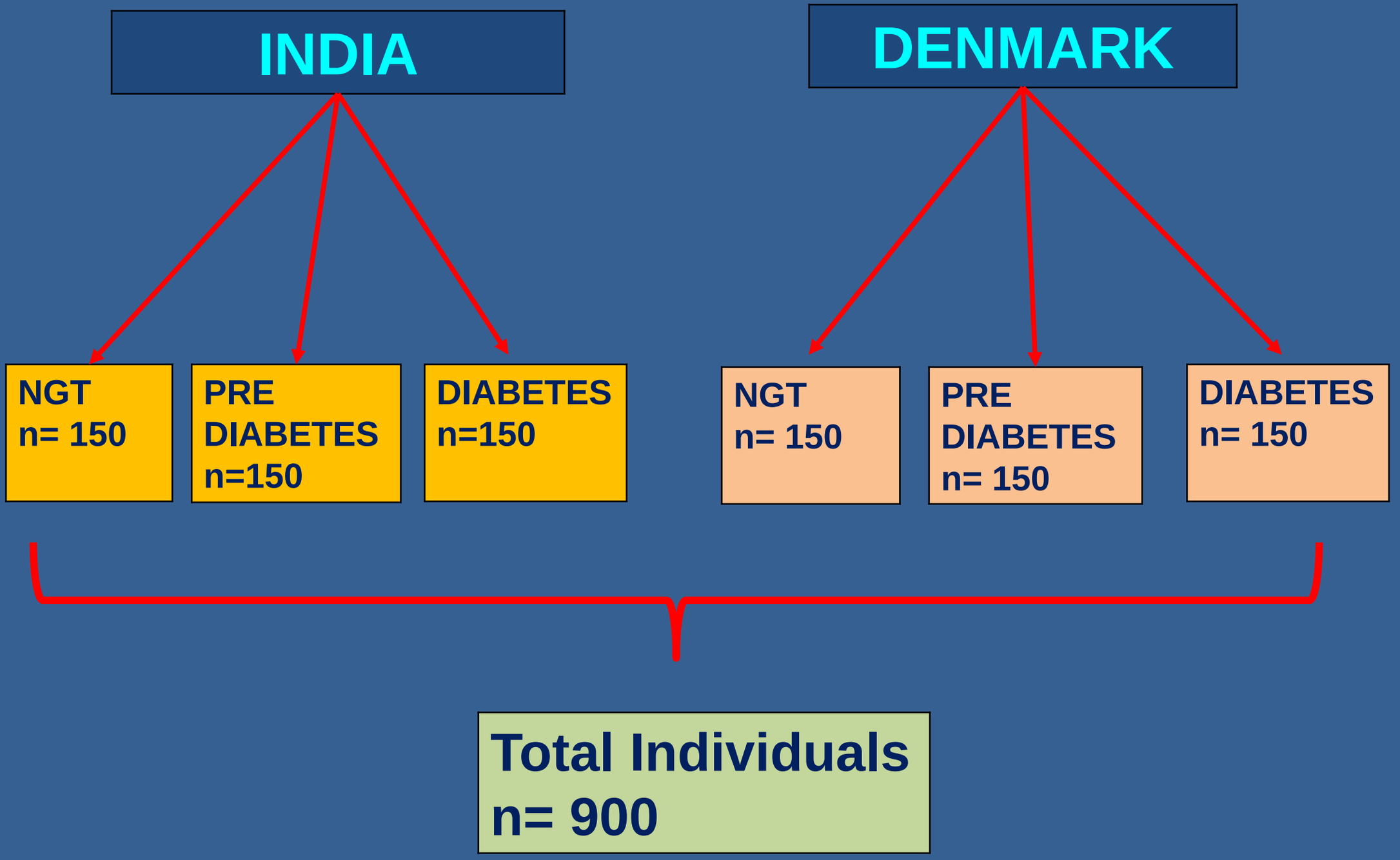
Dr. R. M Anjana, MDRF

Investigators from Danish Side

Prof. Oluf B Pedersen, (PI)
Prof. Torben Hansen
Dr. Henrik Vestergaard

SAMPLING


INDIA
DENMARK
NGT
n= 150
PRE
DIABETES
n=150
DIABETES
n=150
NGT
n= 150
PRE
DIABETES
n= 150
DIABETES
n= 150
Total Individuals
n= 900

OBJECTIVE OF THE STUDY

- To identify gut microbiome signatures in Indian subjects associated with pre-diabetes and type 2 diabetes thereby
- Enabling development of novel biomarkers for early diagnosis of people at high risk of progression to overt type 2 diabetes and compare this with the Danish results.
- Looking at trans ethnic differences in gut microbial signatures (Indians/Danes)

SUMMARY

Alterations in microbiota are associated with disease states.

Gut Microbiota in Indian and Danish populations were completely different.

In Indian diabetic patients, Clostridium sensu and Clostridium XI are decreased markedly, whereas pre-diabetes subjects, Megasphaera is increased 3 fold especially in males.

Among Danish diabetic patients, Escherichia Shigella and Clostridium XI were reduced.

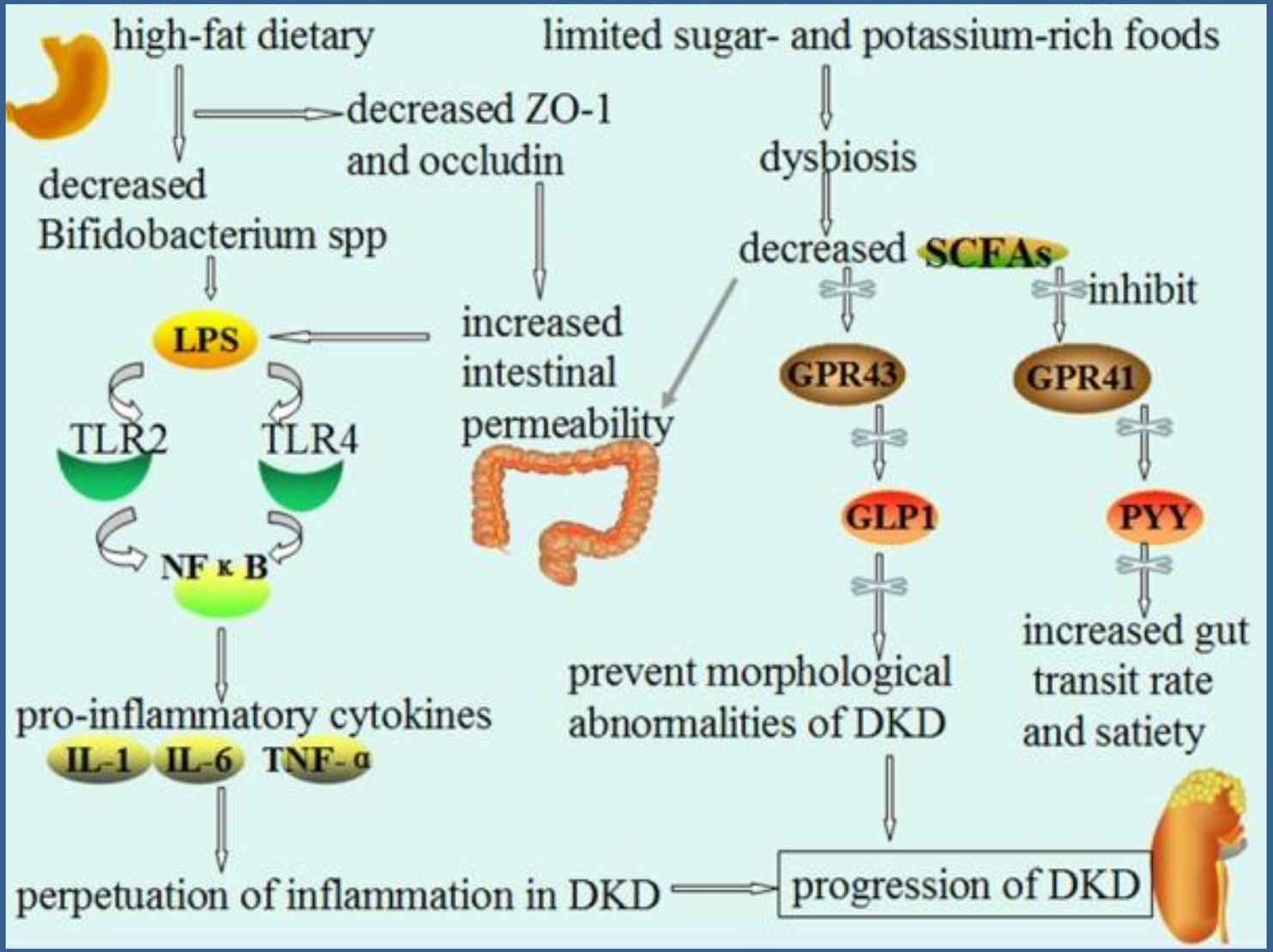
Science News *from research organizations*

Gut microbiota changes in diabetic kidney disease contribute to chronic inflammation and vascular complications

Date: November 6, 2015

Source: American Society of Nephrology (ASN)

Summary: Among patients with type 2 diabetes and advanced chronic kidney disease (CKD), a shift in gut microbiota diversity in combination with elevated plasma zonulin levels substantially impacts the degree of chronic inflammation and endothelial dysfunction. Zonulin could be a potential future target to control inflammatory immune responses, according to a new study.



MICROECOLOGICAL DYSBIOSIS OF GUT MICROBIOTA CONTRIBUTES TO DIABETIC NEPHROPATHY VIA ACTIVATING INTRARENAL RENIN ANGIOTENSIN SYSTEM FREE

Chen Chen Lu, Kun Ling Ma, Ze Bo Hu, Yang Zhang, Gui Hua Wang, Jian Lu, Pei Pei Chen, Bi Cheng Liu

Nephrology Dialysis Transplantation, Volume 33, Issue suppl_1, 1 May 2018, Pages i57–i58,

RESULTS:

1. **DM group displayed an abnormal state of gut microbiota.**
2. **Glomerular endothelial cells and podocytes were damaged obviously and the basement membrane was thickened in DM group.**
3. **Administration of antibiotics ameliorated renal injuries caused by DM.**
4. **the levels of plasma renin activity (PRA), angiotensin II (Ang II) were significantly increased in DM rats, (activated RAS), the degree of which has been reduced by antibiotic treatment.**

MICROECOLOGICAL DYSBIOSIS OF GUT MICROBIOTA CONTRIBUTES TO DIABETIC NEPHROPATHY VIA ACTIVATING INTRARENAL RENIN ANGIOTENSIN SYSTEM FREE

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CONCLUSIONS: Our findings suggested that the dysbiosis of intestinal microflora might be a potential mechanism for the progression of early DN, which leads to kidney injuries via the RAS activation.

Gut-renal axis

Immunologic issues

AND

Increased Inflammation

Oxidative STRESS & pro-inflammation in type 2 diabetes

Several studies from the
Madras Diabetes Research Foundation(MDRF),
have demonstrated the association of
Oxidative Stress
and
pro-inflammation
with diabetes

Increased inflammatory STRESS in patients with Type 2 diabetes and its vascular complications

Association of C-reactive protein with body fat, diabetes and coronary artery disease in Asian Indians: The Chennai Urban Rural Epidemiology Study (CURES-6)

V. Mohan, R. Deepa, K. Velmurugan and G. Premalatha

Available online at www.sciencedirect.com
ScienceDirect
ELSEVIER
Metabolism Clinical and Experimental 55 (2006) 1232–1238
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Serum levels of interleukin 6, C-reactive protein, vascular cell adhesion molecule 1, and monocyte chemotactic protein 1 in relation to insulin resistance and glucose intolerance—the Chennai Urban Rural Epidemiology Study (CURES)☆

Raj Deepa[a], Kaliyaperumal Velmurugan[a], Kannan Arvind[a], Pillarisetti Sivaram[b], Cahoon Sientay[b], Saxena Uday[b], Viswanathan Mohan[a,*]
[a]Madras Diabetes Research Foundation and Dr. Mohan's Diabetes Specialities Centre, Gopalapuram, Chennai 600 086, India

Available online at www.sciencedirect.com
ScienceDirect
ELSEVIER
Clinical Biochemistry 41 (2008) 480–485
CLINICAL BIOCHEMISTRY

Association of high sensitivity C-Reactive Protein [hsCRP] and Tumour Necrosis Factor-α [TNF-α] with carotid Intimal Medial Thickness in subjects with different grades of glucose intolerance—The Chennai Urban Rural Epidemiology Study (CURES-31)

Kuppan Gokulakrishnan, Raj Deepa, Viswanathan Mohan *

Original Article#

Association of Leukocyte Count and hsCRP with Metabolic Abnormalities in Subjects with Normal Glucose Tolerance (CURES – 64)

K Gokulakrishnan, R Deepa, R Sampathkumar, M Balasubramanyam, V Mohan

Subclinical inflammation/oxidation as revealed by altered gene expression profiles in subjects with impaired glucose tolerance and Type 2 diabetes patients

Kuppan Gokulakrishnan · Kutuva Tulasi Mohanavalli · Finny Monickaraj · Viswanathan Mohan · Muthuswamy Balasubramanyam

Mol Cell Biochem
DOI 10.1007/s11010-011-0727-3

Impaired miR-146a expression links subclinical inflammation and insulin resistance in type 2 diabetes

M. Balasubramanyam · S. Aravind · K. Gokulakrishnan · P. Prabu · C. Sathishkumar · H. Ranjini · V. Mohan

Oxidative STRESS & pro-inflammation in type 2 diabetes and its vascular complications

Association of hypoglutathionemia with reduced Na^+/K^+ ATPase activity in type 2 diabetes and microangiopathy

Rangasamy Sampathkumar, Muthuswamy Balasubramanyam, Cherian Tara, Mohan Rema and Viswanathan Mohan

Oxidative DNA damage and augmentation of poly(ADP-ribose) polymerase/nuclear factor-kappa B signaling in patients with Type 2 diabetes and microangiopathy

Antonysunil Adaikalakoteswari, Mohan Rema, Viswanathan Mohan, Muthuswamy Balasubramanyam*

Differential gene expression of NADPH oxidase ($p22^{phox}$) and hemoxygenase-1 in patients with Type 2 diabetes and microangiopathy

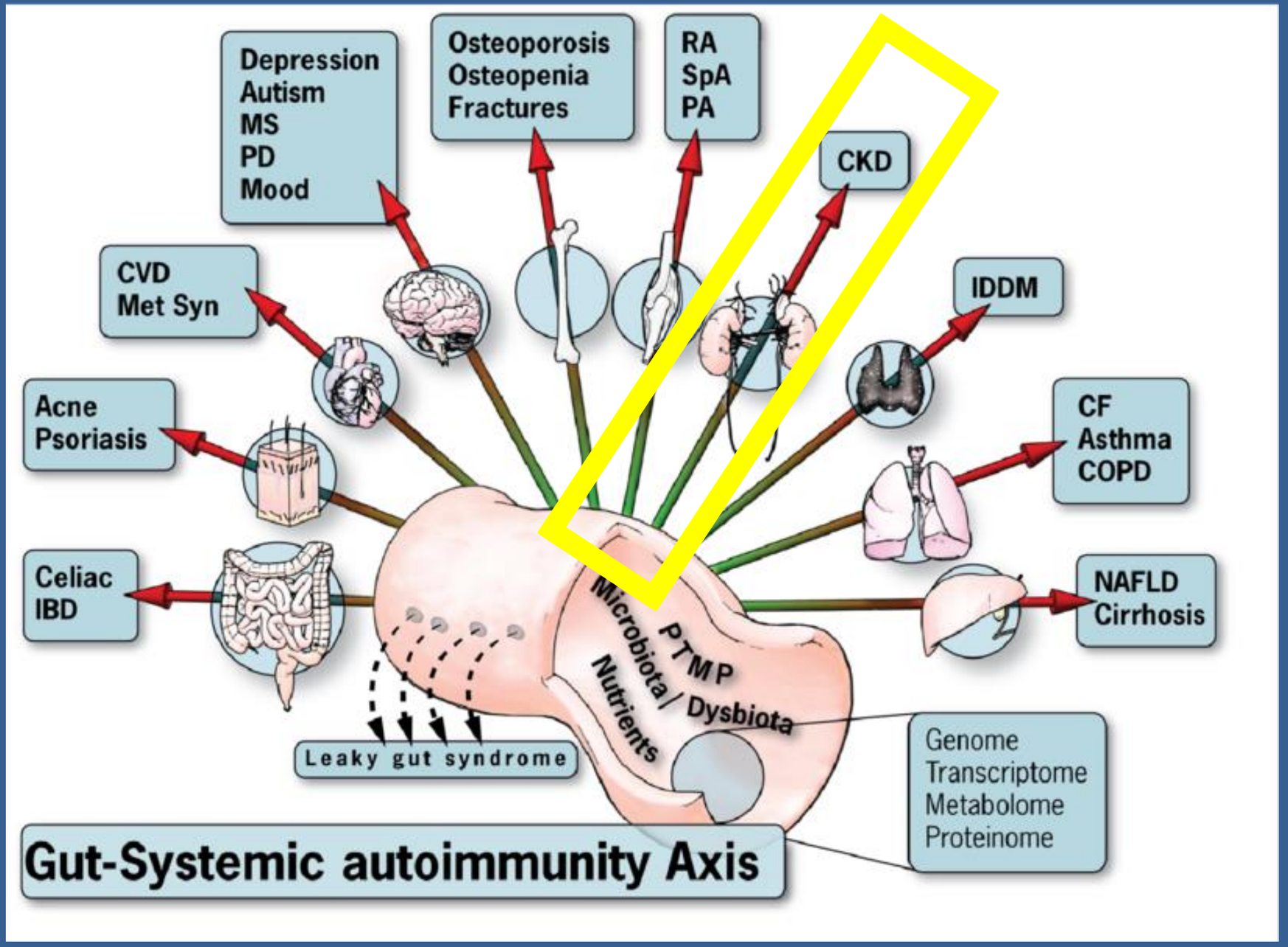
A. Adaikalakoteswari, M. Balasubramanyam, M. Rema and V. Mohan

Subclinical inflammation/oxidation as revealed by altered gene expression profiles in subjects with impaired glucose tolerance and Type 2 diabetes patients

Kuppan Gokulakrishnan · Kutuva Tulasi Mohanavalli · Finny Monickaraj · Viswanathan Mohan · Muthuswamy Balasubramanyam

The interplay between the gut microbiome, gut immune system, and systemic immune system in CKD

- The gut mucosal system is the largest lymphoid organ in the body.
- It is a site at which there is continuous antigenic challenge in the form of food antigens, antigens of normal bacterial flora, and pathogens.
- The intestinal microbiome exerts a profound effect on mucosal immune regulation affecting the systemic immune system, contributing to immune balance.


Depression
Autism
MS
PD
Mood
Osteoporosis
Osteopenia
Fractures
RA
SpA
PA
CKD
IDDM
CVD
Met Syn
Acne
Psoriasis
CF
Asthma
COPD
Celiac
IBD
NAFLD
Cirrhosis
Microbiota/ Dysbiota
PTMP
Nutrients
Leaky gut syndrome
Genome
Transcriptome
Metabolome
Proteinome
Gut-Systemic autoimmunity Axis

The interplay between the gut microbiome, gut immune system, and systemic immune system in CKD

- Any disruption of the microbiome can induce systemic immune imbalance, contributing to the pathogenesis of immune-mediated disorders.

- Gut epithelial cells participate in immune surveillance and in determining the direction of host responses in the gut.

The interplay between the gut microbiome, gut immune system, and systemic immune system in CKD

- Gut barrier cells express pattern recognition receptors, including TLR5, TLR1, TLR2, TLR3, TLR9, and nucleotide oligomerization domain 2, and produce chemotactic factors for both myeloid and lymphoid cells.

- Innate immune cells in the gut produce effector cytokines and exert both protective and pathogenic roles during inflammation.

Immunologic and immflamatory issues of Gut –Renal Axisis

In Diabetic Nephropathy

SCIENTIFIC REPORTS

OPEN

Nature online (2018) 8:8319

Received: 26 January 2018

Blockade of HMGB1 Attenuates Diabetic Nephropathy in Mice

Xiaochen Chen[1], Jin Ma[1], Tony Kwan[1], Elisabeth G. D. Stribos[1], A. Lianne Messchendorp[1], Yik W. Loh[1], Xiaoyu Wang[1], Moumita Paul[3], Eithne C. Cunningham[3], Miriam Habib[3], Ian E. Alexander[4,5], Alexandra F. Sharland[3], Steven J. Chadban[1,2] & Huiling Wu[1,2]

- TLRs are innate immune receptors that can be activated by exogenous ligands from microbes, and endogenous ligands from injury cells.
- TLR2 and 4 activation by endogenous ligands including high mobility group box 1 (HMGB1), heat-shock proteins (HSPs) and biglycan, leads to translocation of NF-κB , release of pro-inflammatory cytokines (TNFα & IL6) and chemokines (CCL2) triggering a inflammation as known to participate in the pathogenesis of DN.

SCIENTIFIC REPORTS

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- Upregulation of TLR2 or 4 and HMGB1 occurs in early diabetic kidneys in STZ-induced diabetes.
- Either absence of TLR2 or TLR4 was protective against development of DN in mice.
- HMGB1 is candidate as a responsible ligand for TLR activation in DN.

SCIENTIFIC REPORTS

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RAGE plays a crucial role in the pathogenesis of DN.

Engagement of RAGE by HMGB1, can initiate cellular signals that activate NF-κB and trigger pro-inflammatory responses.

TLR4−/− mice or RAGE−/− were protected against DN.

Blocking the interaction between HMGB1 and its signaling via its receptors prevents the development of DN:

A pathogenic role for HMGB1

SCIENTIFIC REPORTS

OPEN

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Blockade of HMGB1 Attenuates Diabetic Nephropathy in Mice

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Evidence from clinical and experimental studies has demonstrated that :

sterile inflammatory processes triggered by innate immune responses via TLRs and RAGE play vital roles in th pathogenesis and progression of DN.

Hormonal issues of Gut- Renal Axis

GI system is largest Entro –Endocrine organ in the body

The gut–renal axis

- **Intestinal regulation of renal functions, especially following a meal that disturbs water and ion homeostasis, is crucial .**

- **A putative rapid-acting gut–renal axis might assist renal solute excretion in response to acute solute ingestion, forming a crucial feed-forward loop.**

Nature I FEBRUARY 2014 | VOLUME 10

The gut–renal axis

Entero-endocrine cells seem to contribute to the physiological control of water and electrolyte balance upon meal ingestion by :

- **Affecting the CNS to adjust thirst**
- **Affecting solute intake**
- **Intestinal transport to control fluid and electrolyte absorption and secretion;**
- **Intracellular and extracellular compartments to dispose the absorbed content**
- **The kidney to stimulate excretion or reabsorption of fluid and electrolytes.**

The gut–renal axis

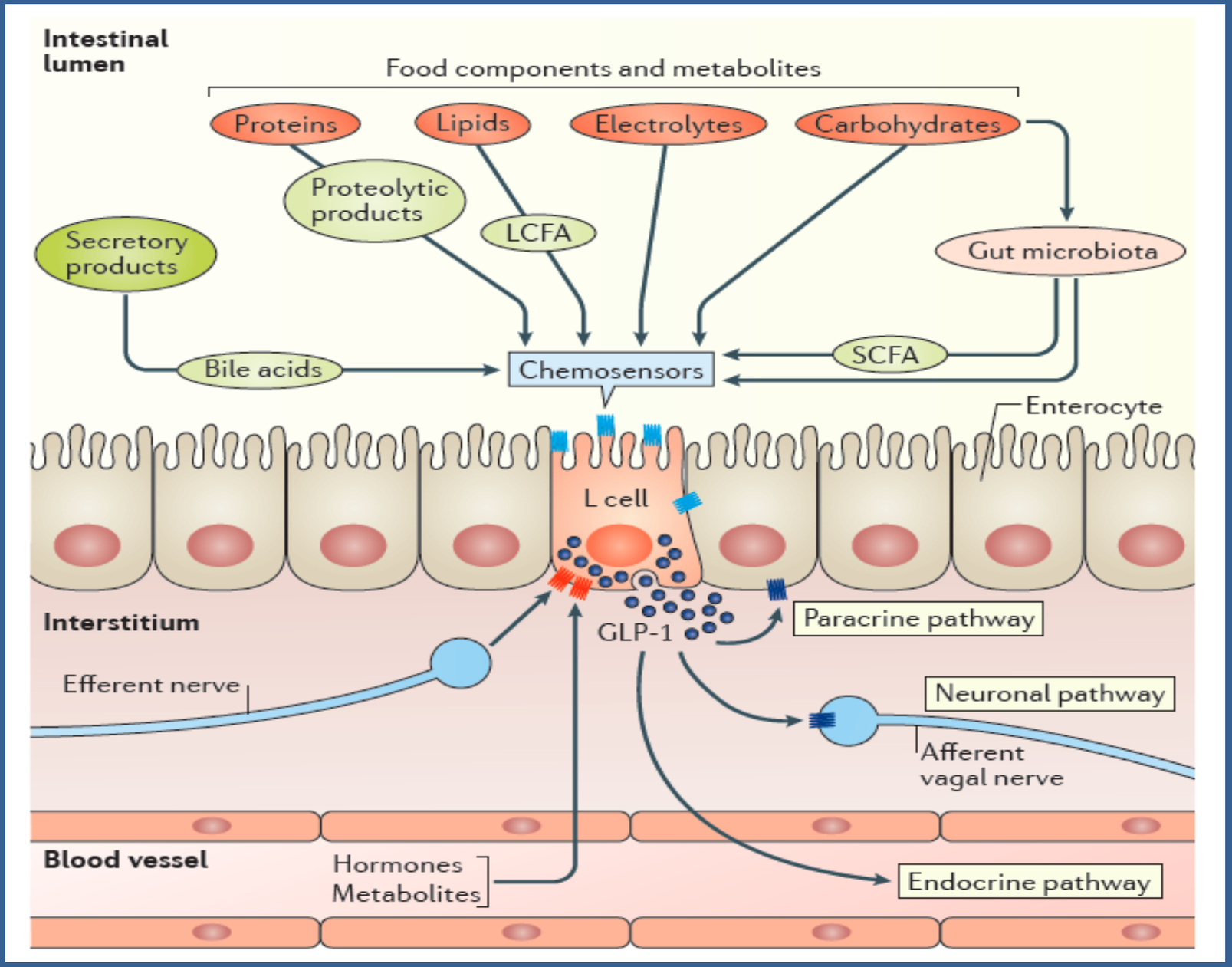
Several gut hormones and peptides have been proposed to be effectors of, or have a role in, the gut–renal (natriuretic) axis, including

- **gastrin (via interaction with renal dopamine88),**
- **Ghrelin**
- **Uroguanylin**
- **Guanylin**
- **Secretin**
- **vasoactive intestinal polypeptide**
- **peptide YY (PYY)**
- **Incretin Hormones :**

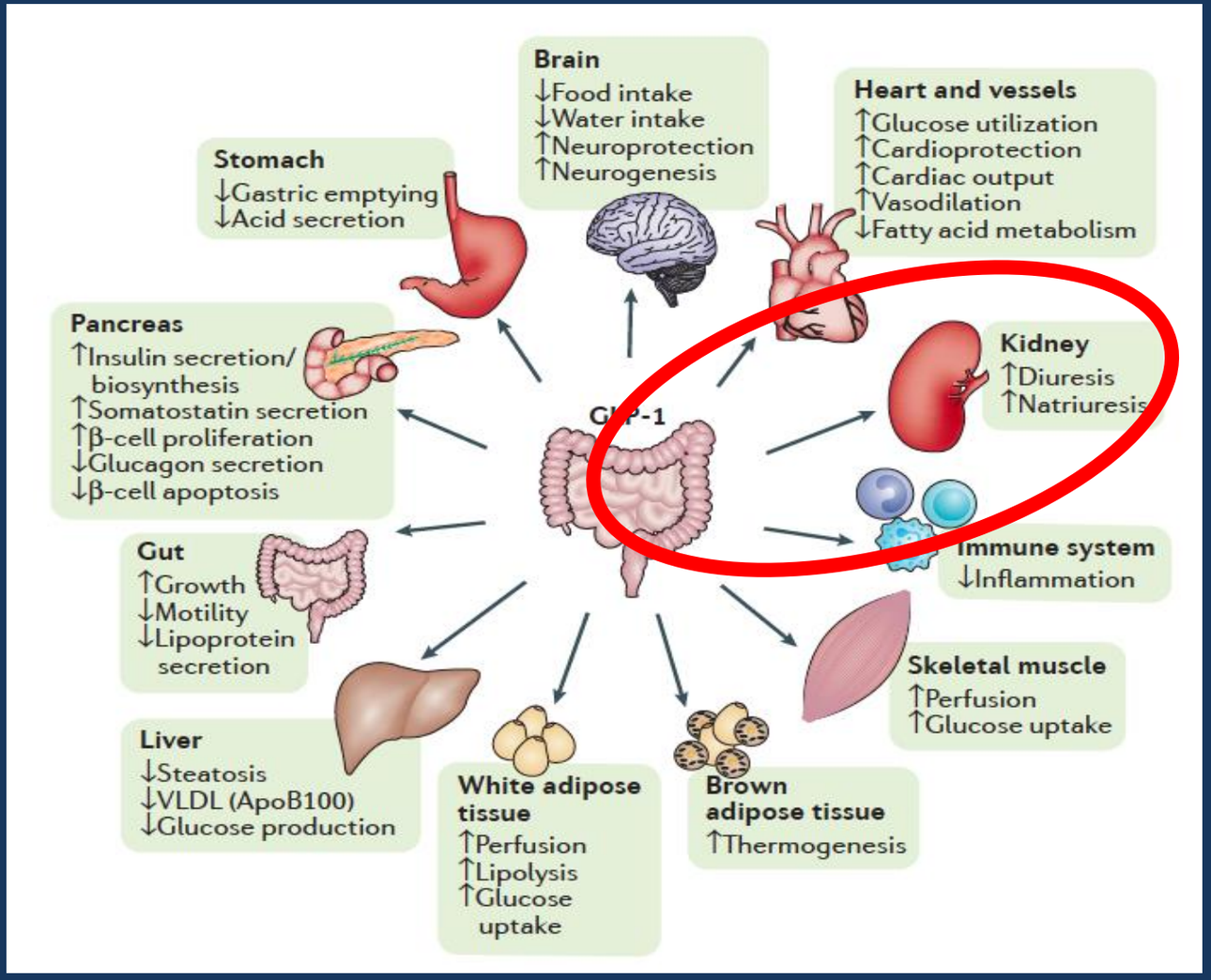
GLP-1

GIP

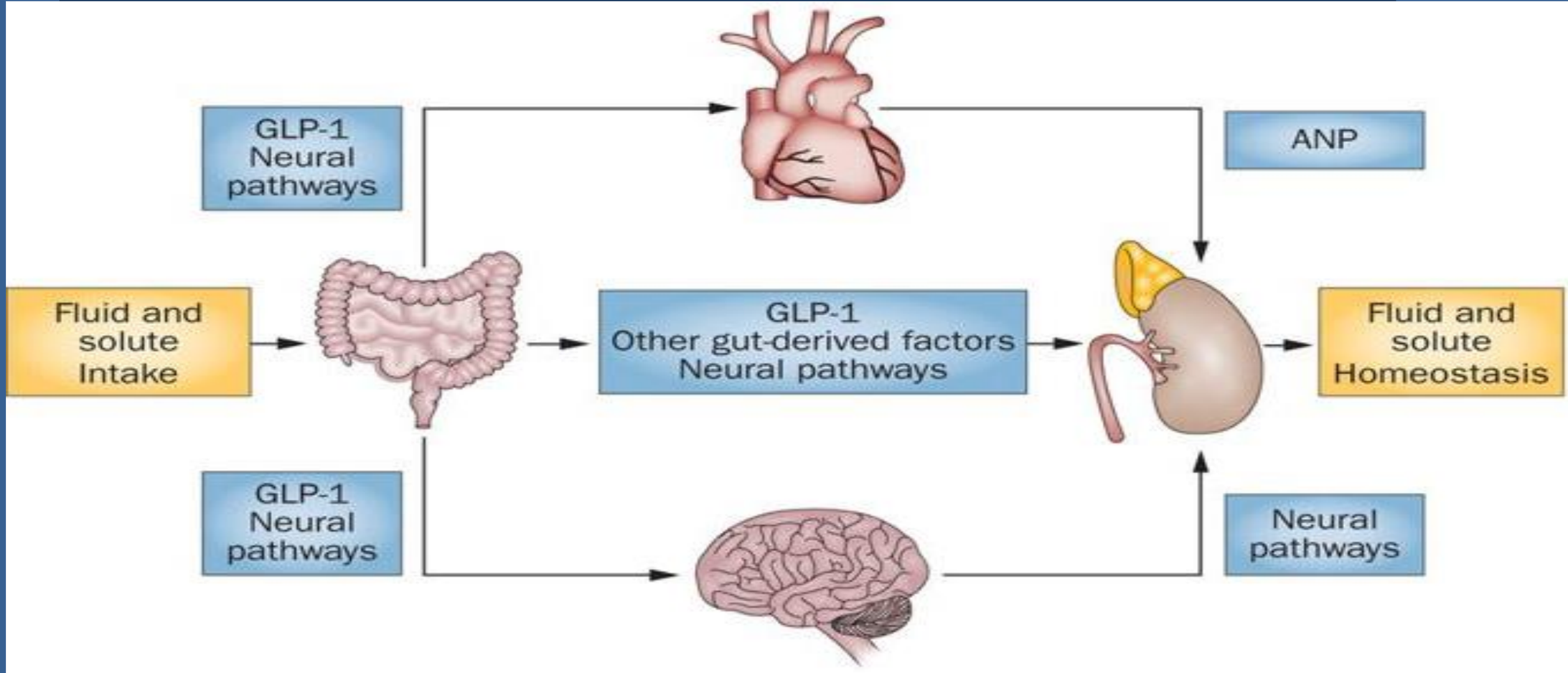
GUT-Renal Axis
GLP-1



Putative actions of glucagon-like peptide1(GLP-1)



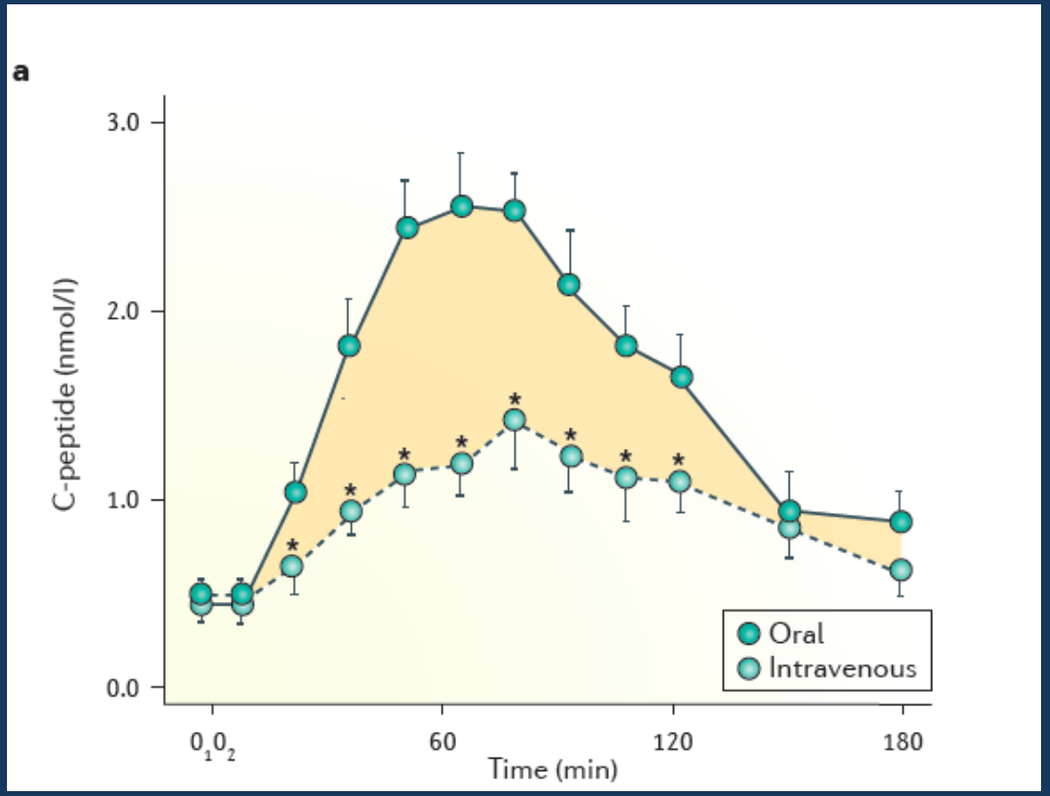
The gut–renal axis GLP1



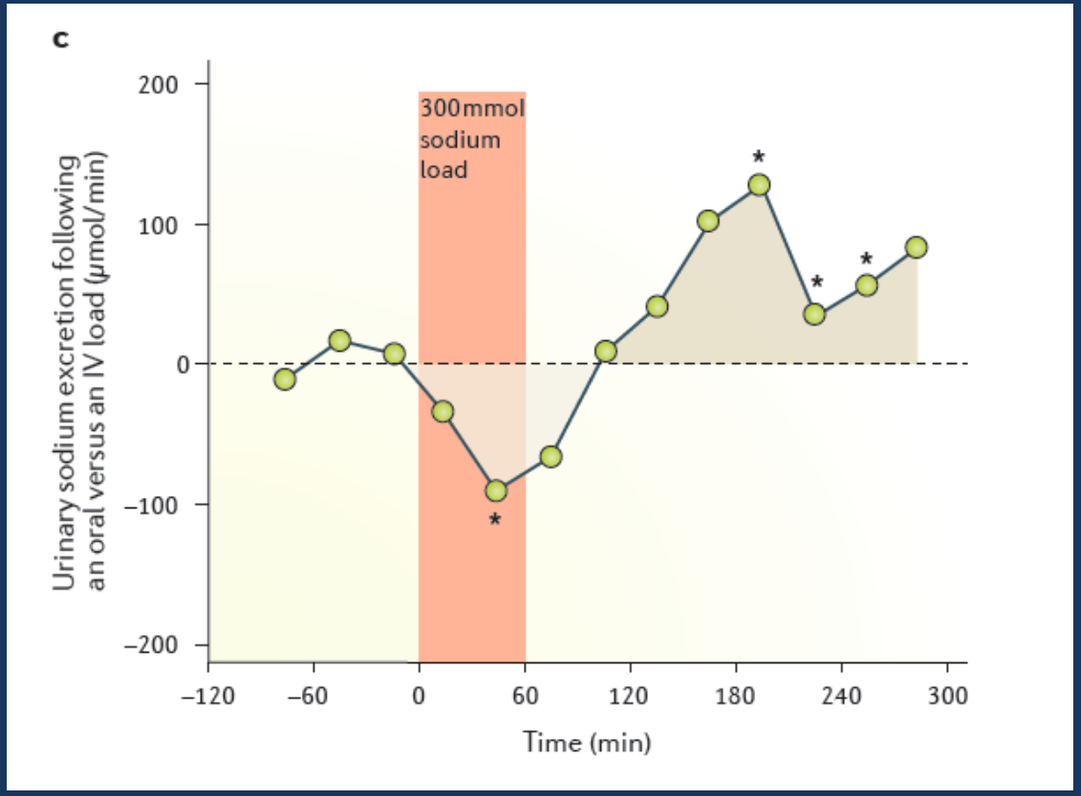
Are thought to affect renal function

1. **Directly influence the kidney,**
2. **Indirect effects** **Neural pathways or**
   Cardiac-derived ANP,
   Increase postprandial natriuresis.

Incretin effect of GLP-1

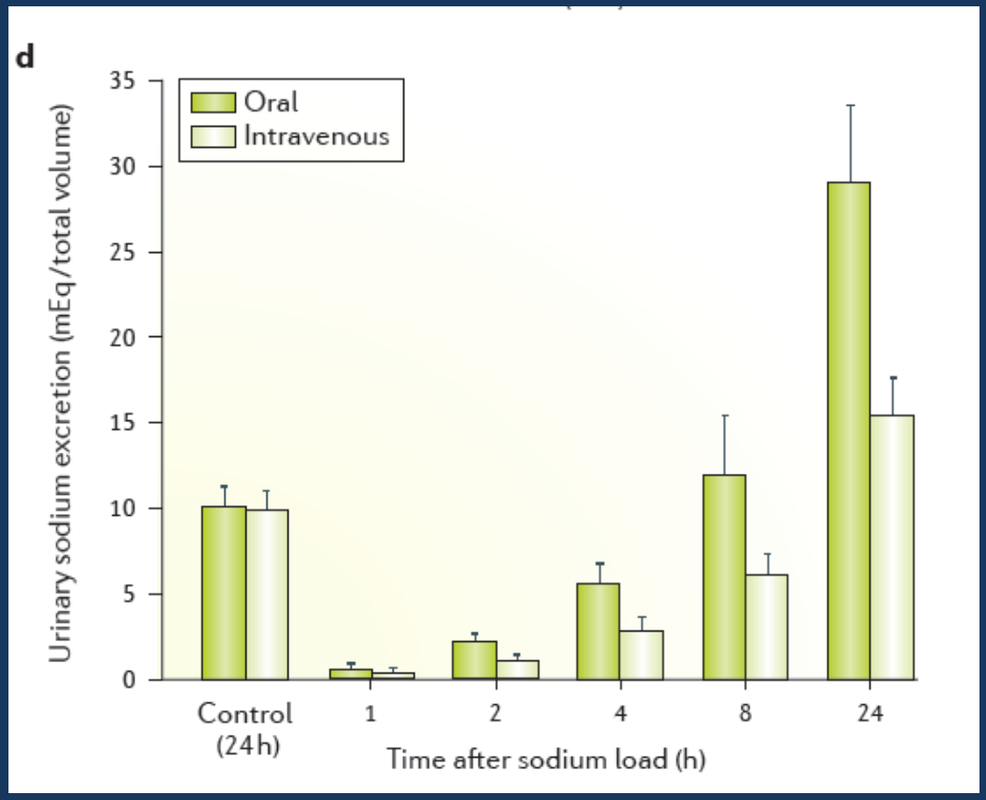


Incretin effect and the putative gastrointestinal regulation of urinary sodium excretion.



This result are independent of changes in the levels of circulating atrial natriuretic peptide (ANP) and aldosterone.

Incretin effect and the putative gastrointestinal regulation of urinary sodium excretion.



The gut–renal axis

Several lines of evidence suggest similar feed-forward loops for

- Potassium
- Phosphate balance
- Other electrolytes.

The gut has been suggested to directly detect changes in the levels of ingested electrolytes and couple these changes to release of hormones and/or activation of neural pathways that regulate renal tubular and gastrointestinal transport.

The gut–renal axis

An impaired gut–renal axis in urinary sodium excretion:

- Hypo secretion
- Reduced receptor signaling of entro-endocrine-cell-derived hormones
- Inability of these signals to suppress anti natriuretic systems (such as the RAAS) in response to a salt load

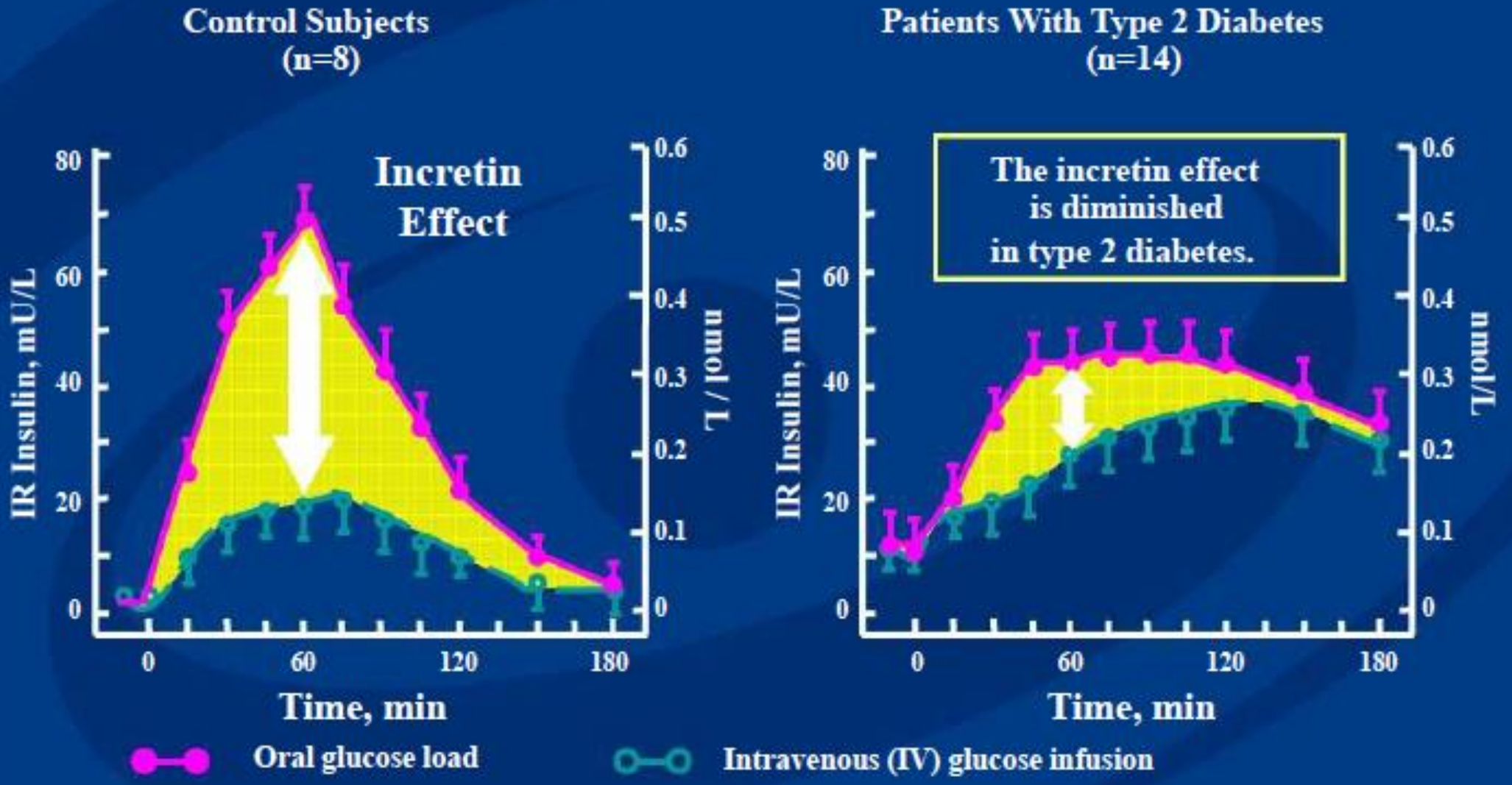
Might contribute to salt-sensitive hypertension

These concept are important for the development of novel targeted therapies.

Hormonal issues of Gut- Renal Axsis

In Diabetic Nephropathy

The Incretin Effect in Persons without and with Type 2 Diabetes



Gut- renal axis in diabetic Nephropathy

Novel blood-glucose-lowering drugs used in the treatment of type 2 diabetes mellitus (T2DM):

The incretin-based agents

1. **Agonists of glucagon-like peptide 1 receptor (GLP-1R)**
2. **Inhibitors of dipeptidyl peptidase 4 (DPP-4),**

(an enzyme that degrades glucagon-like peptide 1)

Improve pancreatic islet function and induce extra pancreatic effects that ameliorate various phenotypic defects of T2DM that are beyond glucose control.

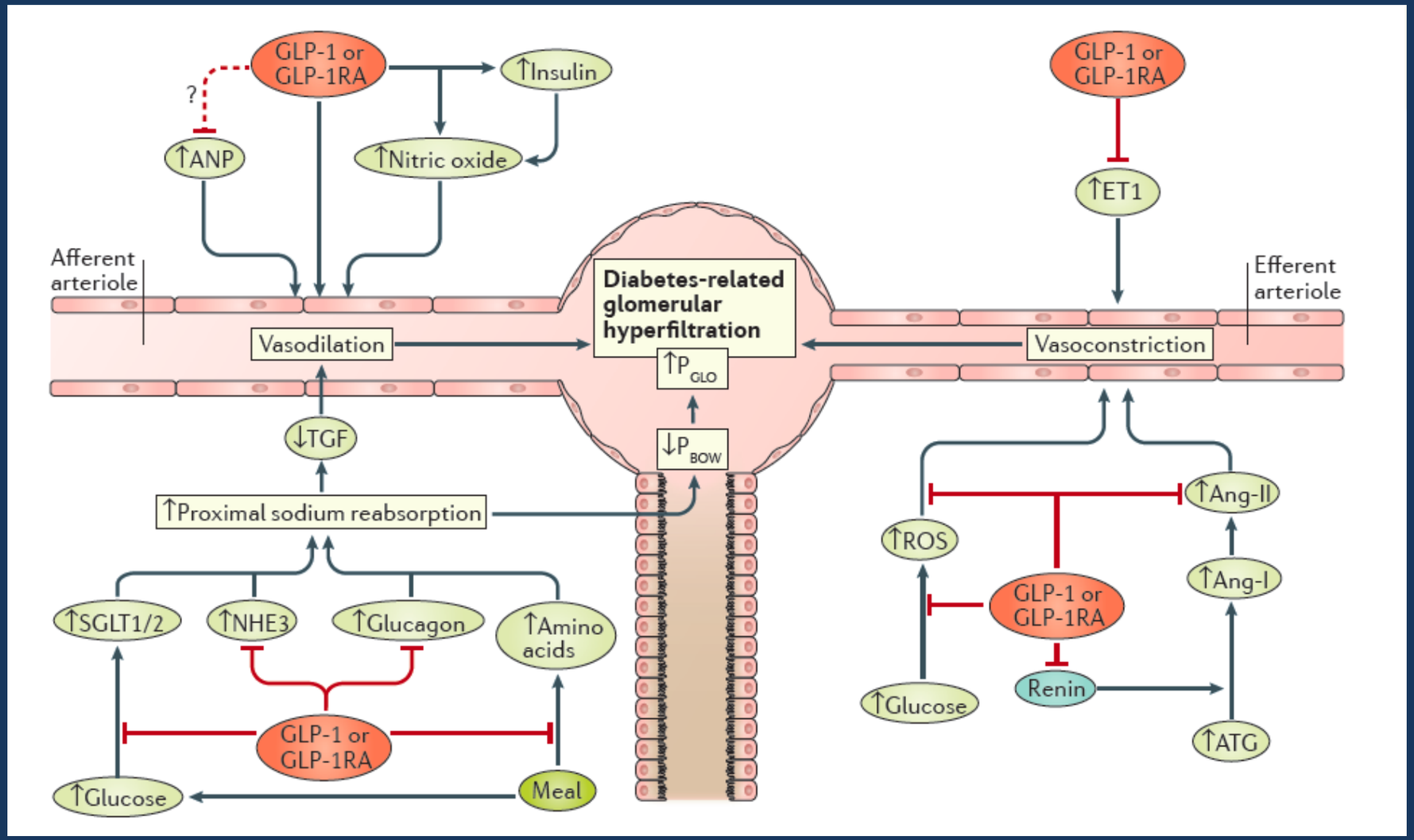
Putative renal distribution of GLP-1

Location	Species	mRNA or protein	Detection method
GLP-1R			
Preglomerular* vascular smooth muscle cells	Monkey; human	Protein	Immunohistochemistry
	Rat	Protein	Autoradiography of ^{125}I-labelled GLP-1, exendin 4 (GLP-1 agonist) and exendin 9–39 (GLP-1R antagonist)
Hilar and intralobular arteries	Human	Protein	Autoradiography of ^{125}I-labelled GLP-1
Glomerular capillary and vascular walls	Mouse	mRNA	*In situ* hybridization; RT-PCR
Glomerular endothelial cells and macrophages	Rat	Protein	Immunofluorescence
Glomerulus (not specified)	Rat	mRNA	RT-PCR
Juxtaglomerular cells	Monkey; human	Protein	Immunohistochemistry
	Rat	Protein	Immunohistochemistry
Proximal tubule	Rat	mRNA	RT-PCR

Putative renal distribution membrane-bound DPP-4

Membrane-bound DPP-4			
Preglomerular vascular smooth muscle cells	Rat	mRNA, protein	RT-PCR, Western blotting
Mesangial cells	Rat	mRNA, protein	RT-PCR, Western blotting
Podocytes	Rat	Protein	Immunohistochemistry
Proximal tubule	Pig; human	mRNA	RT-PCR, immunocytochemistry
	Rat	Protein	Immunohistochemistry
Loop of Henle, distal convoluted tubule, connecting tubule, cortical collecting duct	Rat	mRNAs	Deep sequencing of RNA species

Effects of GLP-1 and GLP-1RAs on renal haemodynamics in diabetes mellitus

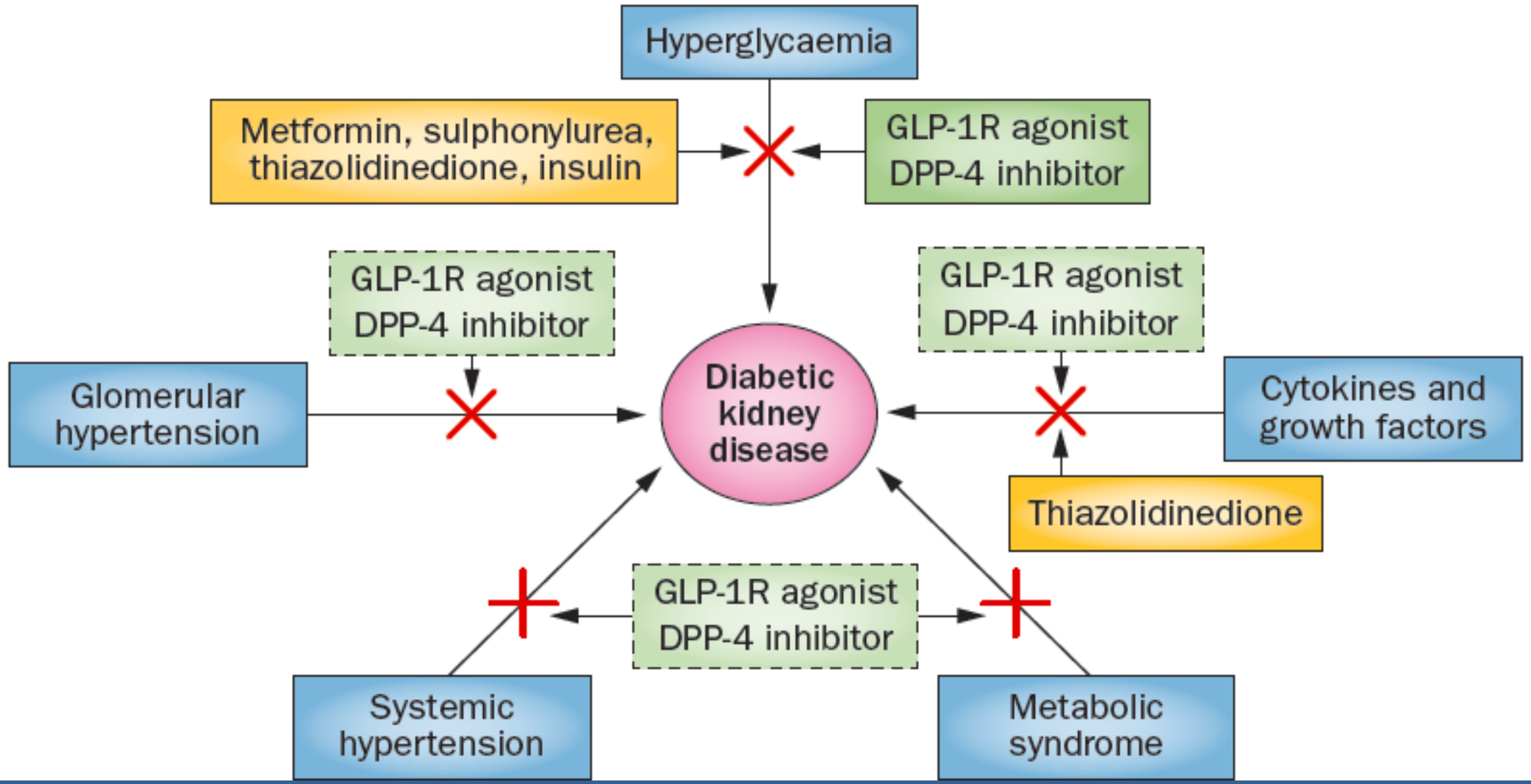


Incretin-based agents

Agonists of GLP-1R and inhibitors of DPP-4:

- Inhibit renal tubular sodium reabsorption
- Decrease glomerular pressure
- Decrease albuminuria (in rodents and humans).
- Prevent onset of the morphological abnormalities of diabetic nephropathy. (In rodents)

Renoprotection of Incretin agents



Indirect Reno protective effects of incretin based agents

Renal Risk Factor	GLP-1RA	DPP4	Putative GLP-1-mediated mechanisms
Dyslipidemia	Decrease	Neutral effect	↓ Body weight ↓ Intestinal lipid uptake (partly by ↓ GEE*) ↓ Hepatic lipoprotein synthesis and secretion ↑ Insulin sensitivity (partly by ↓ body weight) ↑ Insulin and ↓glucagon ↑ Triglyceride uptake in white adipose tissue ↑ Brown adipose tissue activation
Obesity	Decrease	Neutral effect	↓ Appetite (direct effect on CNS or via vagal afferents, ↓ GEE* and ↑ ?nausea) ↑ Energy expenditure35? ↑ Natriuresis and/or diuresis?

Marcel H. A. Muskiet1 et Al* :GLP-1 and the kidney ,NATURE REVIEWS | **NEPHROLOGY I** 2017

Indirect Reno protective effects of incretin based agents

Renal Risk Factor	GLP-1RA	DPP4	Putative GLP-1-mediated mechanisms
Blood pressure	Decrease	Decrease or neutral effect	↓ Body weight ↑ Endothelial independent vasodilation ↑ Natriuresis ↓ Intestinal sodium reabsorption ↓ Sodium intake (direct effect on CNS) ↓ RAAS activity ↑ ANP
Inflammation and fibrosis	Decrease Decrease	Decrease	↓ Renal ROS production (cAMP and PKA) ↓ AGE–RAGE-mediated renal ROS production (cAMP) ↓ Angiotensin II-induced renal ROS production (PKC) ↑ Adiponectin (reduces podocyte inflammation; PKA in adipocytes)
Glomerular hyperfiltration	Decrease or neutral effect	Neutral effect	↑ Tubuloglomerular feedback (by ↓ ?NHE3 activity) ↓ Postprandial glucagon ↓ Body weigh ↓ GEE* (postprandial hyperfiltration) ↓ RAAS activity

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European Review for Medical and Pharmacological Sciences 2017; 21: 3523-3529

Analysis on difference in gastrointestinal hormone levels of patients with the history of diabetes and concurrent nephropathy and study on the role of liraglutide

Group category	GAS (pg/ml)	MTL (pg/ml)	GLC (pg/ml)	Gastric emptying time (h)
Group A	55.72 ± 26.67	168.45 ± 26.47	90.23 ± 20.44	3.48 ± 0.54
Group B	83.66 ± 38.44[a]	310.02 ± 166.34[a]	166.33 ± 58.62[a]	5.26 ± 0.98[a]
Control group	45.22 ± 18.06[b]	86.33 ± 12.65[b]	78.33 ± 26.23[b]	2.76 ± 0.33[b]

European Review for Medical and Pharmacological Sciences 2017; 21: 3523-3529

Analysis on difference in gastrointestinal hormone levels of patients with the history of diabetes and concurrent nephropathy and study on the role of liraglutide

Group category	Group category	Microalbuminuria (mg/24h)
Group A	Before treatment	257.84 ± 31.85
	After 10 weeks' treatment	163.58 ± 23.92 [b,c,e]
Group B	Before treatment	564.13 ± 51.74
	After 10 weeks' treatment	391.42 ± 39.05[b,c]
Control group	Before treatment	21.64 ± 4.26
	After 10 weeks' treatment	19.31 ± 3.47[b]

Group category	Group category	IL-6 (pg/mL)	TNF-α (pg/mL)	TGF-β1 (μg/L)
Group A	Before treatment	33.15 ± 7.32	53.22 ± 15.83	80.13 ± 16.75
	After 10 weeks' treatment	15.41 ± 4.26[a]	27.61 ± 9.42[a]	40.69 ± 10.26[a]
Group B	Before treatment	33.18 ± 7.28	53.26 ± 15.79	80.14 ± 17.03
	After 10 weeks' treatment	17.95 ± 5.26[a]	29.26 ± 10.16[a]	43.64 ± 12.69[a]
Control group	Before treatment	33.21 ± 7.36	53.25 ± 15.85	80.16 ± 16.97
	After 10 weeks' treatment	14.26 ± 4.56[a]	26.55 ± 10.27[a]	38.47 ± 12.26[a]

In conclotion:

The challenge is…….

The strategy of Intensive control of glucose levels and blood pressure as the main stay of both prevention and treatment of diabetic nephropathy, cannot fully prevent the development and progression of diabetic nephropathy

An unmet need remains for additional novel therapies.

Science News *from research organizations*

Gut microbiota changes in diabetic kidney disease contribute to chronic inflammation and vascular complications

Date: November 6, 2015

Source: American Society of Nephrology (ASN)

Summary: Among patients with type 2 diabetes and advanced chronic kidney disease (CKD), a shift in gut microbiota diversity in combination with elevated plasma zonulin levels substantially impacts the degree of chronic inflammation and endothelial dysfunction. Zonulin could be a potential future target to control inflammatory immune responses, according to a new study.

- The gut microbiota plays critical roles in the lipid metabolism abnormalities and the progress of DKD.
- The decreased Bifidobacterium spp as well as the expressions of tight junction proteins ZO-1 and occludin due to high-fat diets are negatively correlated with high portal plasma concentration of LPS.
- LPS initiates inflammatory responses through Toll-like receptor TLR2/4-related pathways, and mediates the activation of NFκB and leads to the secretion of pro-inflammatory cytokines TNF-α, IL-1 and IL-6.

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- **In DKD limited consumption of sugar and potassium-rich foods**

(can be fermented to SCFAs and provide the major nutrients for the normal colonic bacteria) leads to increases the intestinal permeability and leakage of LPS into the portal blood circulation.

Science News *from research organizations*

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Summary: Among patients with type 2 diabetes and advanced chronic kidney disease (CKD), a shift in gut microbiota diversity in combination with elevated plasma zonulin levels substantially impacts the degree of chronic inflammation and endothelial dysfunction. Zonulin could be a potential future target to control inflammatory immune responses, according to a new study.

The inflammatory responses and decreased SCFAs play the central role in the progression of DKD.

SCFAs can activate GPR41 and GPR43 on the intestinal epithelial cells.

Stimulation of GPR41 leads to the release of peptide YY (PYY) that can increase the gut transit rate and satiety.

Activation of GPR43 alleviates inflammation and stimulates the release of glucagon like peptide 1 (GLP1), which could prevent the onset of the morphological abnormalities of DKD.