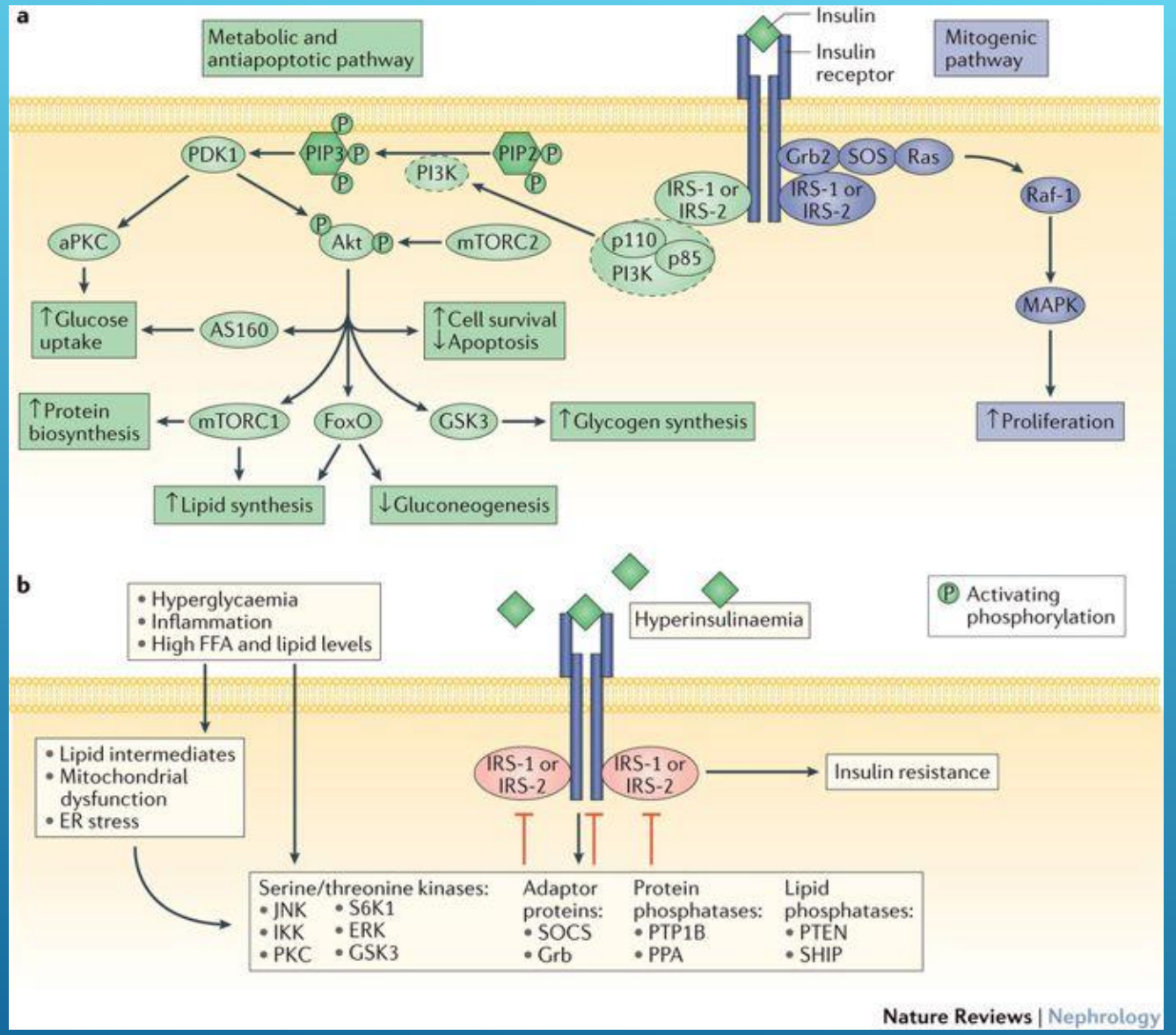
Role of insulin resistance in kidney dysfuntion

Insulin resistance

"hyperinsulinemic euglycemic clamp“

< 4 mg/min vs. > 7mg/min

Obesity , metabolic syndrome & T2DM


a
Metabolic and antiapoptotic pathway
Insulin
Insulin receptor
Mitogenic pathway
PDK1
PIP3
PIP2
PI3K
IRS-1 or IRS-2
Grb2
SOS
Ras
Raf-1
aPKC
Akt
mTORC2
p110
p85
PI3K
MAPK
↑Glucose uptake
AS160
↑Cell survival ↓Apoptosis
↑Protein biosynthesis
mTORC1
FoxO
GSK3
↑Glycogen synthesis
↑Proliferation
↑Lipid synthesis
↓Gluconeogenesis
b
• Hyperglycaemia
• Inflammation
• High FFA and lipid levels
Hyperinsulinaemia
Activating phosphorylation
• Lipid intermediates
• Mitochondrial dysfunction
• ER stress
IRS-1 or IRS-2
IRS-1 or IRS-2
Insulin resistance
Serine/threonine kinases:
• JNK
• IKK
• PKC
• S6K1
• ERK
• GSK3
Adaptor proteins:
• SOCS
• Grb
Protein phosphatases:
• PTP1B
• PPA
Lipid phosphatases:
• PTEN
• SHIP
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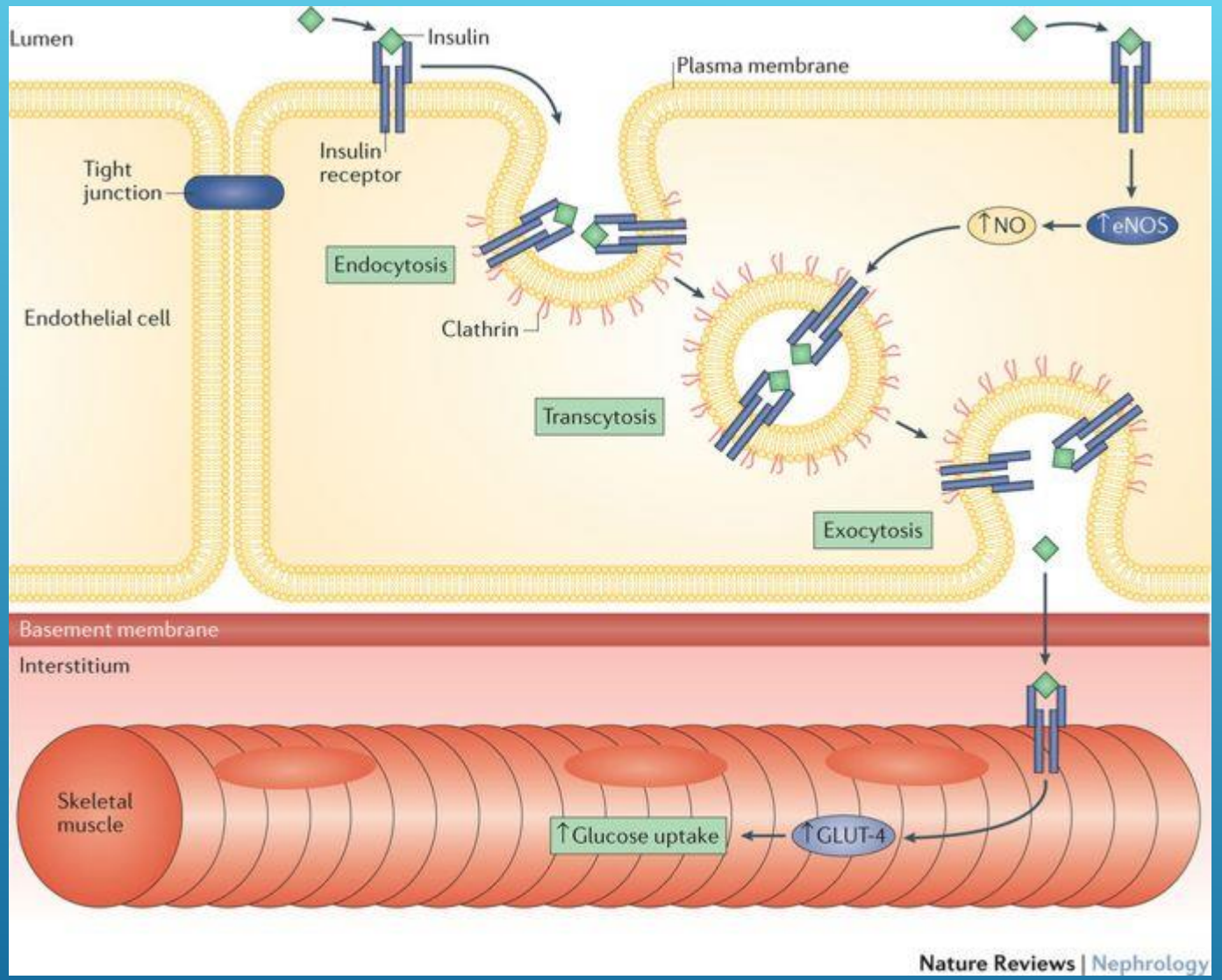
Lumen
Insulin
Plasma membrane
Insulin receptor
Tight junction
↑eNOS
↑NO
Endocytosis
Endothelial cell
Clathrin
Transcytosis
Exocytosis
Basement membrane
Interstitium
Skeletal muscle
↑Glucose uptake
↑GLUT-4
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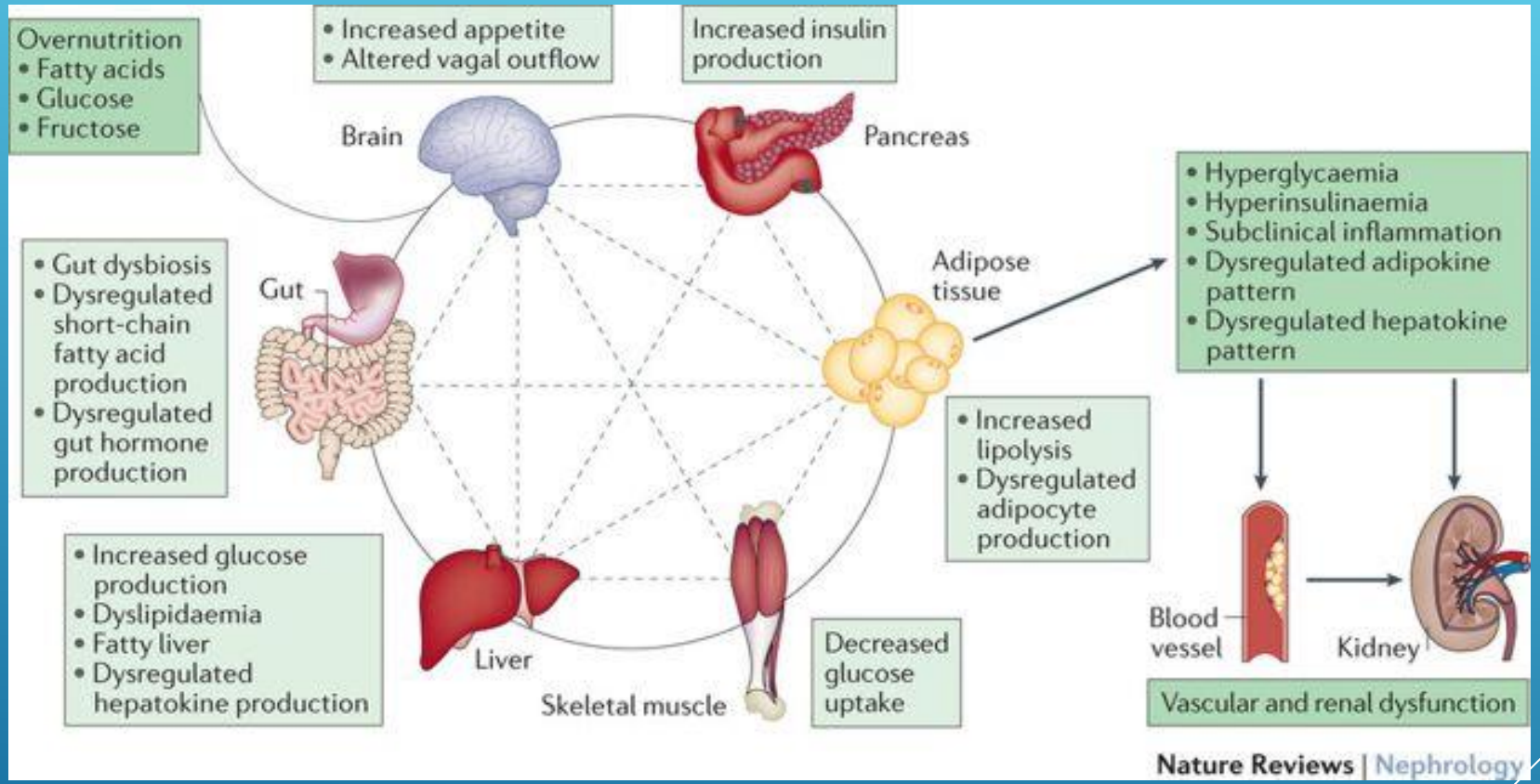
Overnutrition
• Fatty acids
• Glucose
• Fructose
• Increased appetite
• Altered vagal outflow
Increased insulin production
Brain
Pancreas
• Gut dysbiosis
• Dysregulated short-chain fatty acid production
• Dysregulated gut hormone production
Gut
Adipose tissue
• Hyperglycaemia
• Hyperinsulinaemia
• Subclinical inflammation
• Dysregulated adipokine pattern
• Dysregulated hepatokine pattern
• Increased lipolysis
• Dysregulated adipocyte production
• Increased glucose production
• Dyslipidaemia
• Fatty liver
• Dysregulated hepatokine production
Liver
Skeletal muscle
Decreased glucose uptake
Blood vessel
Kidney
Vascular and renal dysfunction
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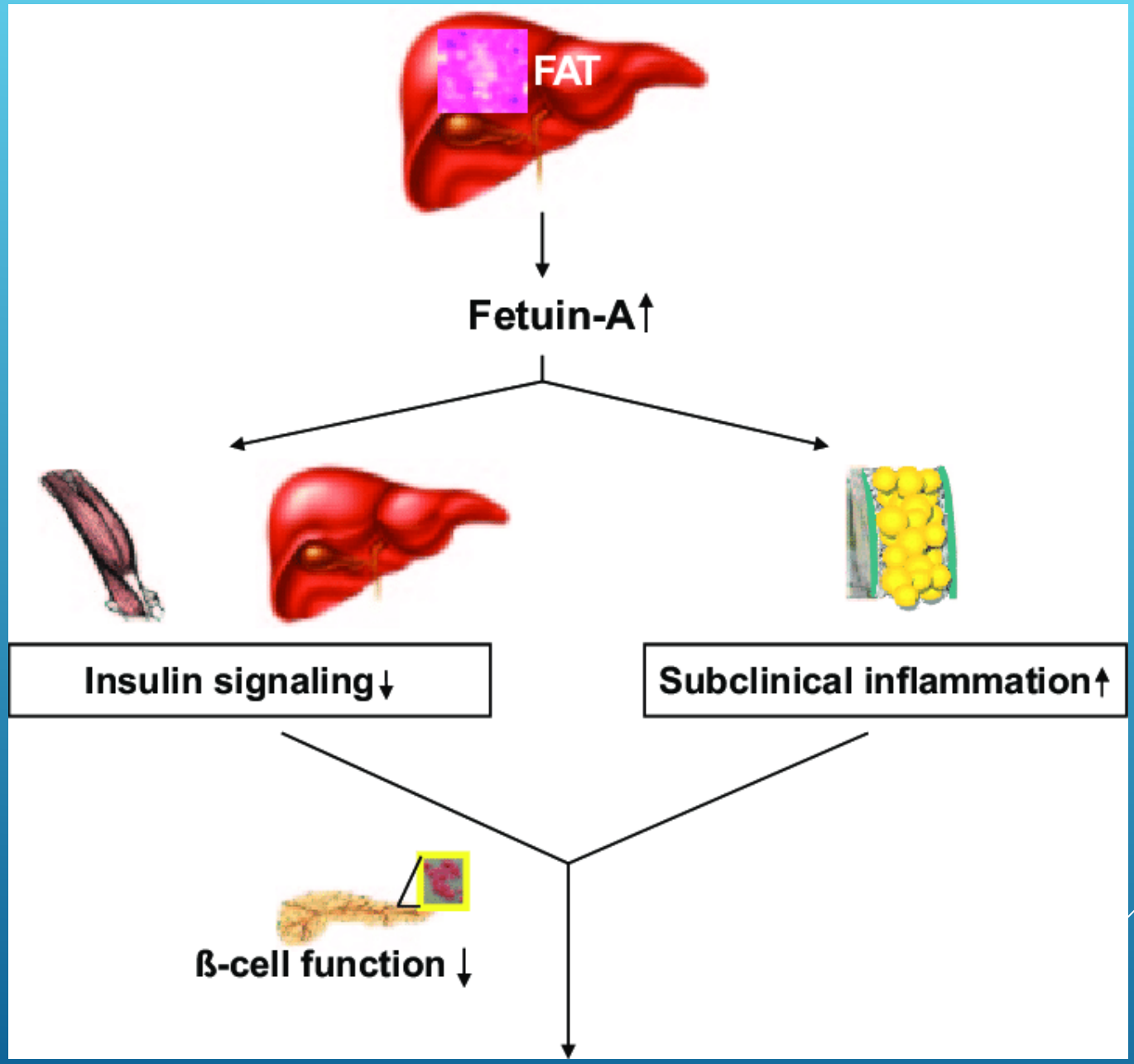
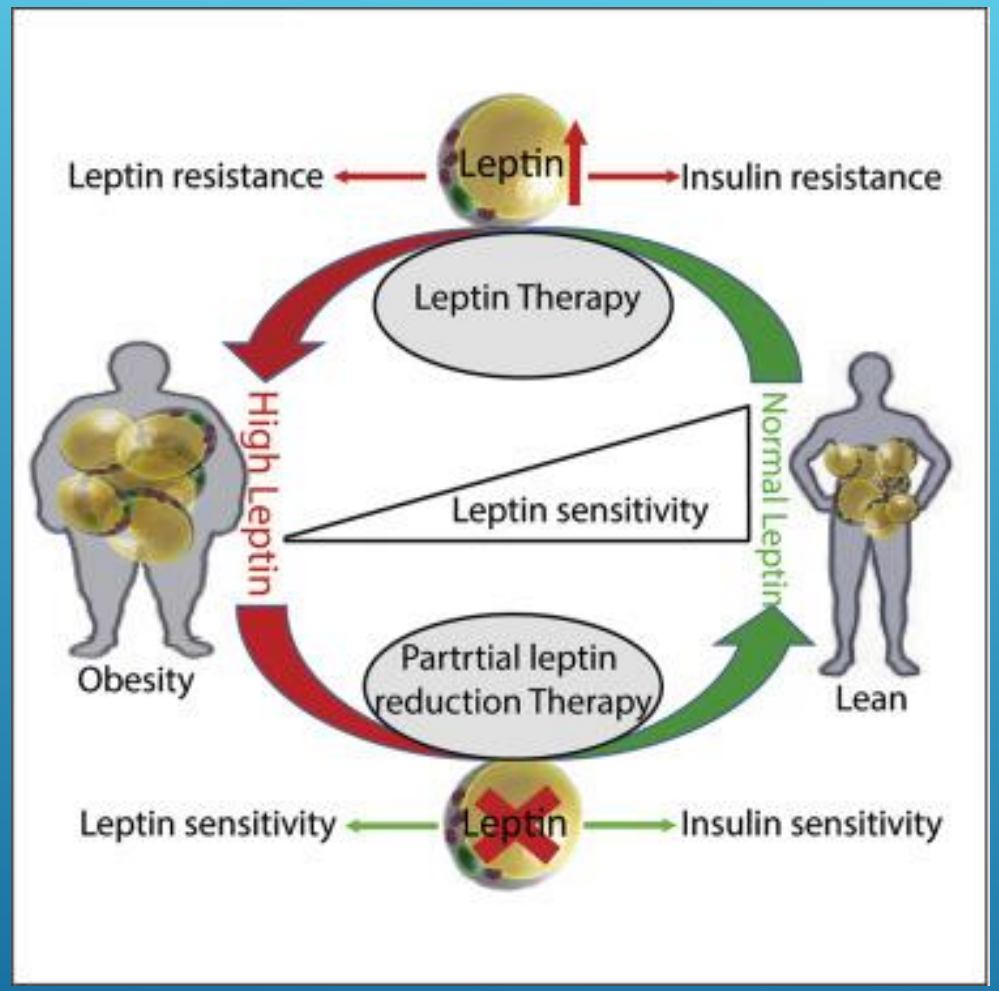
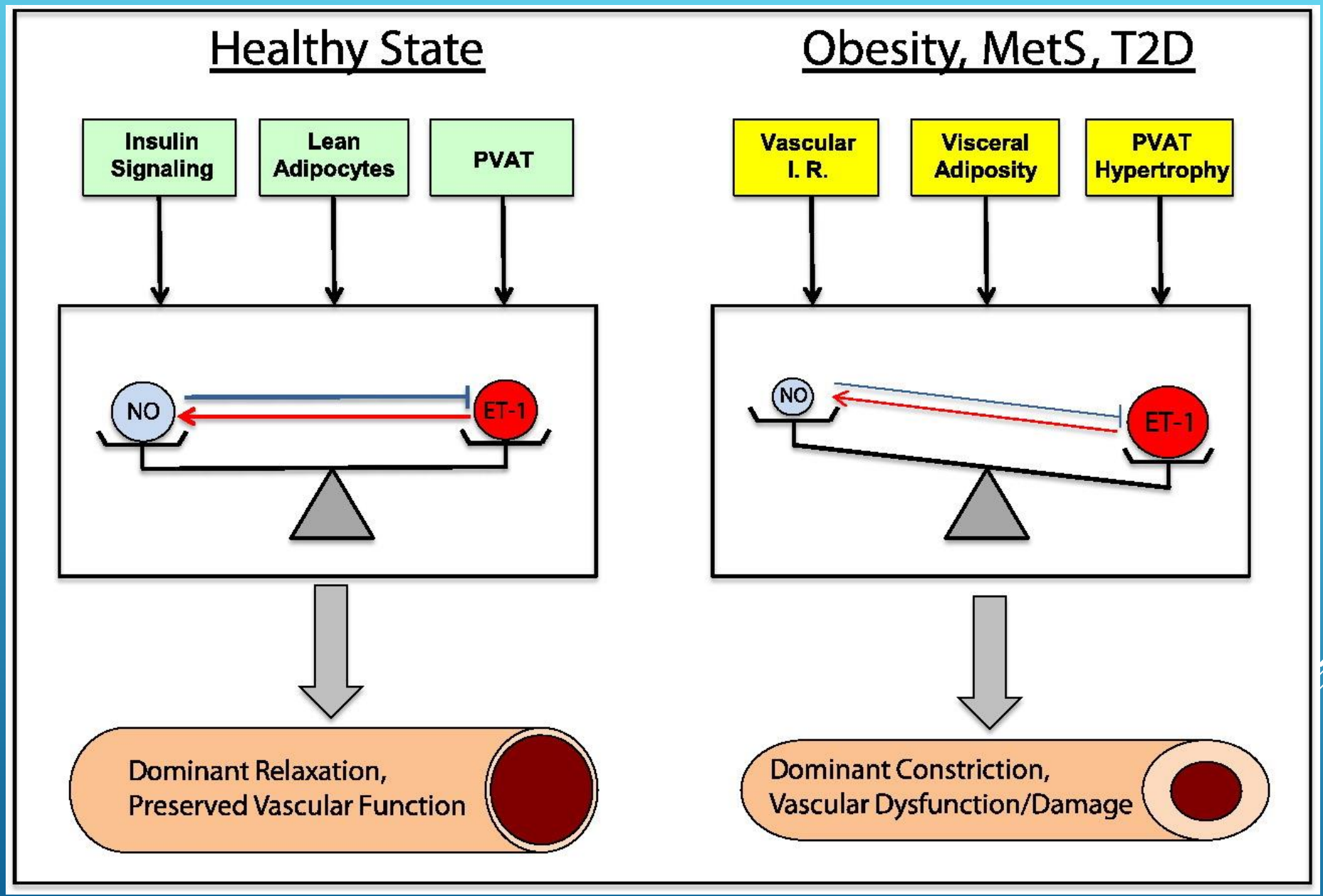
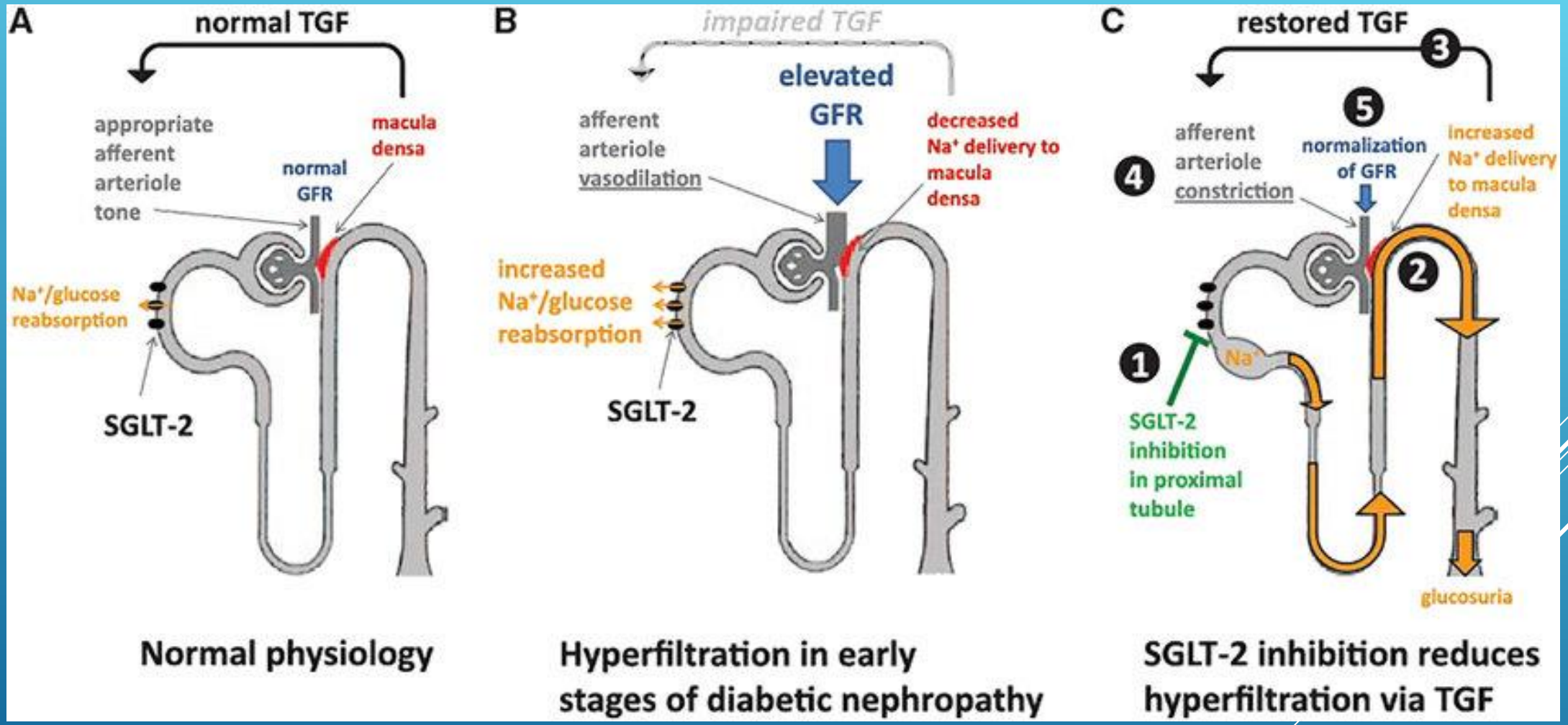
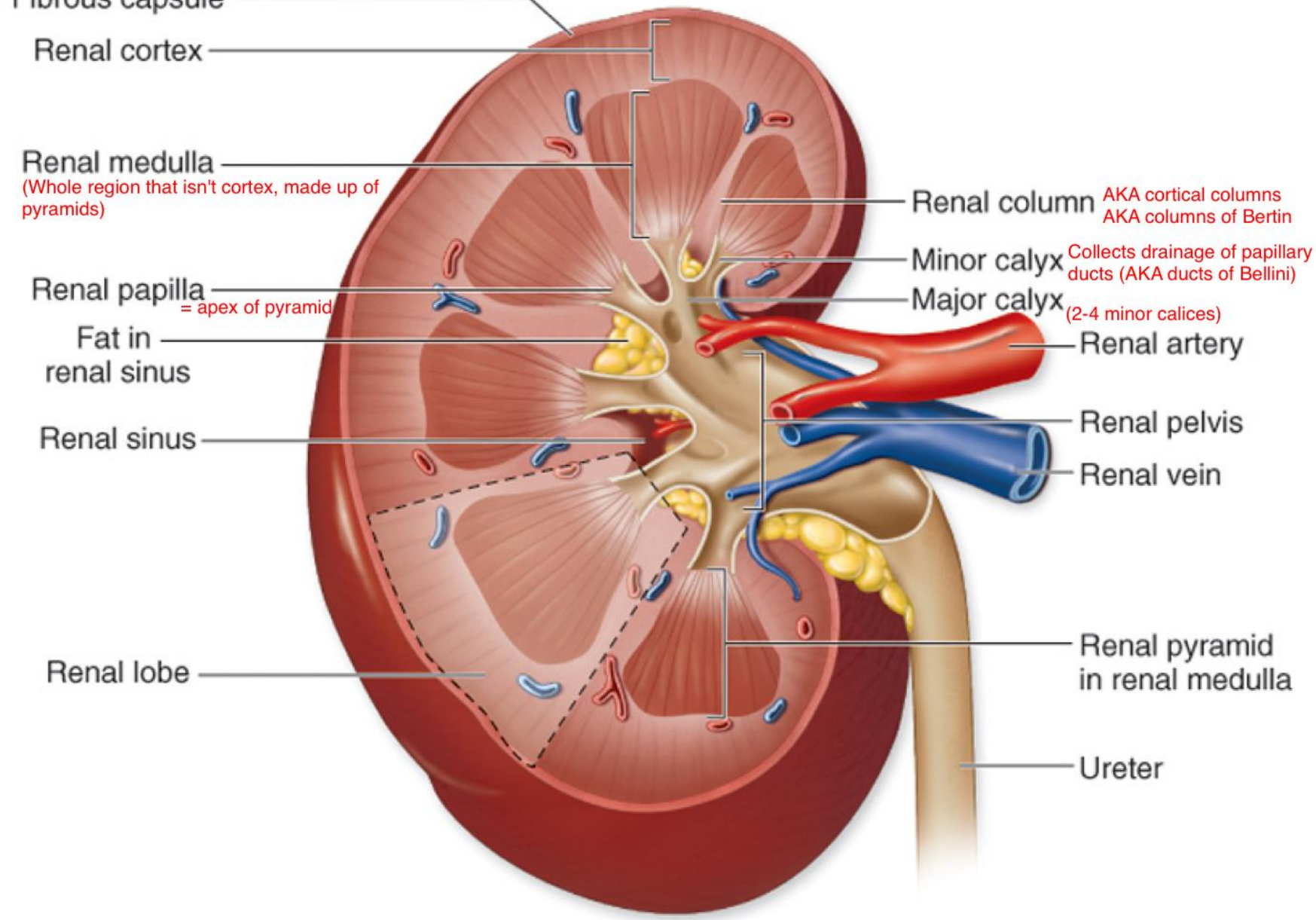

FAT
Fetuin-A↑
Insulin signaling↓
Subclinical inflammation↑
ß-cell function ↓

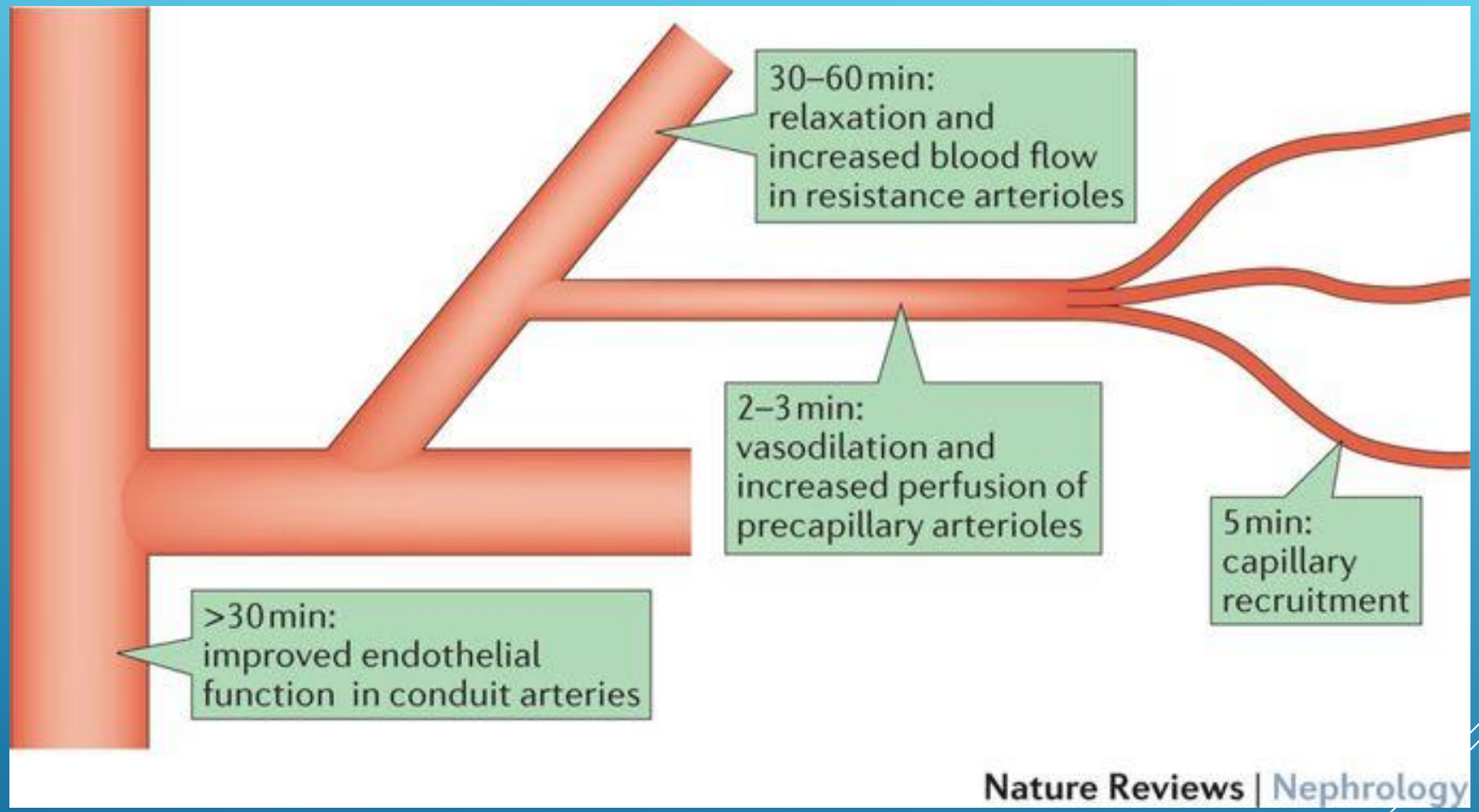

Leptin resistance
Leptin
Insulin resistance
Leptin Therapy
High Leptin
Normal Leptin
Leptin sensitivity
Obesity
Partrtial leptin reduction Therapy
Lean
Leptin sensitivity
Leptin
Insulin sensitivity


Healthy State
Obesity, MetS, T2D
Insulin Signaling
Lean Adipocytes
PVAT
Vascular I. R.
Visceral Adiposity
PVAT Hypertrophy
NO
ET-1
NO
ET-1
Dominant Relaxation, Preserved Vascular Function
Dominant Constriction, Vascular Dysfunction/Damage


A
normal TGF
appropriate afferent arteriole tone
normal GFR
macula densa
Na⁺/glucose reabsorption
SGLT-2
Normal physiology
B
impaired TGF
elevated GFR
afferent arteriole vasodilation
decreased Na⁺ delivery to macula densa
increased Na⁺/glucose reabsorption
SGLT-2
Hyperfiltration in early stages of diabetic nephropathy
C
restored TGF
3
5
afferent arteriole constriction
4
normalization of GFR
increased Na⁺ delivery to macula densa
2
1
Na⁺
SGLT-2 inhibition in proximal tubule
glucosuria
SGLT-2 inhibition reduces hyperfiltration via TGF



Right kidney, coronal section


30–60 min:
relaxation and
increased blood flow
in resistance arterioles
2–3 min:
vasodilation and
increased perfusion of
precapillary arterioles
5 min:
capillary
recruitment
>30 min:
improved endothelial
function in conduit arteries
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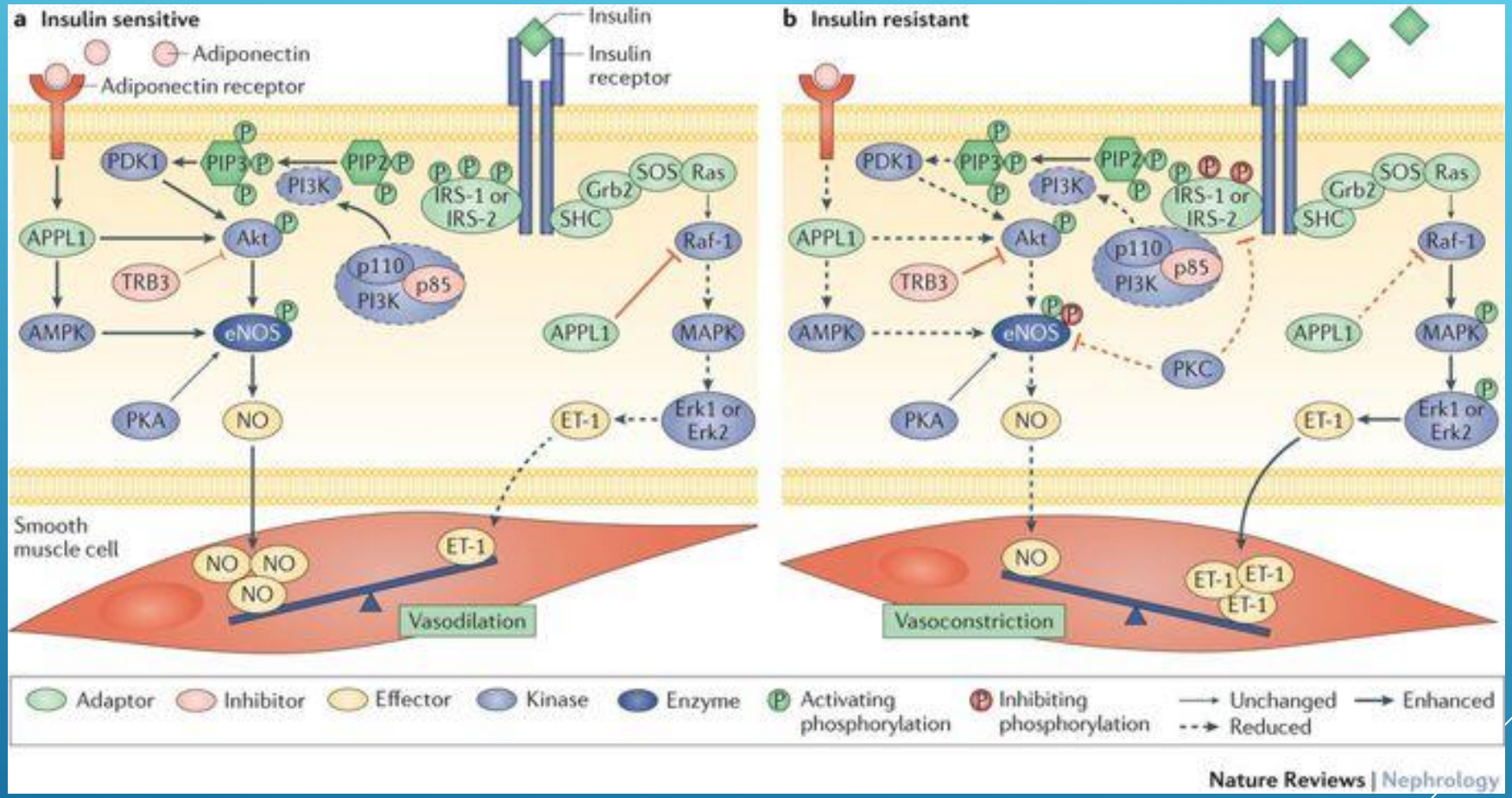
a Insulin sensitive
Adiponectin
Adiponectin receptor
Insulin
Insulin receptor
PDK1
PIP3
PIP2
PI3K
IRS-1 or IRS-2
Grb2
SOS
Ras
SHC
APPL1
Akt
TRB3
p110
p85
PI3K
Raf-1
AMPK
eNOS
APPL1
MAPK
PKA
NO
ET-1
Erk1 or Erk2
Smooth muscle cell
NO
NO
NO
ET-1
Vasodilation
b Insulin resistant
PDK1
PIP3
PIP2
PI3K
IRS-1 or IRS-2
Grb2
SOS
Ras
SHC
APPL1
Akt
TRB3
p110
p85
PI3K
Raf-1
AMPK
eNOS
PKC
APPL1
MAPK
PKA
NO
ET-1
Erk1 or Erk2
NO
ET-1
ET-1
ET-1
Vasoconstriction
Adaptor
Inhibitor
Effector
Kinase
Enzyme
Activating phosphorylation
Inhibiting phosphorylation
Unchanged
Reduced
Enhanced
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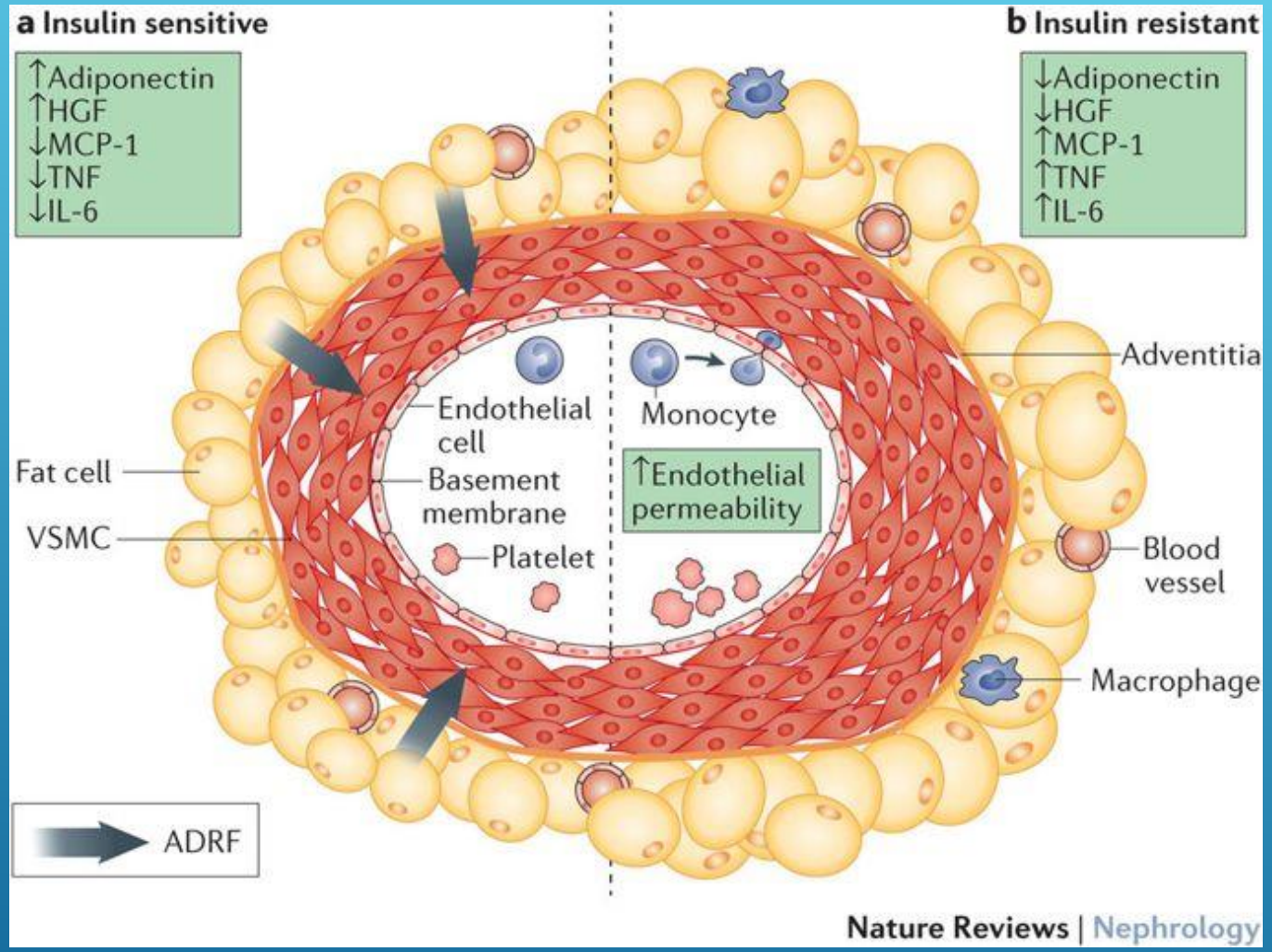
a Insulin sensitive
↑Adiponectin
↑HGF
↓MCP-1
↓TNF
↓IL-6
b Insulin resistant
↓Adiponectin
↓HGF
↑MCP-1
↑TNF
↑IL-6
Adventitia
Endothelial cell
Monocyte
Fat cell
Basement membrane
↑Endothelial permeability
VSMC
Platelet
Blood vessel
Macrophage
ADRF
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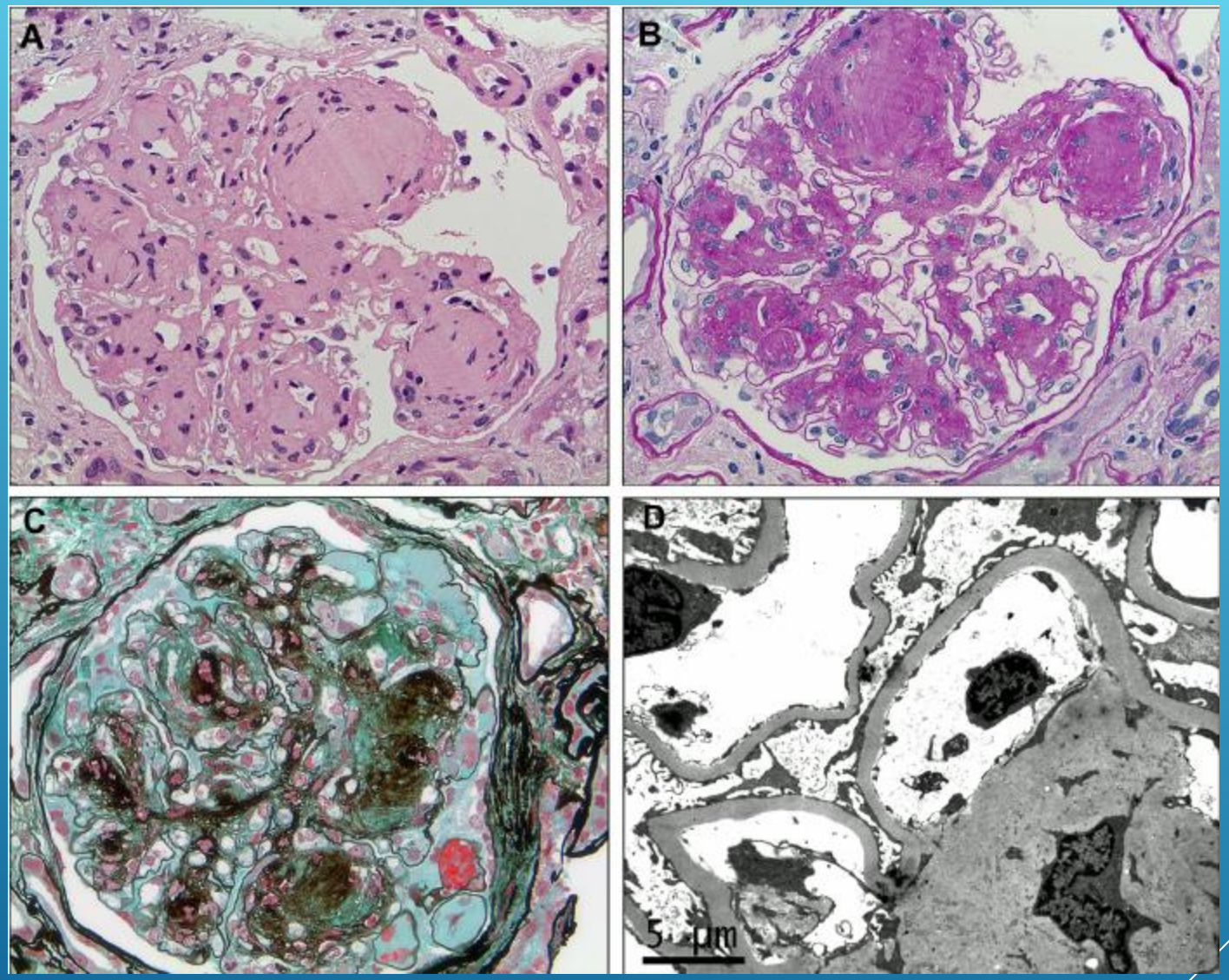
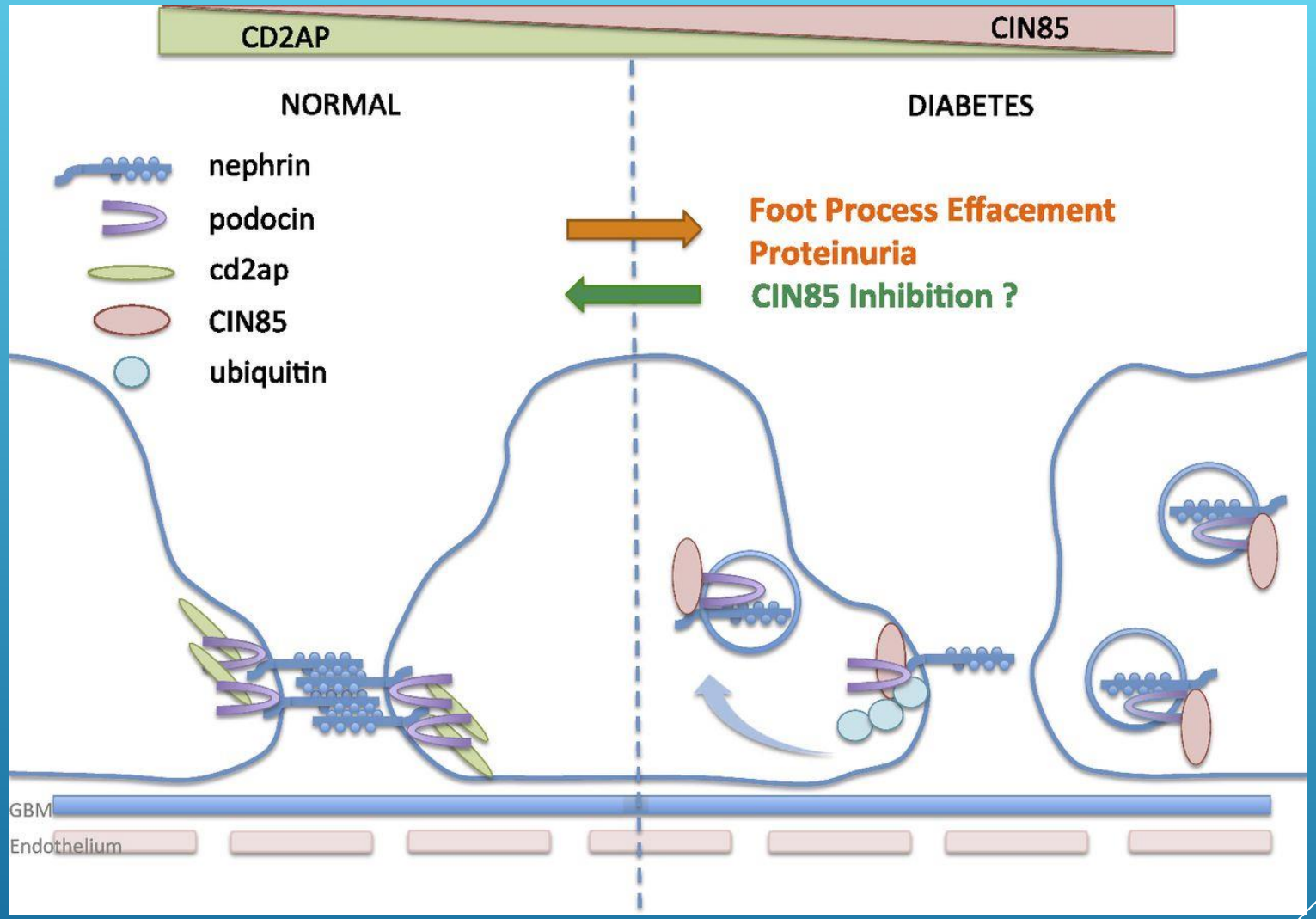
PVAT quantity around the renal sinus was associated with increased risks of hypertension, increased albumin excretion rate and CKD

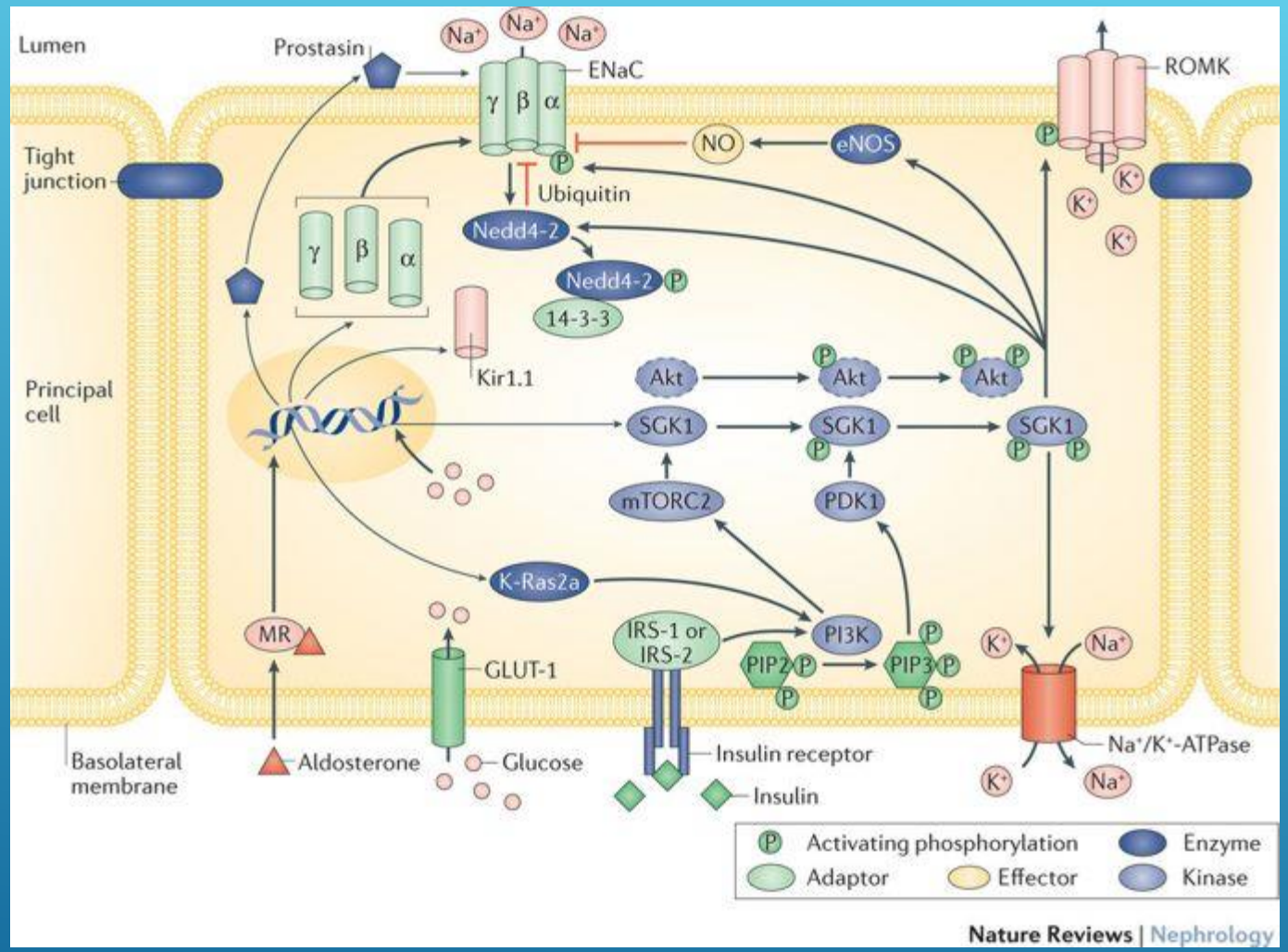
REDUCED INSULIN SIGNALLING IN MESANGIAL CELLS COULD CONTRIBUTE TO MESANGIAL CELL HYPERTROPHY, PROLIFERATION AND MATRIX DEPOSITION OF FIBRONECTIN AND COLLAGEN IV.

IMPAIRED INSULIN SIGNALLING IN MESANGIAL CELLS MIGHT BE ASSOCIATED WITH REDUCED GFR, AS SHOWN IN A CROSS-SECTIONAL STUDY OF 670 INDIVIDUALS THAT INVESTIGATED THE EFFECTS OF THE GLY972ARG VARIANT OF IRS1


A
B
C
D
5 µm


CD2AP
CIN85
NORMAL
DIABETES
nephrin
podocin
cd2ap
CIN85
ubiquitin
Foot Process Effacement
Proteinuria
CIN85 Inhibition ?
GBM
Endothelium

PODOCYTE-SPECIFIC DELETION OF THE INSULIN RECEPTOR DEVELOPED ALBUMINURIA, GLOMERULOSCLEROSIS AND MESANGIAL EXPANSION


Lumen
Prostasin
Na+
Na+
Na+
ENaC
γ β α
ROMK
Tight junction
NO
eNOS
P
Ubiquitin
K+
K+
K+
Nedd4-2
γ β α
Nedd4-2 P
14-3-3
Kir1.1
Principal cell
Akt
Akt
Akt
SGK1
SGK1
SGK1
mTORC2
PDK1
K-Ras2a
MR
GLUT-1
IRS-1 or IRS-2
PI3K
PIP2
PIP3
K+
Na+
Na+/K+-ATPase
Basolateral membrane
Aldosterone
Glucose
Insulin receptor
Insulin
P Activating phosphorylation
Enzyme
Adaptor
Effector
Kinase
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PROXIMAL TUBULE

Glucose reabsorption is increased in patients with T2DM, suggesting that SGLT2 upregulation is not affected by insulin-resistance in this disease.

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DISTAL TUBULE

INSULIN ACTS AS AN ANTINATRIURETIC HORMONE

Renal gluconeogenesis

In patients with T2DM, both renal and hepatic gluconeogenesis are increased and contribute to hyperglycaemia during the fasting state

Reduced IRS-1 expression might be responsible for reserved disinhibition of gluconeogenesis and reduced NO production, whereas preserved IRS-2 expression seems to maintain stimulation of sodium transport in the proximal tubule.

CKD itself, rather than the underlying specific disease process, was driving the systemic insulin resistance .

compared to early stages (e.g., CKD stage 1 and 2), insulin sensitivity measures were more reduced in patients with CKD stage 3.