August 28, 2014

Semmelweis University

The 21st Budapest Nephrology School

The Kidney and Metabolism

Division of nephrology, Endocrinology and Vascular Medicine
Tohoku University School of Medicine

Sadayoshi Ito

Case：46 years old, female

CC：Repetitive urinary tract uric acid stone

Hyperuricemia: Non, present and past

Physical Ex: Hypertension（150/100mmHg）
Moderate obesity

・Recommended to take a plenty of water

(Kamel KS, et al: *Q J Med* 98; 57-68, 2005)

24 Hr urine analysis

GFR, concentration: Normal

	Controls	Patient
pH	6.0±0.2	5.6
Volume (l/day)	1.3±0.1	2.6
Total urate (mg/day)	565±25	600

Why, repeated uric acid stone?

Data represent means ±SEM for the controls (13 males and 4 females).

(Kamel KS, et al: *Q J Med* 98; 57-68, 2005)

Nucleic acids $\xrightarrow{\text{Uricase}}$ Uric acid $\longrightarrow$ allantoin

～10mg/1kg, 600mg/day （60kg）

$H^+ + Urate^-$ $\rightleftharpoons$ Uric acid

P_K 5.35

Saturation of UA ～200mg/l

Urine pH, urine volume and uric acid concentration

600	5.6	2.6	
Total urate (mg/day)	**Urine pH**	**Urine volume (l/day)**	**Uric acid (mg/l)**
600	5.3	1	300
600	5.3	3	100
600	6.0	1	100
600	6.0	0.6	167

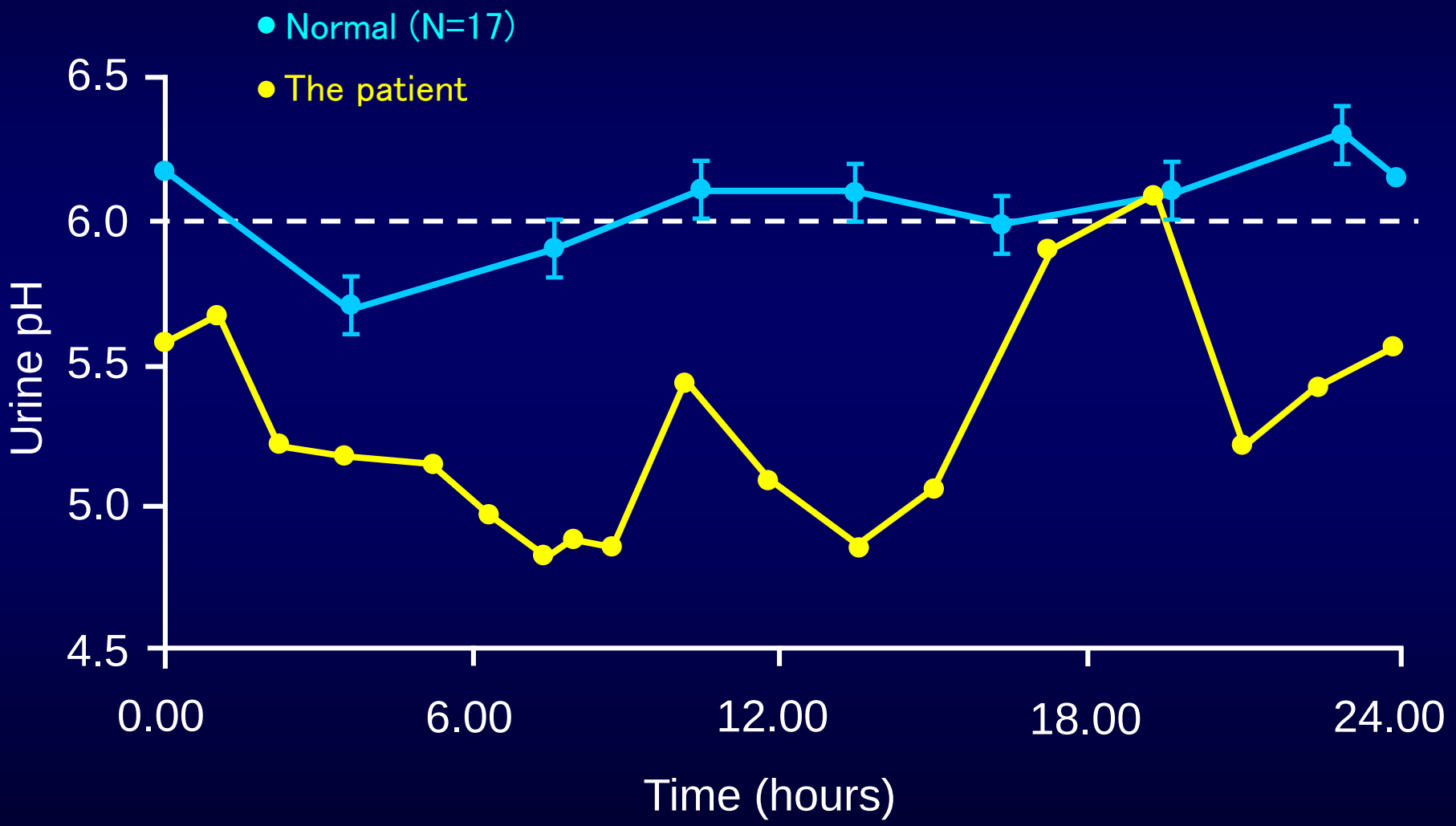
This table is provided to illustrate the effects of the urine volume and the urine pH on the uric acid concentration when the total urate excretion rate is 600mg/day.

(Kamel KS, et al: *Q J Med* 98; 57-68, 2005)

Why uric acid stone

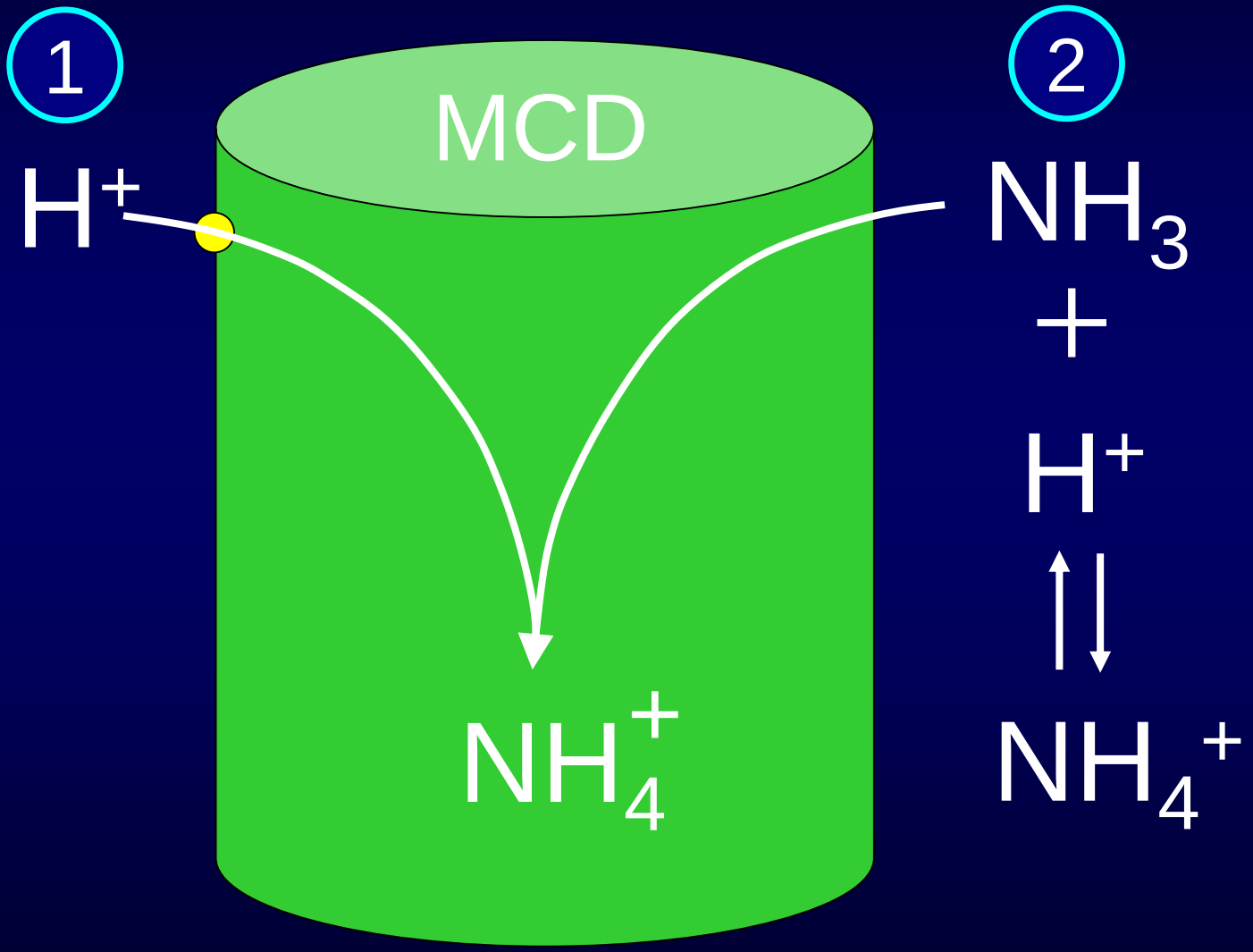
- pH: OK
- Urine volume: OK
- Diurnal variations

Diurnal changes in Urine pH



(Kamel KS, et al: *Q J Med* 98; 57-68, 2005)

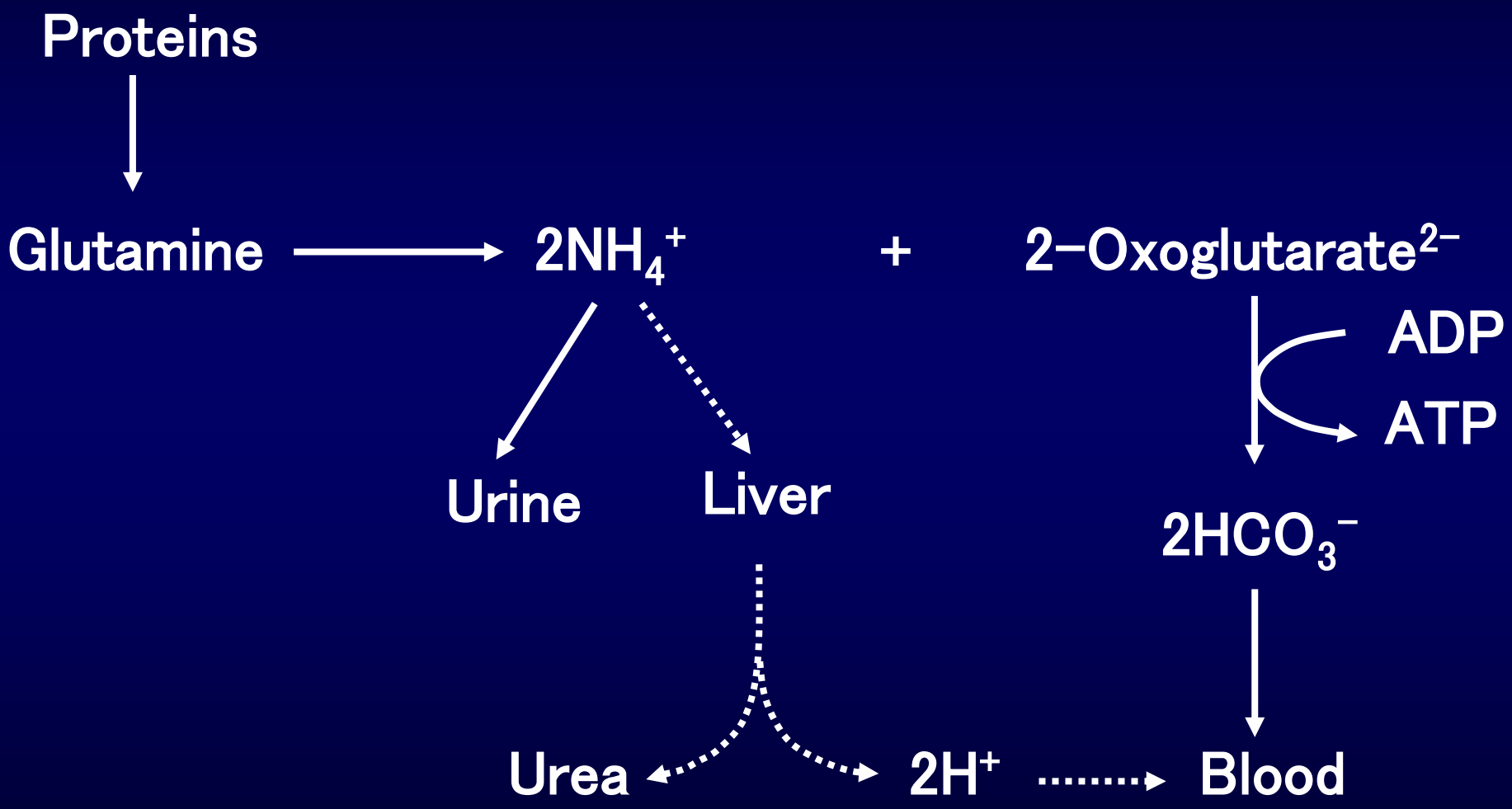
Urine pH is determined by H^+ and NH3

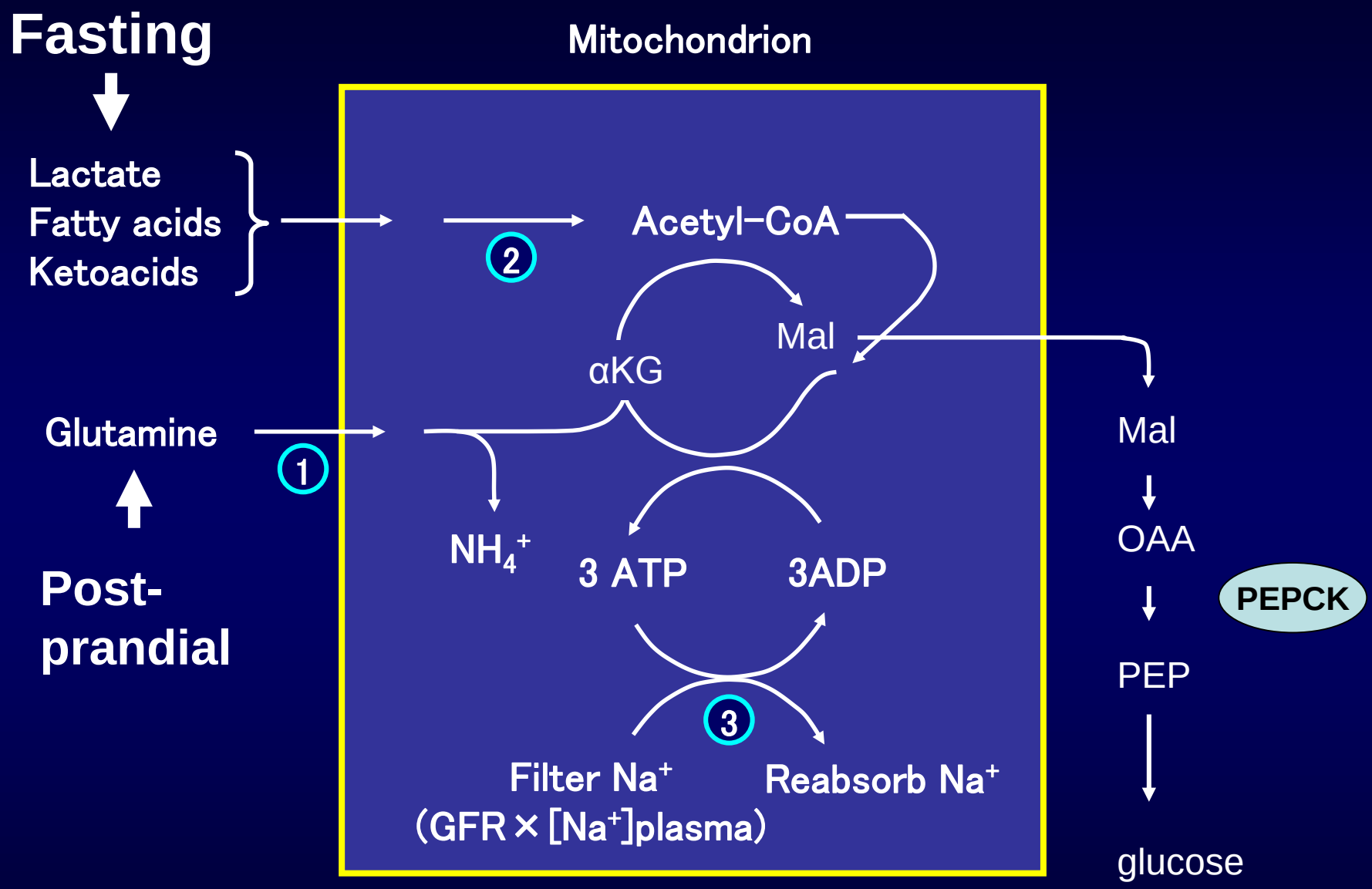


(Kamel KS, et al: *Q J Med* 98; 57-68, 2005)

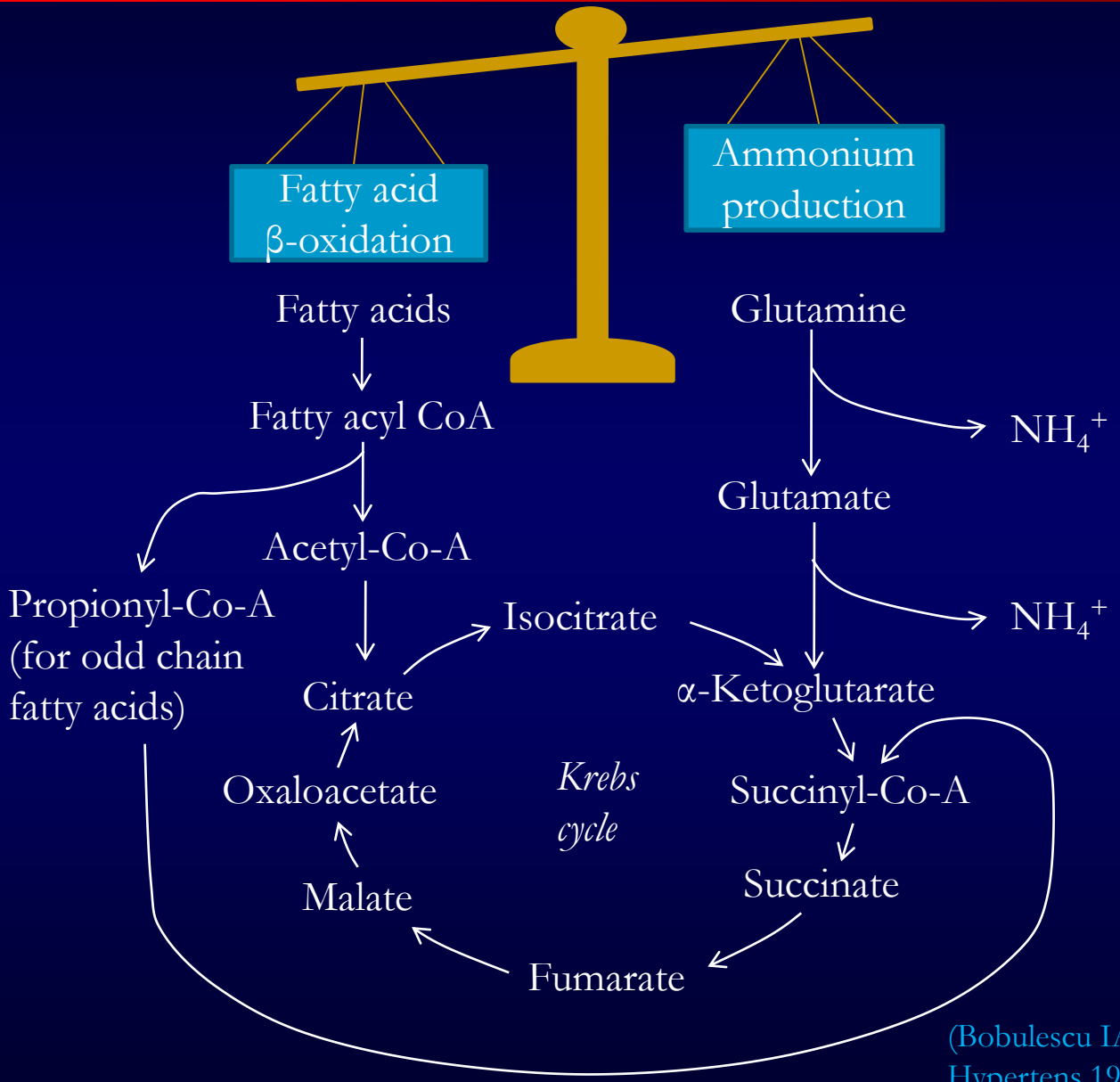
Relative underproduction of NH_3

Ammonium production




Fasting
Mitochondrion
Lactate
Fatty acids
Ketoacids
Acetyl-CoA
2
Mal
αKG
Glutamine
1
Mal
OAA
PEPCK
PEP
NH_4^+
3 ATP
3ADP
3
Filter Na^+
Reabsorb Na^+
(GFR × $[Na^+]$plasma)
glucose
Post-
prandial

Metabolic syndrome

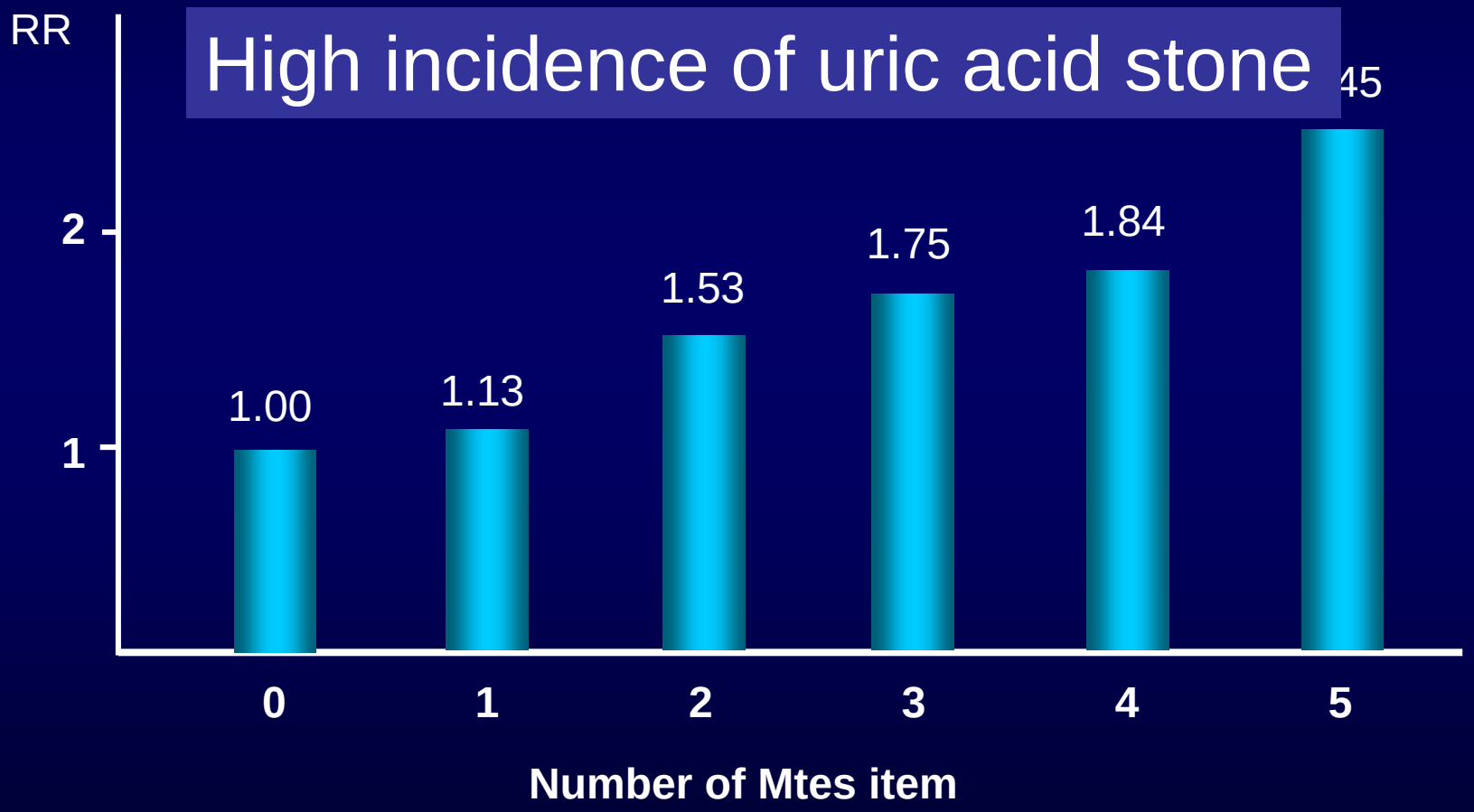


(Bobulescu IA: Curr Opin Nephrol Hypertens 19; 393-402, 2010)

Incidence of CKD

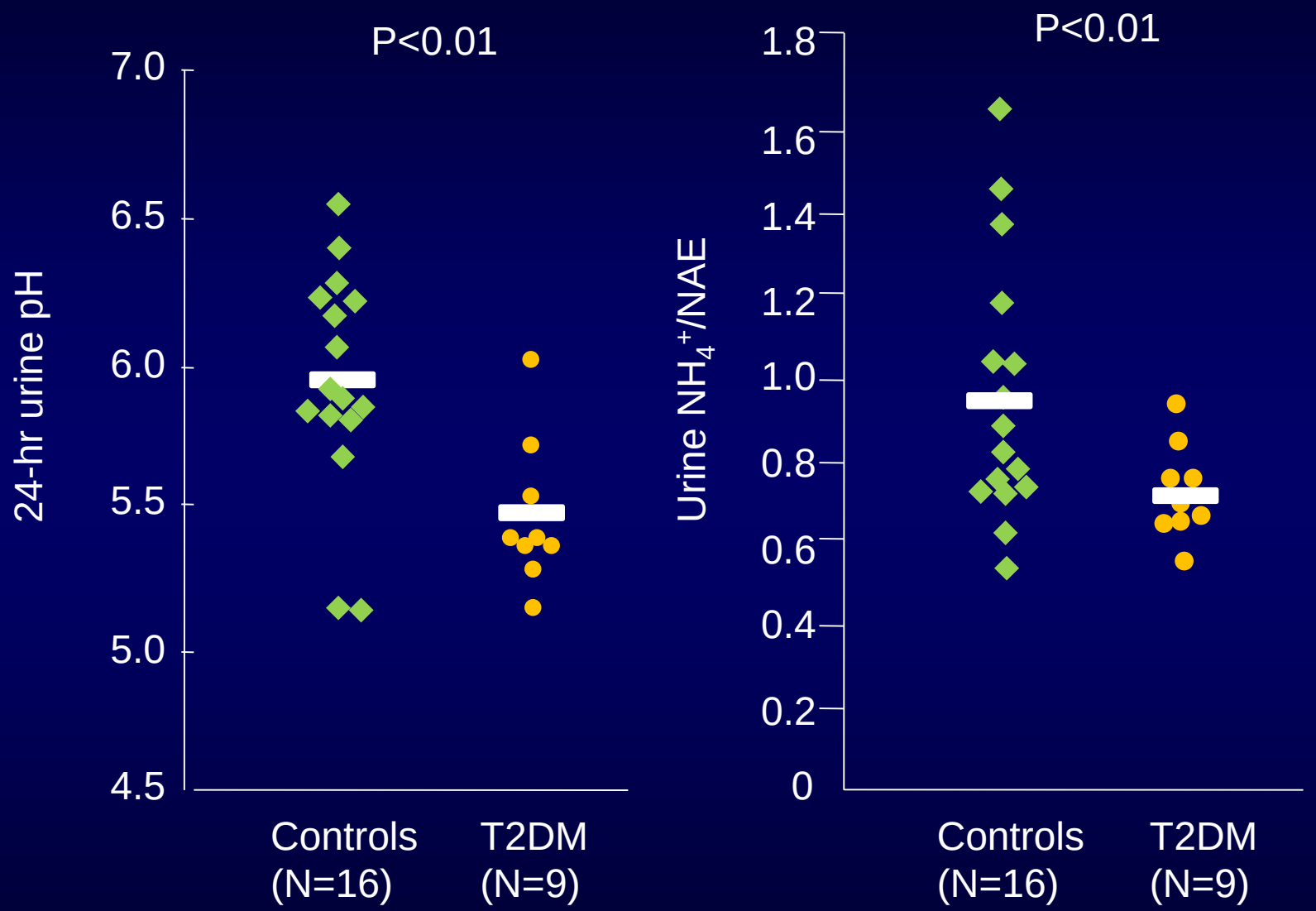
CKD : GFR<60ml/min/1.73m^2

ARIC



(Sedor JR, et al: *J Am Soc Nephrol* 16; 1880-1882, 2005)

Urine pH and ammonium production



Proportion of NAE excreted as ammonium (NH_4^+/NAE) in nine volunteers with type 2 diabetes (T2DM; ●) and 16 age- and BMI-matched volunteers without type 2 diabetes (Controls; ♦) evaluated while consuming a fixed metabolic diet. Horizontal bars indicate means for each group. NH_4^+/NAE was significantly lower in patients with type 2 diabetes than in control subjects (0.70 ± 0.12 *versus* 0.94 ± 0.36; $P < 0.01$). Results represent the mean of two 24-hour urine collections for each participant

(Maalouf NM, CJASN 5; 1277-1281, 2010)

Predictors of stage 3 CKD by Cox regression analysis（health chek-up、n＝1,811）

Variables	Univariate Cox regression analysis		Multiple Cox regression analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age, per 10 years	1.87 (1.74–2.00)	<0.0001	1.81 (1.67–1.96)	<0.0001
Male, yes	1.11 (0.95–1.30)	0.1815	0.76 (0.61–0.95)	0.0151
Smoking, yes	0.74 (0.60–0.92)	0.0059	0.88 (0.68–1.12)	0.3142
Alcohol, yes	0.91 (0.77–1.06)	0.2217	0.85 (0.71–1.01)	0.0609
BMI, per 1.0 increase	1.07 (1.05–1.10)	<0.0001	1.02 (0.99–1.06)	0.1185
SBP, per 10-mm Hg increase	1.15 (1.11–1.20)	<0.0001	0.99 (0.94–1.05)	0.8289
Fasting plasma glucose, per 1.0-mmol/l increase	1.11 (1.04–1.16)	0.0017	0.94 (0.86–1.02)	0.1317
Total cholesterol, per 1.0-mmol/l increase	1.29 (1.19–1.39)	<0.0001	1.02 (0.93–1.12)	0.7011
Uric acid, per 10.0-μmol/l increase	1.00 (1.00–1.01)	<0.0001	1.04 (1.03–1.05)	<0.0001
Total leukocyte count, % $\times 10^6$/l increase	1.02 (0.97–1.07)	0.4590	0.99 (0.93–1.05)	0.6981
CKD				
Stage 1 (reference)	1.0		1.0	
Stage 2	4.09 (2.89–5.26)	<0.0001	3.73 (2.62–4.91)	<0.0001
Proteinuria				
(-)or (±)(reference)	1.0		1.0	
(＋)	1.31 (0.92–1.80)	0.1342	1.33 (0.89–1.90)	0.1537
Urine pH				
5.0-5.5	1.26 (1.03–1.54)	0.0221	1.32 (1.06–1.65)	0.0129
6.0	1.03 (0.84–1.29)	0.7414	1.17 (0.93–1.49)	0.1895
6.5-7.0(reference)	1.0		1.0	

(Nakanishi N, et al: Kidney Blood Press Res 35; 77-81, 2012)

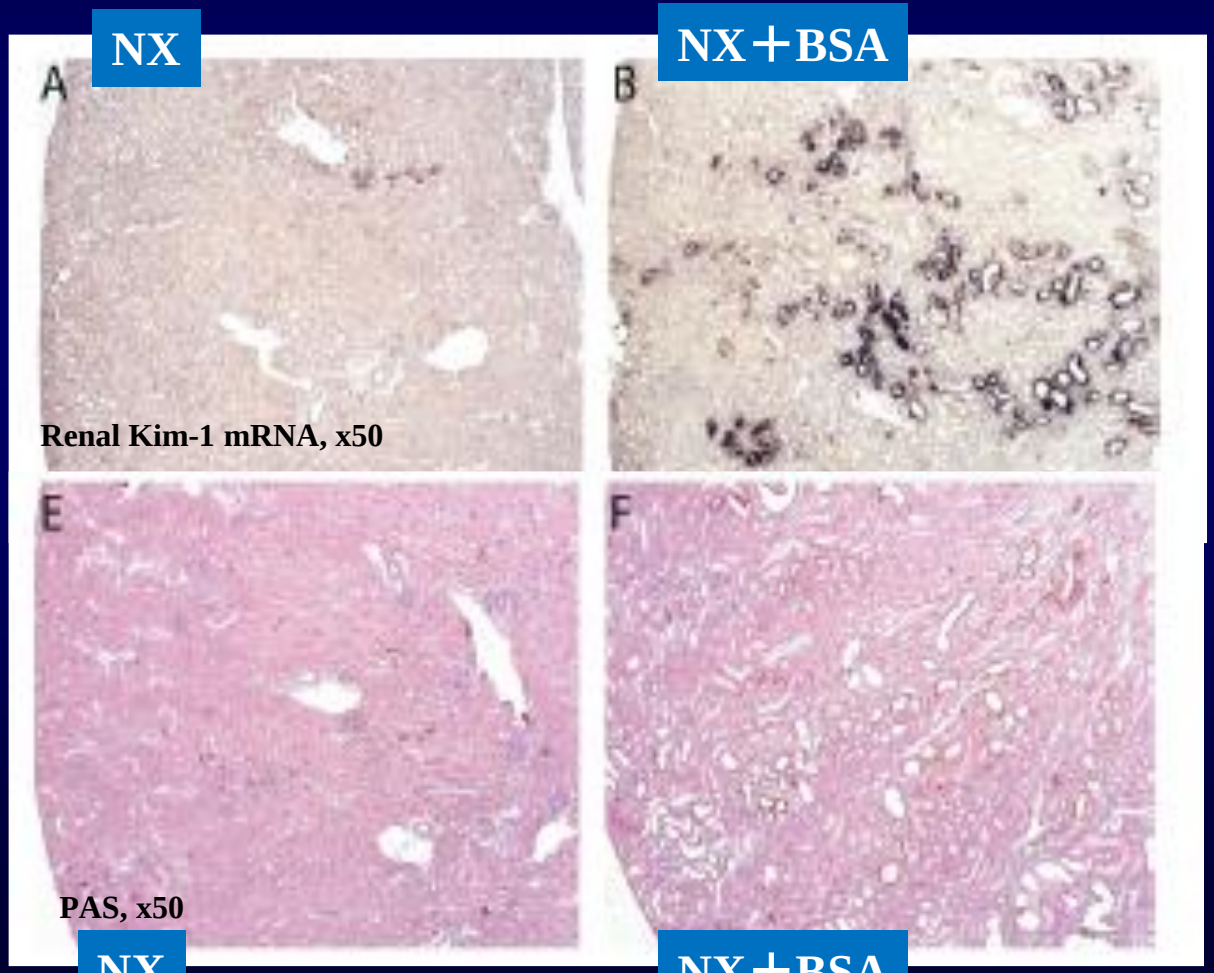
Tubular kidney injury molecule-1 in protein-overload nephropathy

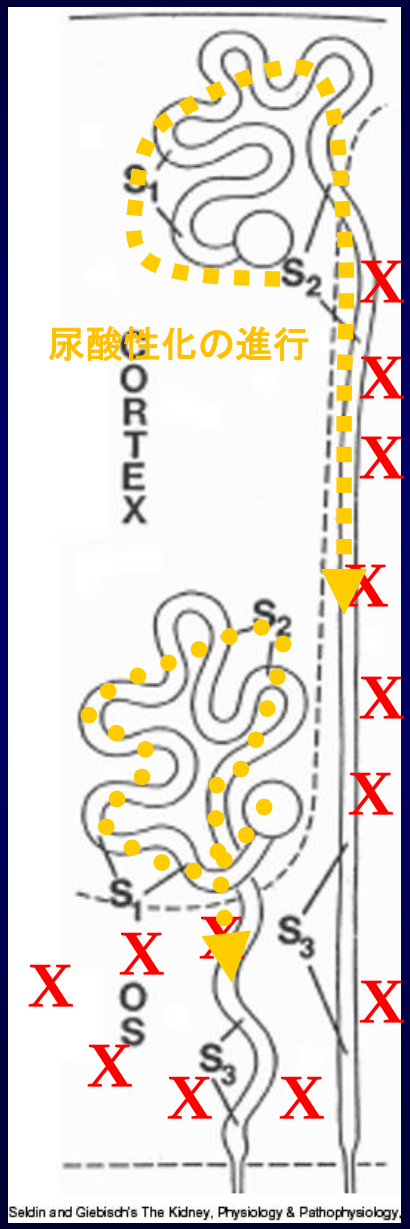
Mirjan M. van Timmeren, Stephan J. L. Bakker, Vishal S. Vaidya, Veronique Bailly,
Theo A. Schuurs, Jeffrey Damman, Coen A. Stegeman, Joseph V. Bonventre, and Harry van Goor

heminephrectomy＋2g BSA
Extending form medulla

→

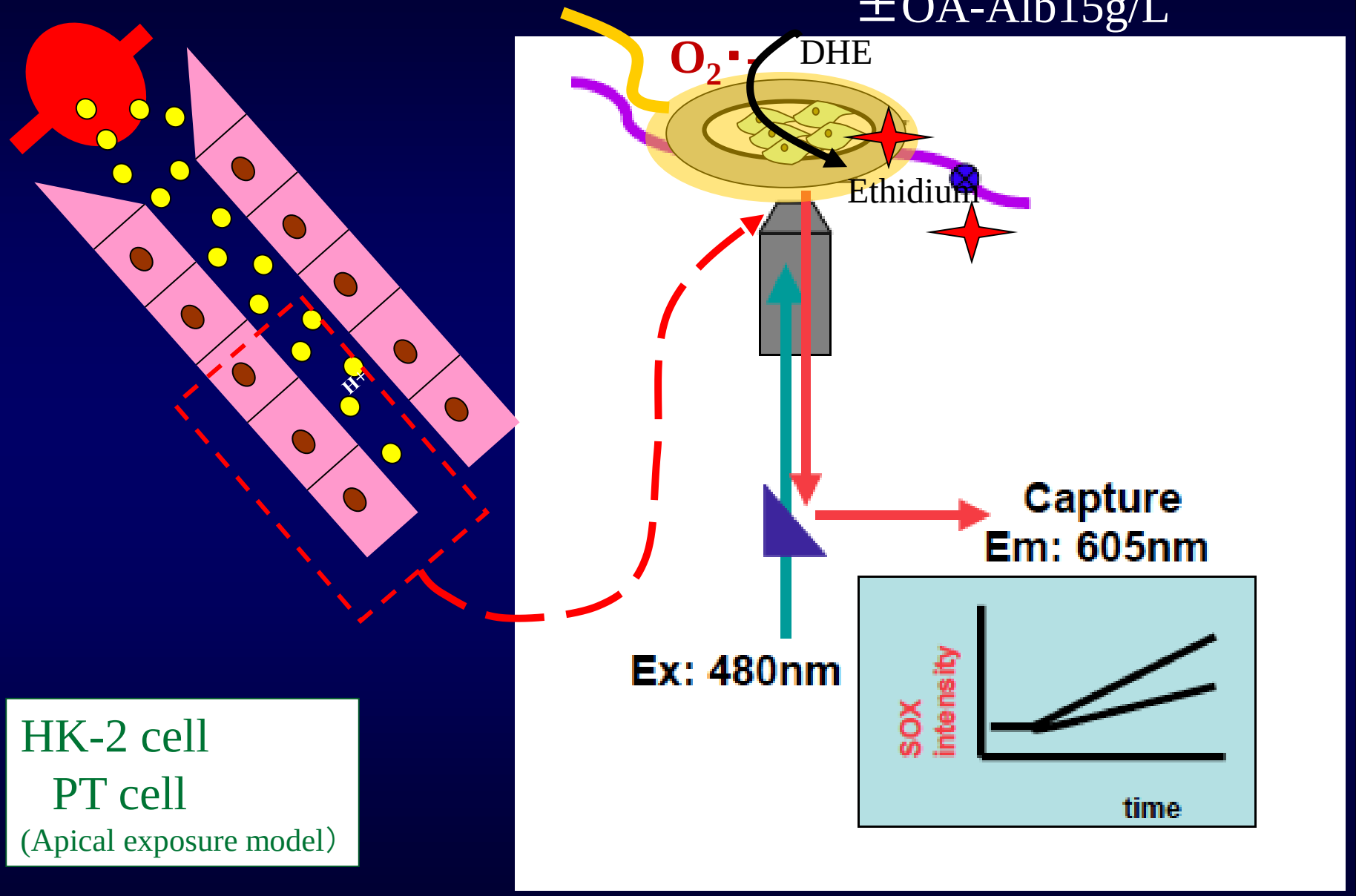
hypothesis：
Involvement of urine pH





Chamber pH：7.0, 6.6, 6.4, 6.0

±OA-Alb15g/L



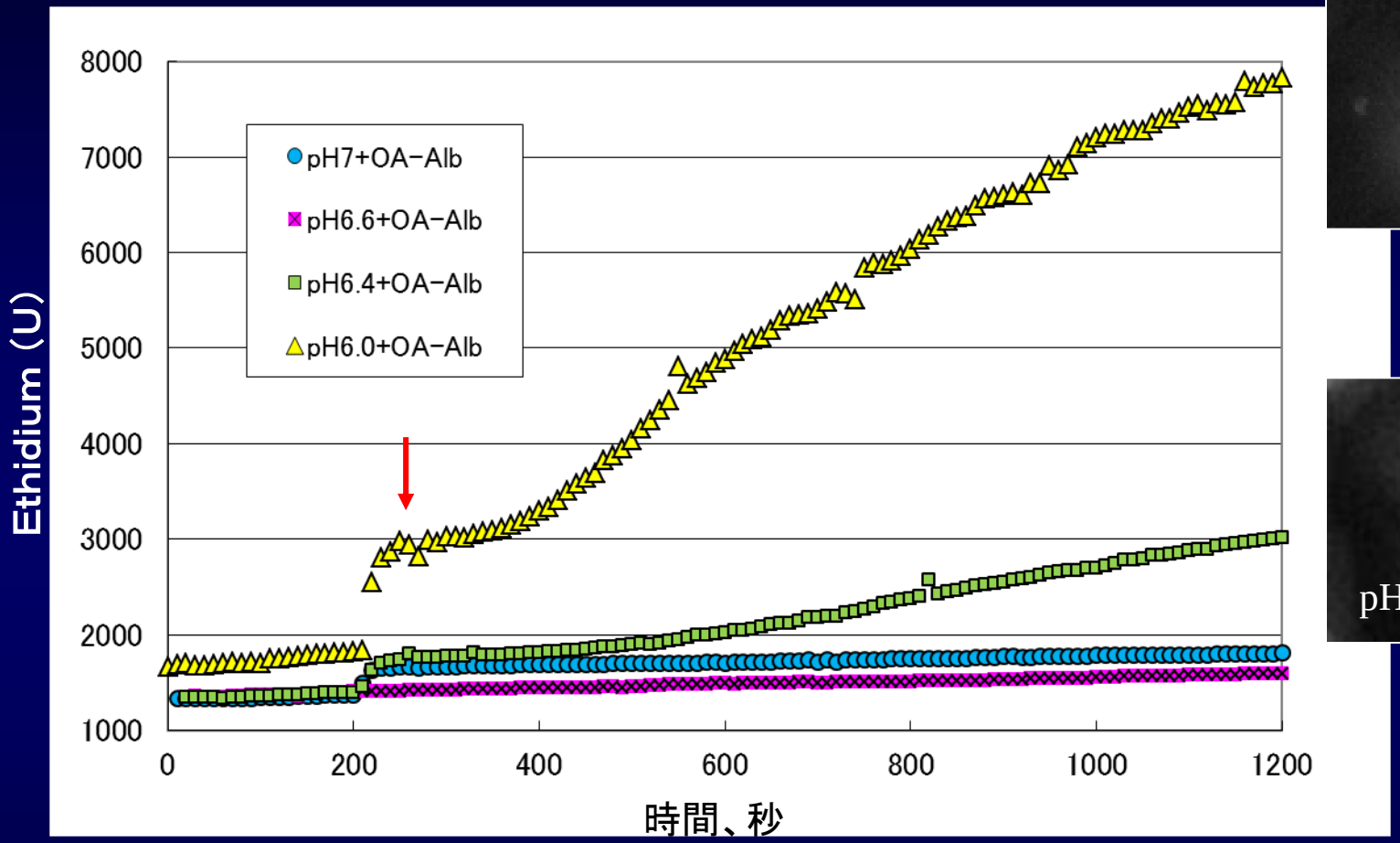
HK-2 cell

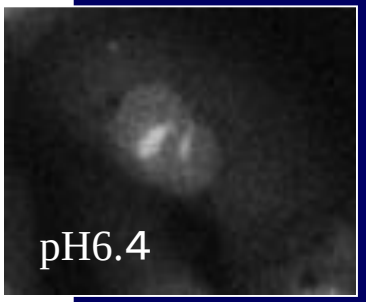
PT cell

(Apical exposure model)

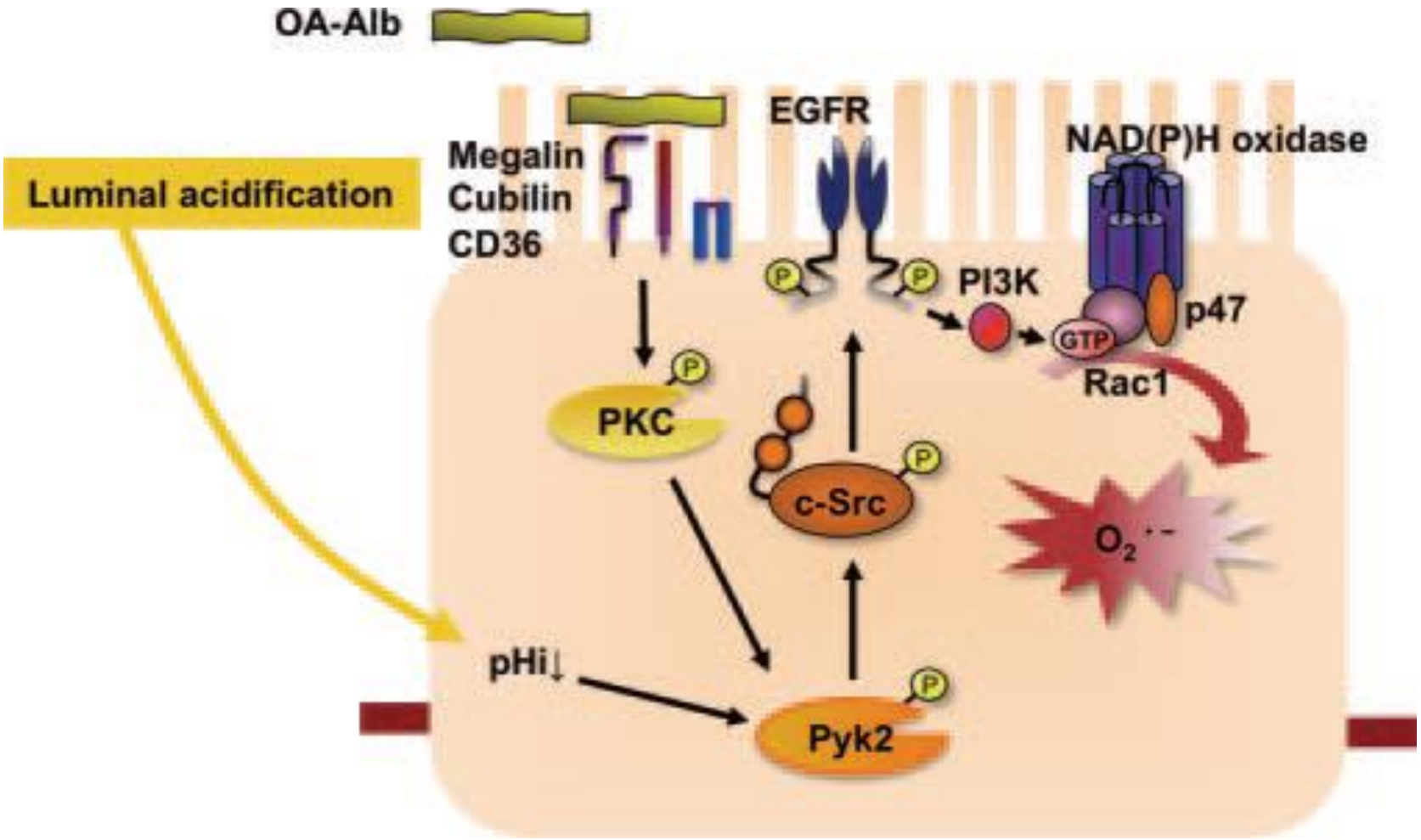
(Am J Physiol Renal Physiol. (2002) 283:F20-8.)

ROS generation by OA-Alb; influence of pHの





(Souma T, Abe M, et al: JASN 22:635-48, 2011)



Souma T, Abe M, et al: JASN 22:635-48, 2011

The Kidney and metabolism

- High energy expenditure（10% of basal metabolic rate）
- Gluconeogensis

Mechanisms and sources of glucose release into the circulation in the post-absorptive state

Overall rate［～μmol/(kg min)］	10
Hepatic contribution［～μmol/(kg min)］	7.5-8.0(75-80%)
Glycogenolysis ［～μmol/(kg min)］	4.5-5.0(45-50%)
Gluconeogenesis［～μmol/(kg min)］	2.5-3.0(25-30%)
Renal contribution ［～μmol/(kg min)］	2.0-2.5(20-25%)
Glycogenolysis［～μmol/(kg min)］	0
Gluconeogenesis［～μmol/(kg min)］	2.0-2.5(20-25%)

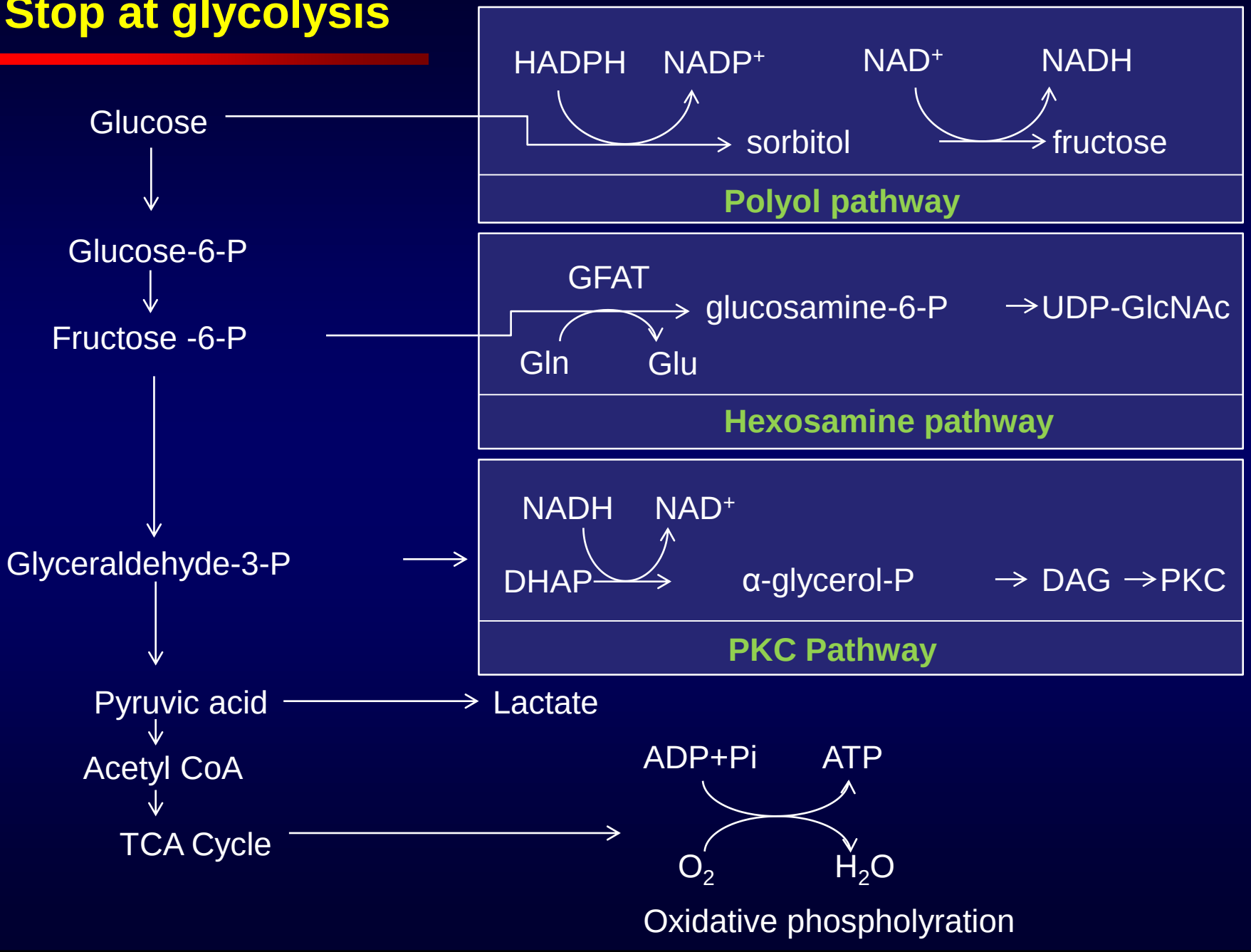
(Gerich JE: Diabet Med 27; 136-142, 2010)

Glucose utilization
（Medulla in the kidney）

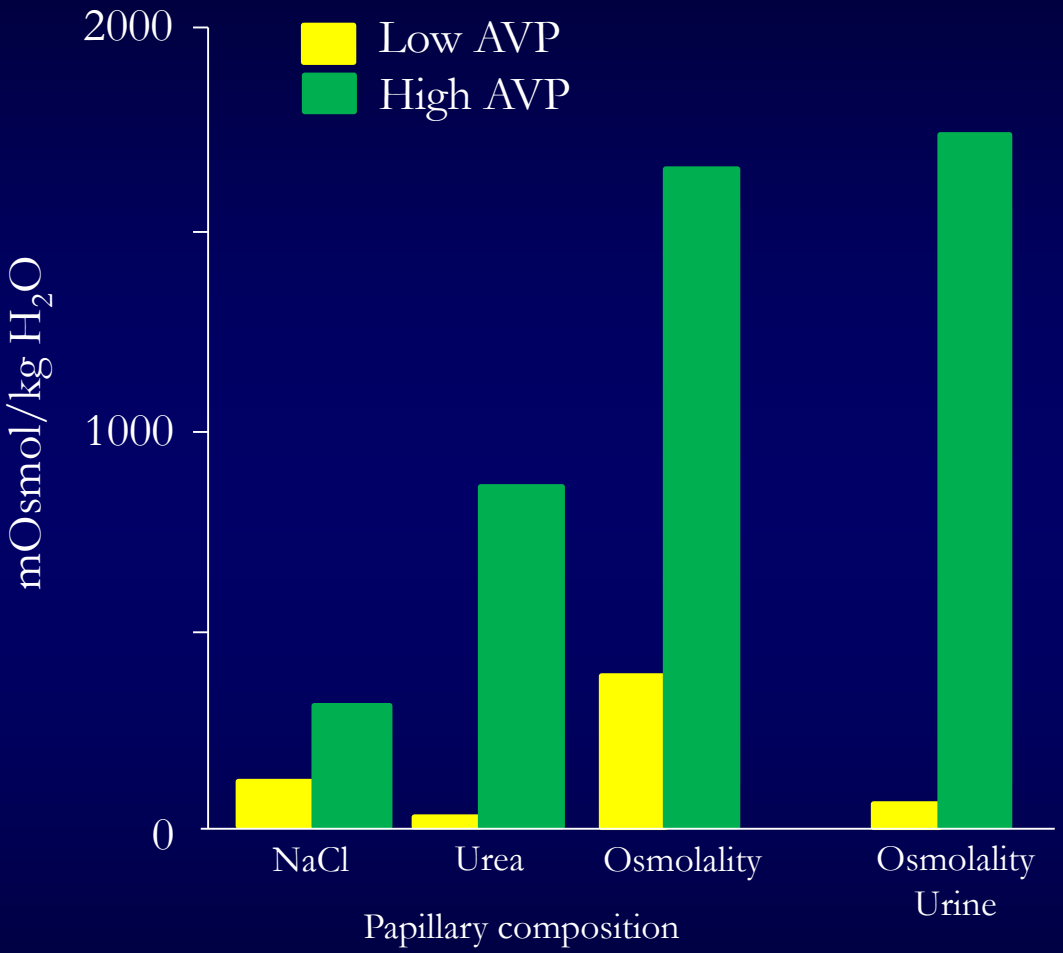
Tissue/organ	Post-absorptive state, ～11.1 μmol/(kg min) (mainly insulin-independent) % of total	Postprandial state, ～55 μmol/(kg min) (mainly insulin-stimulated) % of total
Brain	40-45	～10
Muscle	15-20	30-35
Liver	10-15	25-30
Gastrointerstinal (GI) tract	5-10	10-15
Kidney	5-10	10-15
Other (e.g. skin, blood cells)	5-10	5-10

(Gerich JE: Diabet Med 27; 136-142, 2010)

Stop at glycolysis



Huge variations in osmolality



AVP, arginine vasopressin

(Levitin H, et al: J Clin Invest 41; 1145-1151, 1962)

Driving force for water reabsorption via residual water permeability in the inner MCD during water diuresis

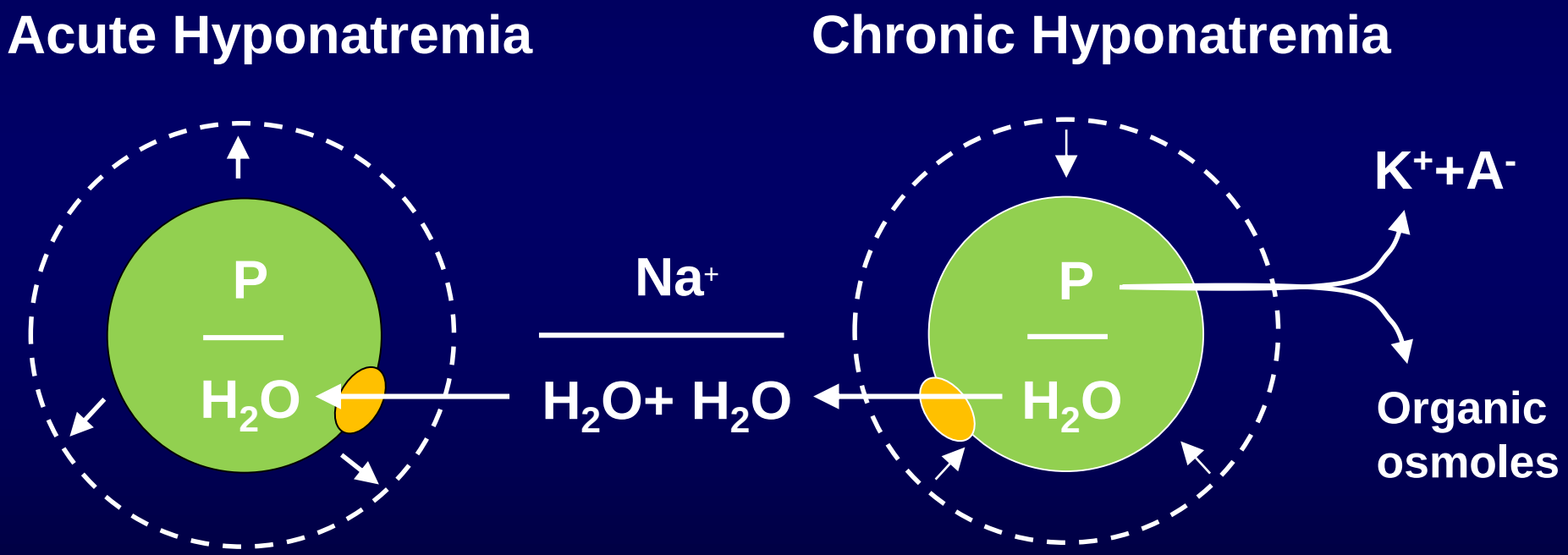
Condition	Interstitial osmolality mosm/l	Lumen osmolality mosm/l	Driving force mmHg
Vasopressin actions	900	~900	~0
No vasopressin actions	450	~50	~8,000

The major factors that influence the reabsorption of water are the small degree of permeability of the inner MCD to water and the large osmotic driving force to draw water from its lumen (i.e., the difference in osmolality between the interstitial compartment and the lumen of the inner medullary collecting duct multiplied by 19.3, the number of mmHg per mosm/l). Note that the osmotic driving force is enormous (shown in bold)

1mOsm = 20mmHg

(Halperin ML, et al: Nephron Physiol 114; 11-17, 2010)

Cellar responses to osmotic changes



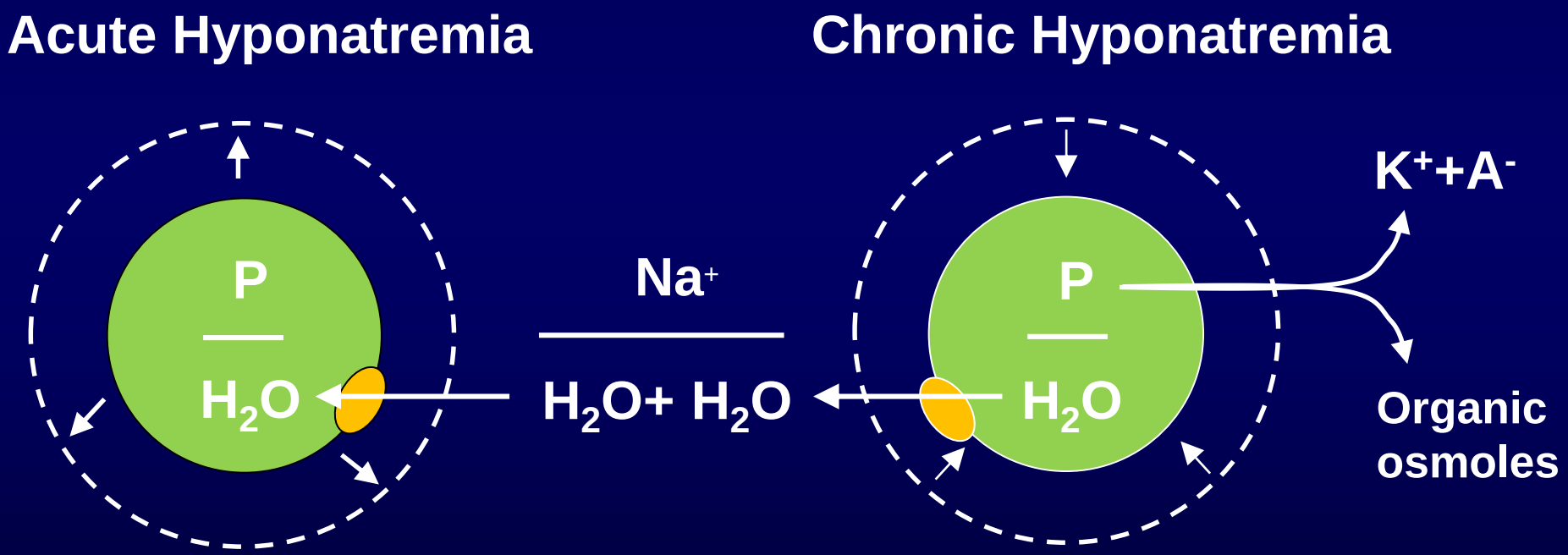
(Lin S.-H. et al: *Q J Med* 96; 935-947, 2003)

Effective osmotic substances

Intracelluar		Extracellar	
K^+	140	Na^+	140
Mg^{2+}	20	Cl^-	108
Na^+	14	HCO_3^-	24
Urea	5	Glucose	5
HCO_3^-	10	Urea	5
Cl^-	4	K^+	4
Othes		Others	

（Unit mOsm/kg H_2O）

Cellar responses to osmotic changes



(Lin S.-H. et al: *Q J Med* 96; 935-947, 2003)

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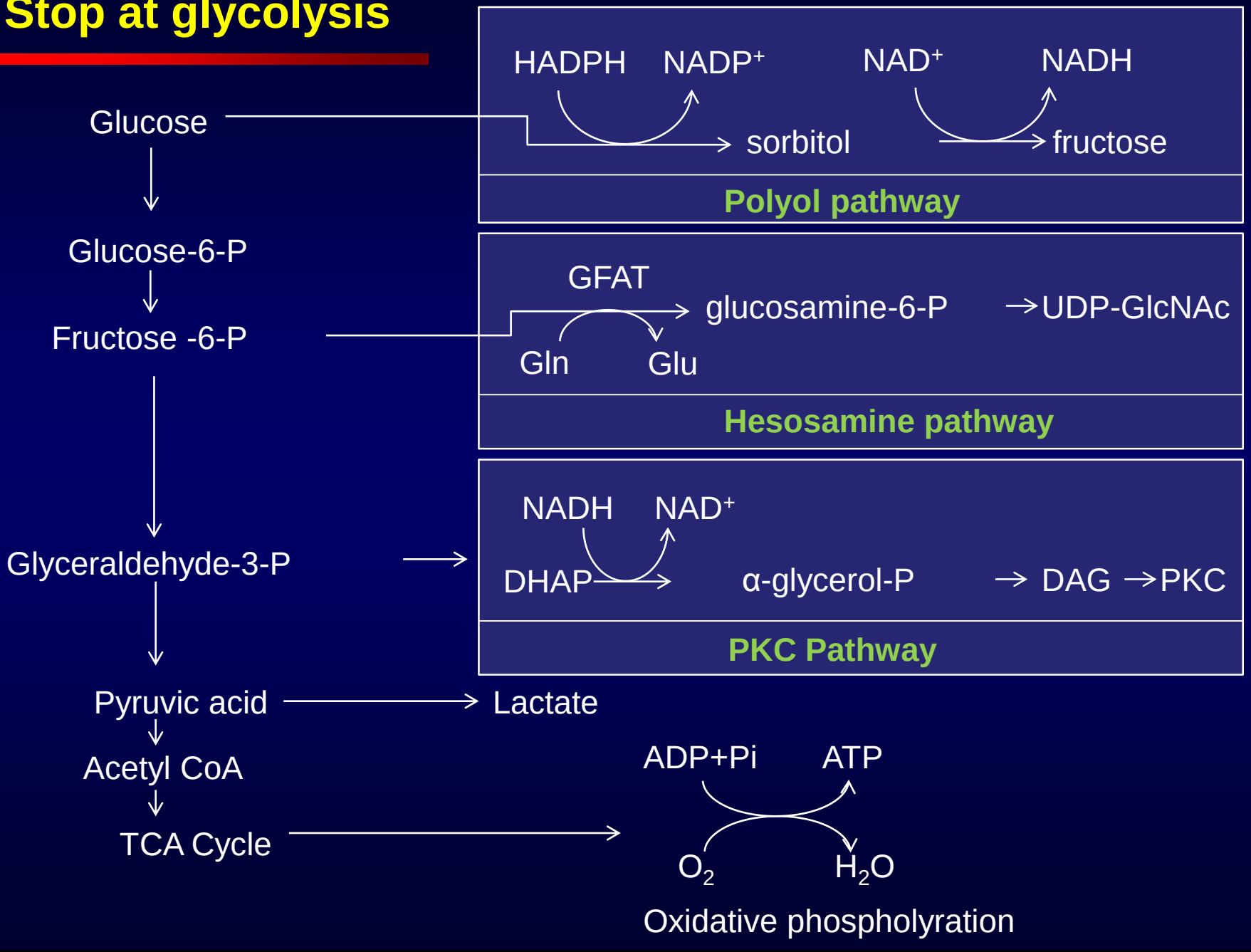
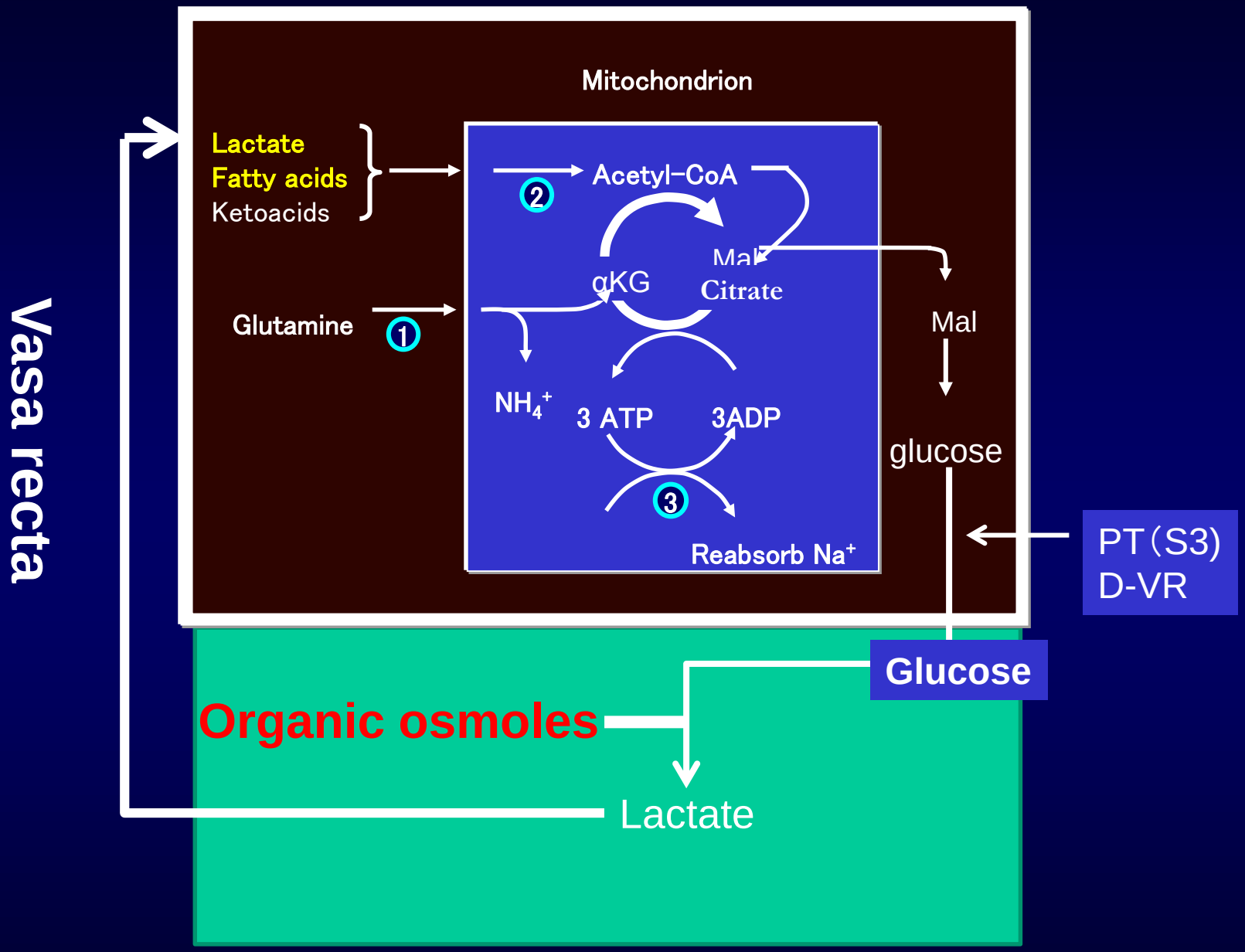
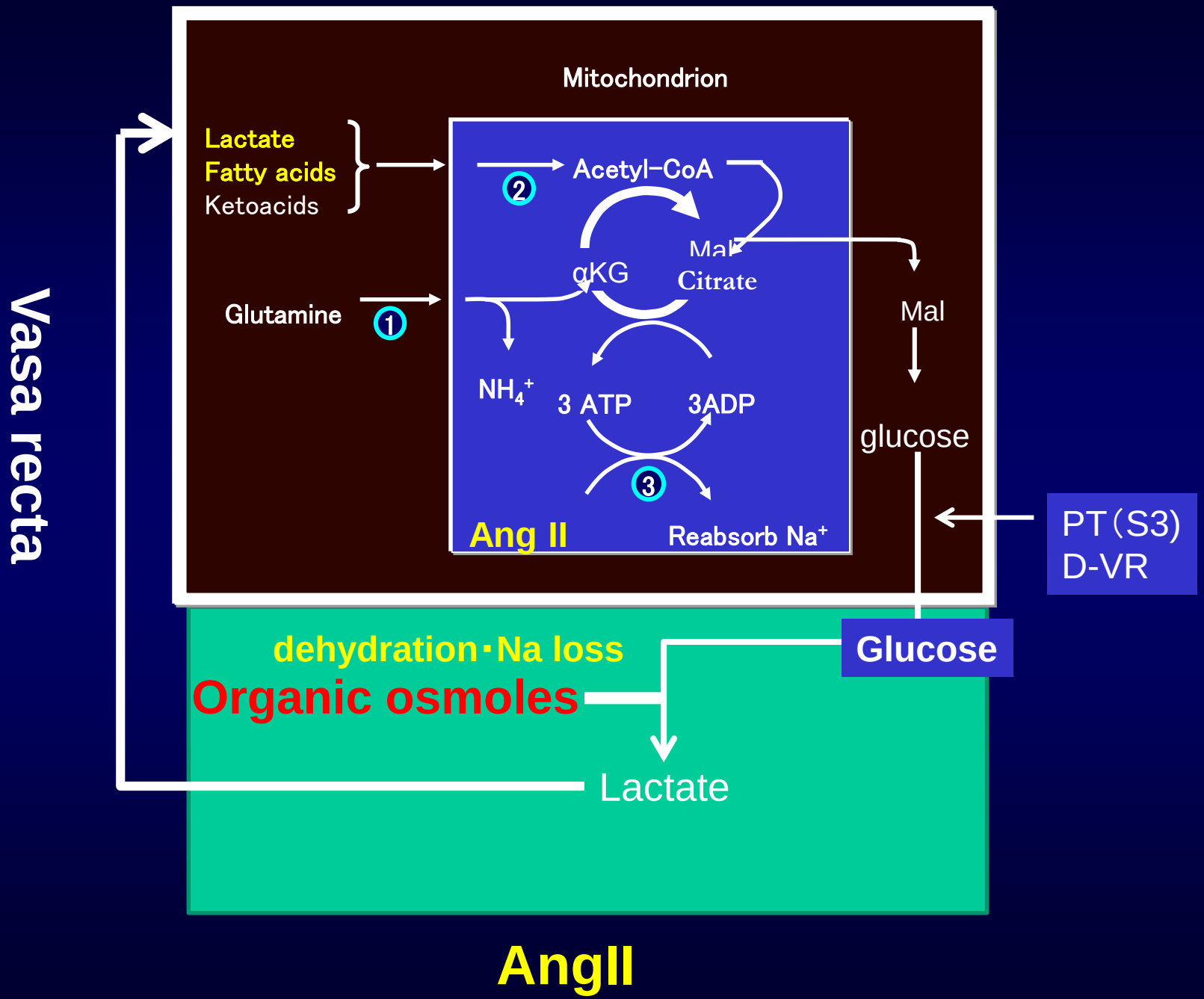



Vasa recta
Mitochondrion
Lactate
Fatty acids
Ketoacids
Glutamine
2
Acetyl-CoA
αKG
Mal
Citrate
1
Mal
NH_4^+
3 ATP
3ADP
glucose
3
Reabsorb Na^+
PT (S3)
D-VR
Glucose
Organic osmoles
Lactate

Substrate of gluconeogenesis

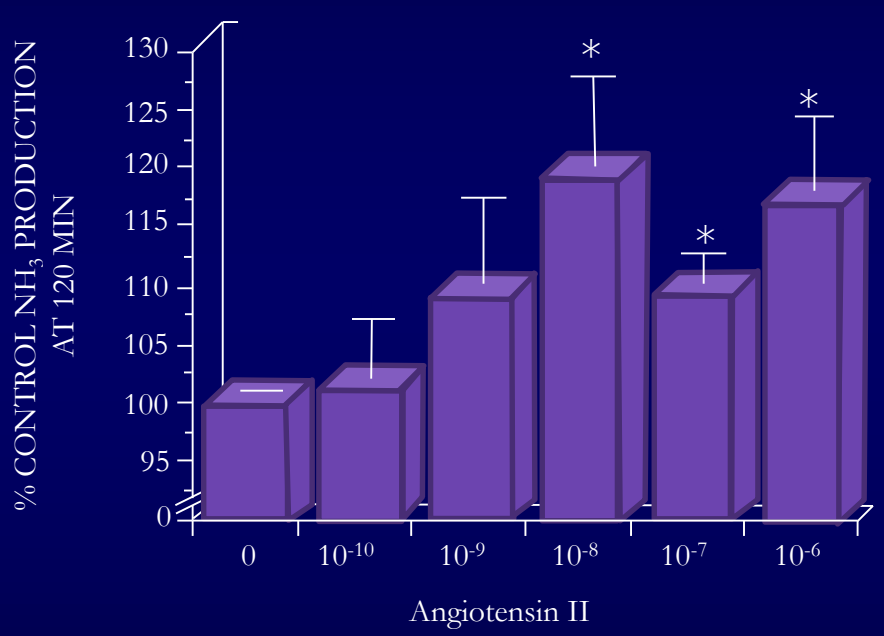
	Lactate(n=16)	Glycerol(n=9)	Glutamine(n=37)	Alanine(n=9)
Overall gluconeogenesis ［～μmol/(kg min)］	1.88±0.15	0.53±0.09	0.58±0.04	0.68±0.07
Renal gluconeogenesis ［～μmol/(kg min)］	0.89±0.09	0.17±0.03	0.36±0.02	0.02±0.01
(% of overall gluconeogenesis)	(47±8)	(32±4)	(62±3)	(3±1)
Hepatic gluconeogenesis ［～μmol/(kg min)］	0.97±0.18	0.39±0.8	0.23±0.02	0.67±0.08
(% of overall gluconeogenesis)	(53±8)	(68±4)	(38±3)	(97±1)

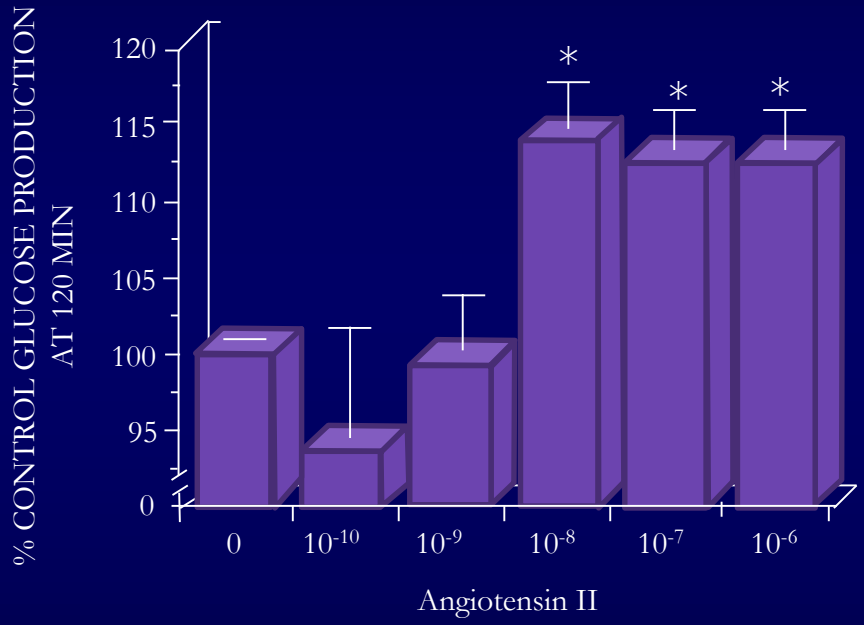
(Gerich JE: Diabet Med 27; 136-142, 2010)


Vasa recta
Mitochondrion
Lactate
Fatty acids
Ketoacids
Glutamine
①
②
③
Acetyl-CoA
αKG
Mal
Citrate
Mal
NH_4^+
3 ATP
3ADP
Ang II
Reabsorb Na^+
glucose
PT (S3)
D-VR
Glucose
dehydration・Na loss
Organic osmoles
Lactate
AngII

When medulla needs glucose

Ang II stimulates production of NH3 and glucose





(GHOBANIAN MC, et al: Am J Physiol 260(1 Pt 2):F19-26, 1991)

Kidney/Metabolism