August 26, 2013

Semmelweis University

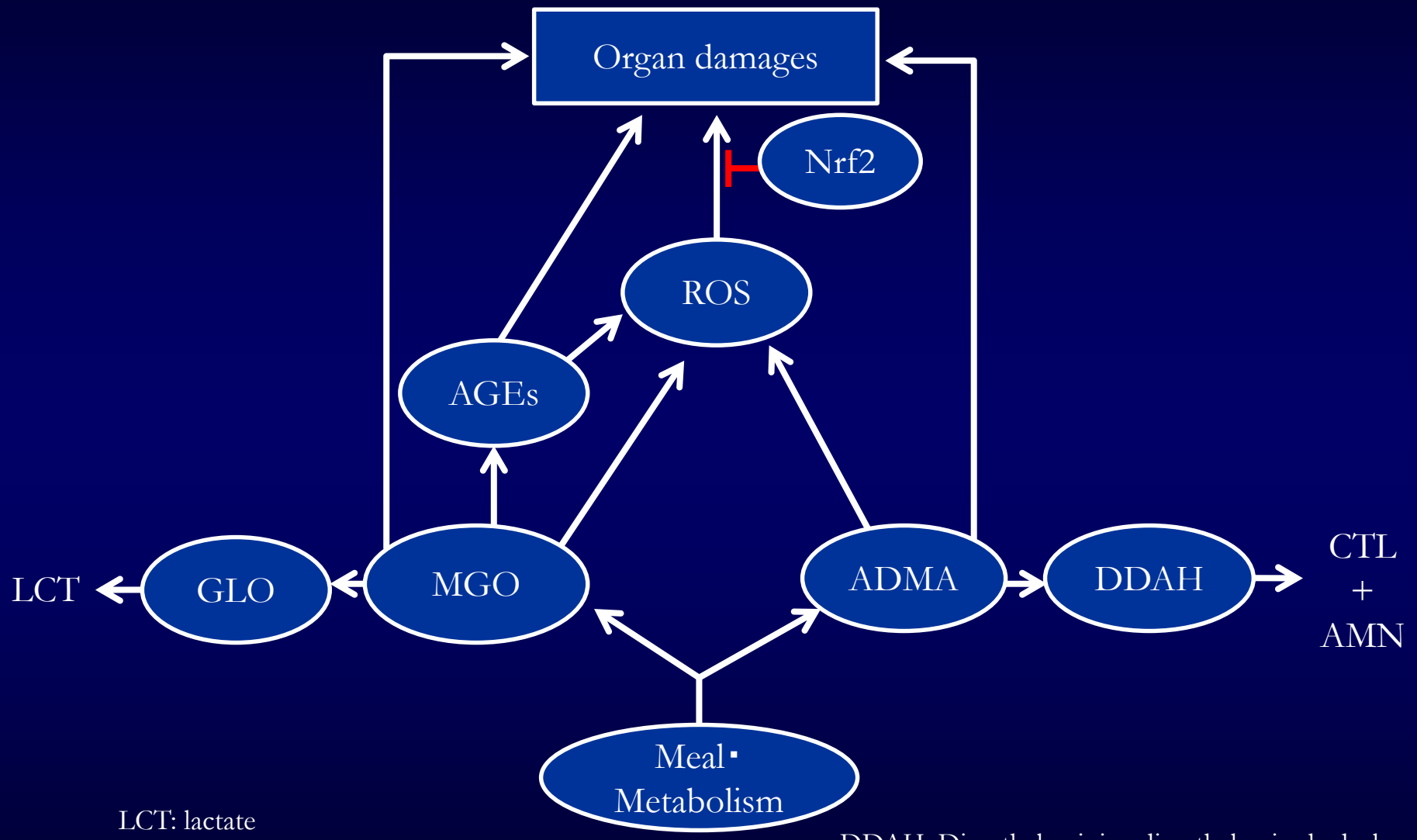
The 20th Budapest Nephrology School

Methylglyoxal: a New Target in CKD

Division of Nephrology, Endocrinology and Vascular Medicine
Department of Medicine, Tohoku University School of Medicine

Sadayoshi Ito

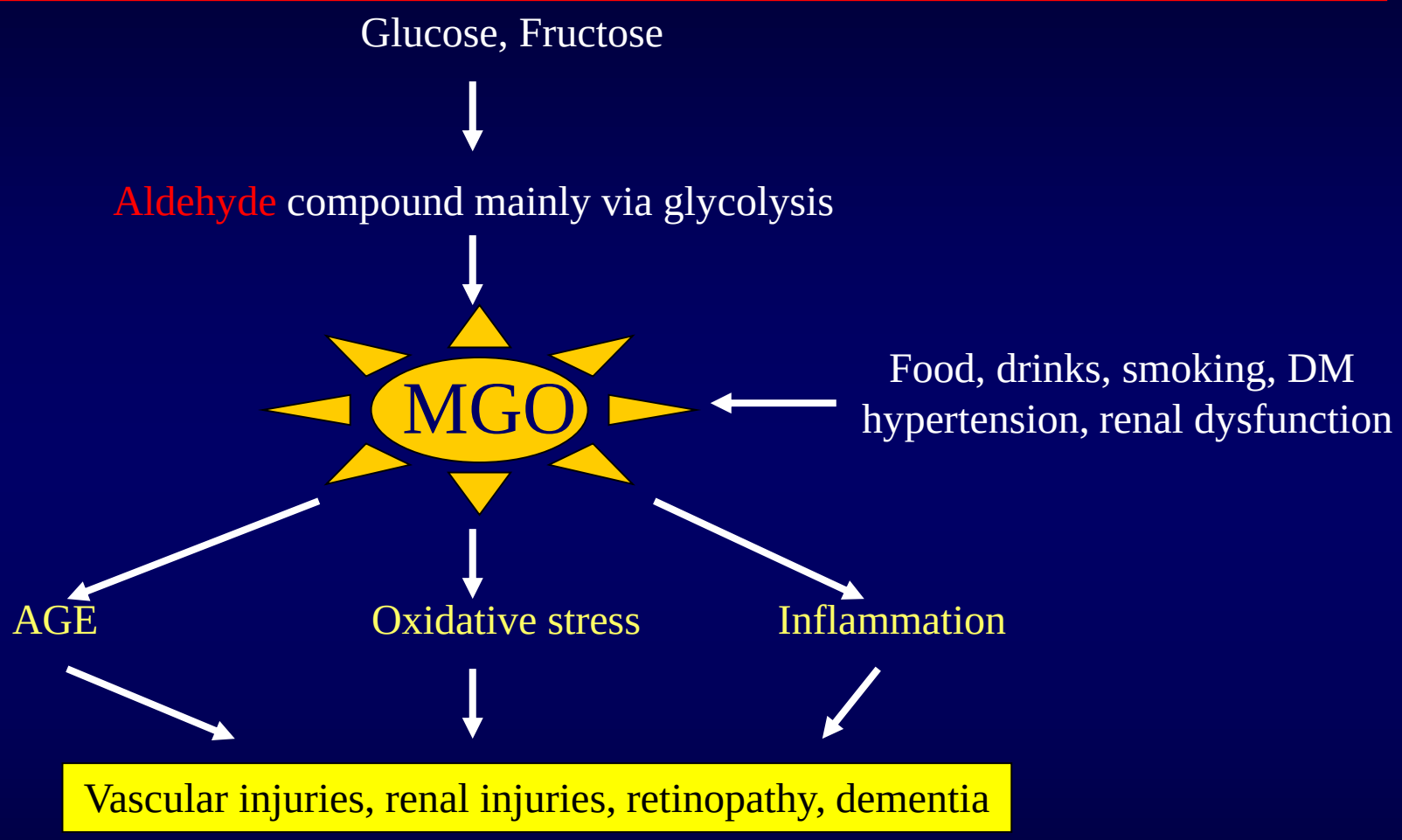
MGO、ADMA、Oxidative Stress



LCT: lactate
GLO : Glyoxalase

DDAH: Dimethylarginine dimethylaminohydrolase
CTL: Citrulline
AMN: Amines

Methylglyoxal (MGO)



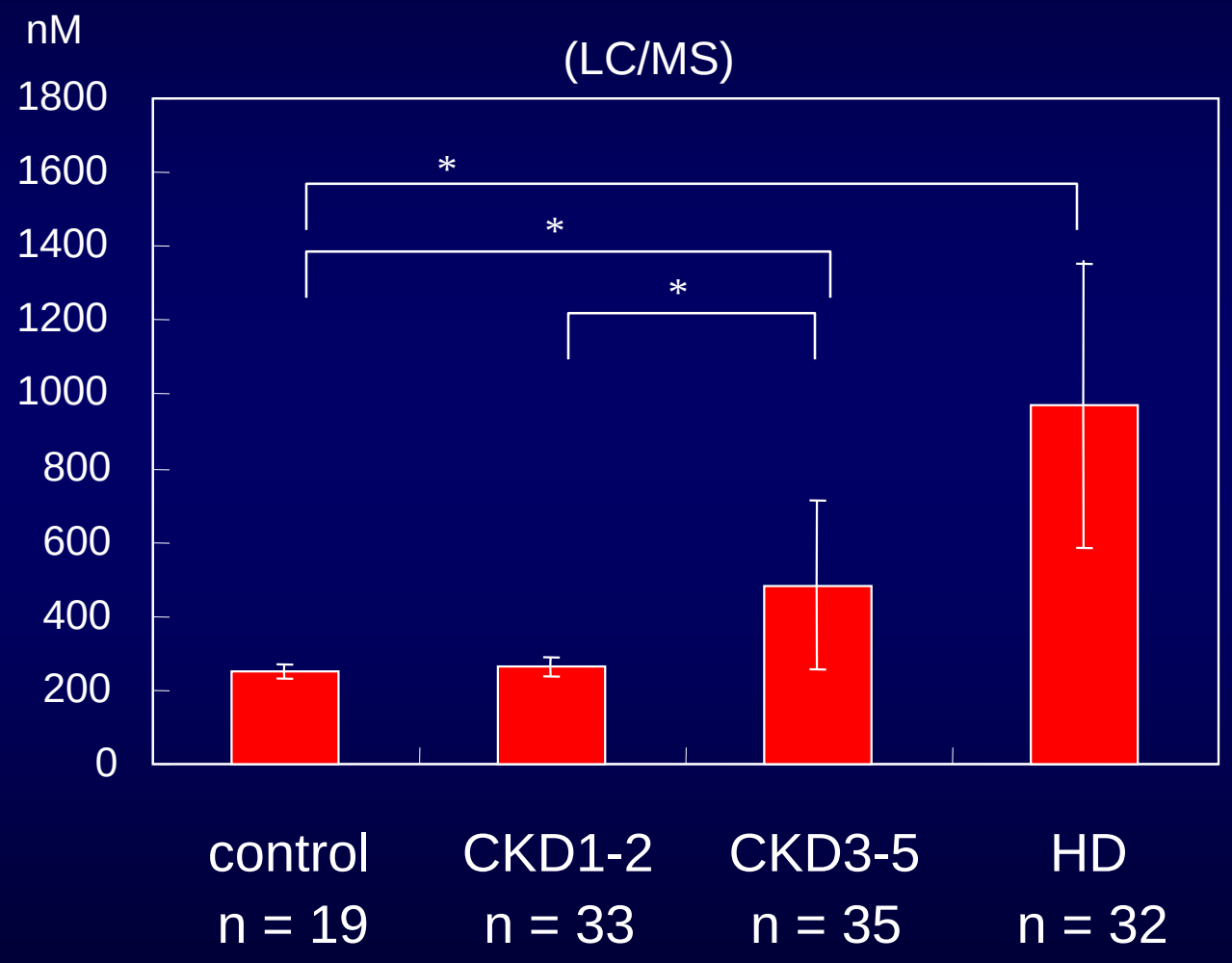
MGO is a very reactive aldehyde-delivertive involved in many biological processes such as AGE formation, glycation-methylation of DNA, transcriptional factors, etc

CKD (GFR<45ml/min/1.73m^2)

- Vascular injuries (heart, brain , kidney, eye)
- Inflammations, Oxidative stress
- Insulin resistance
- Salt sensitive hypertension
- Immune dysfunctions
- Anemia (shortened life span, EPO)
- Cognitive dysfunction

MGO may play important roles in pathophysiology

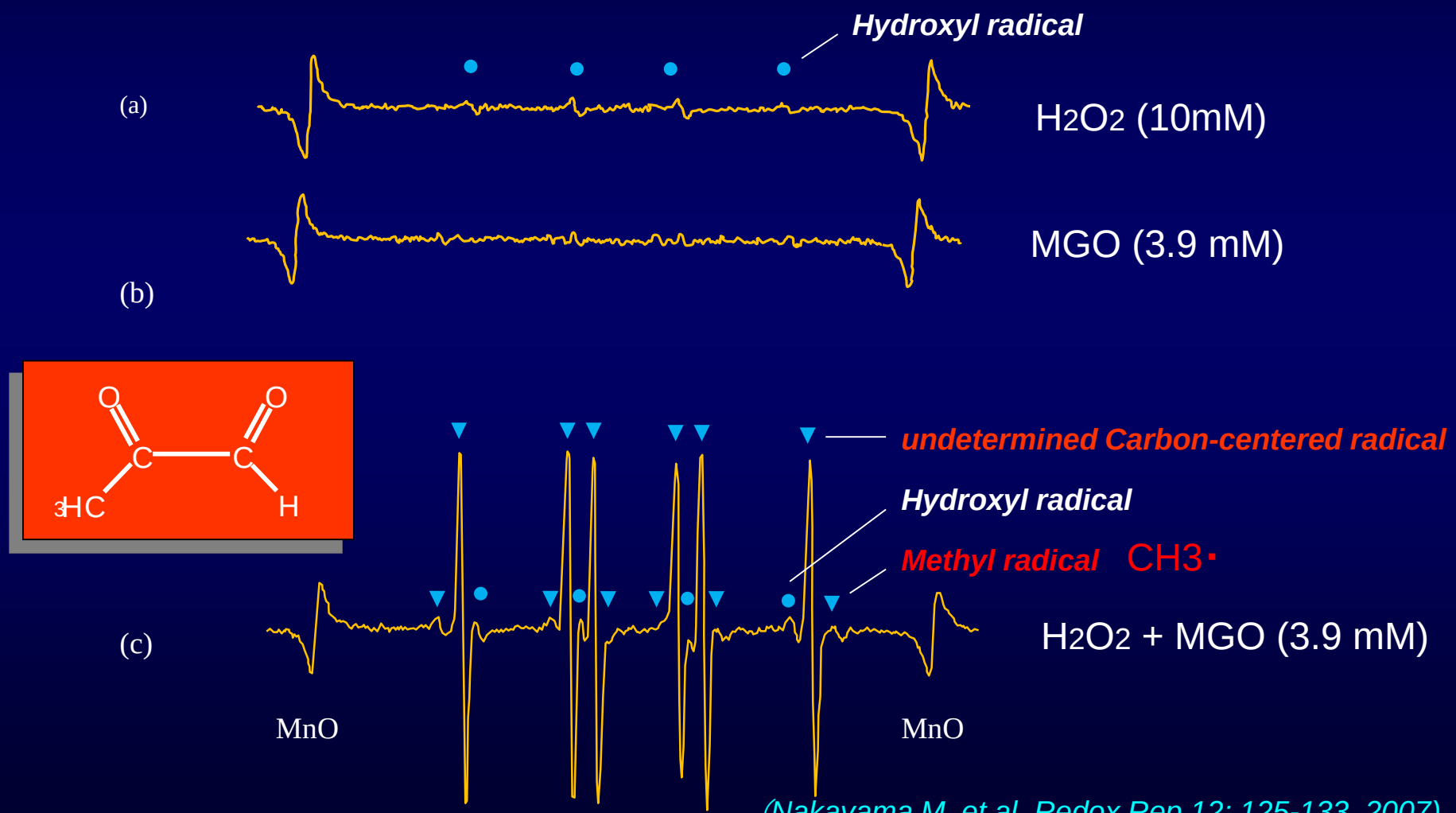
CKD and plasma MGO



（Nakayama K, Am J Nephrol 28(6), 871-878, 2008)

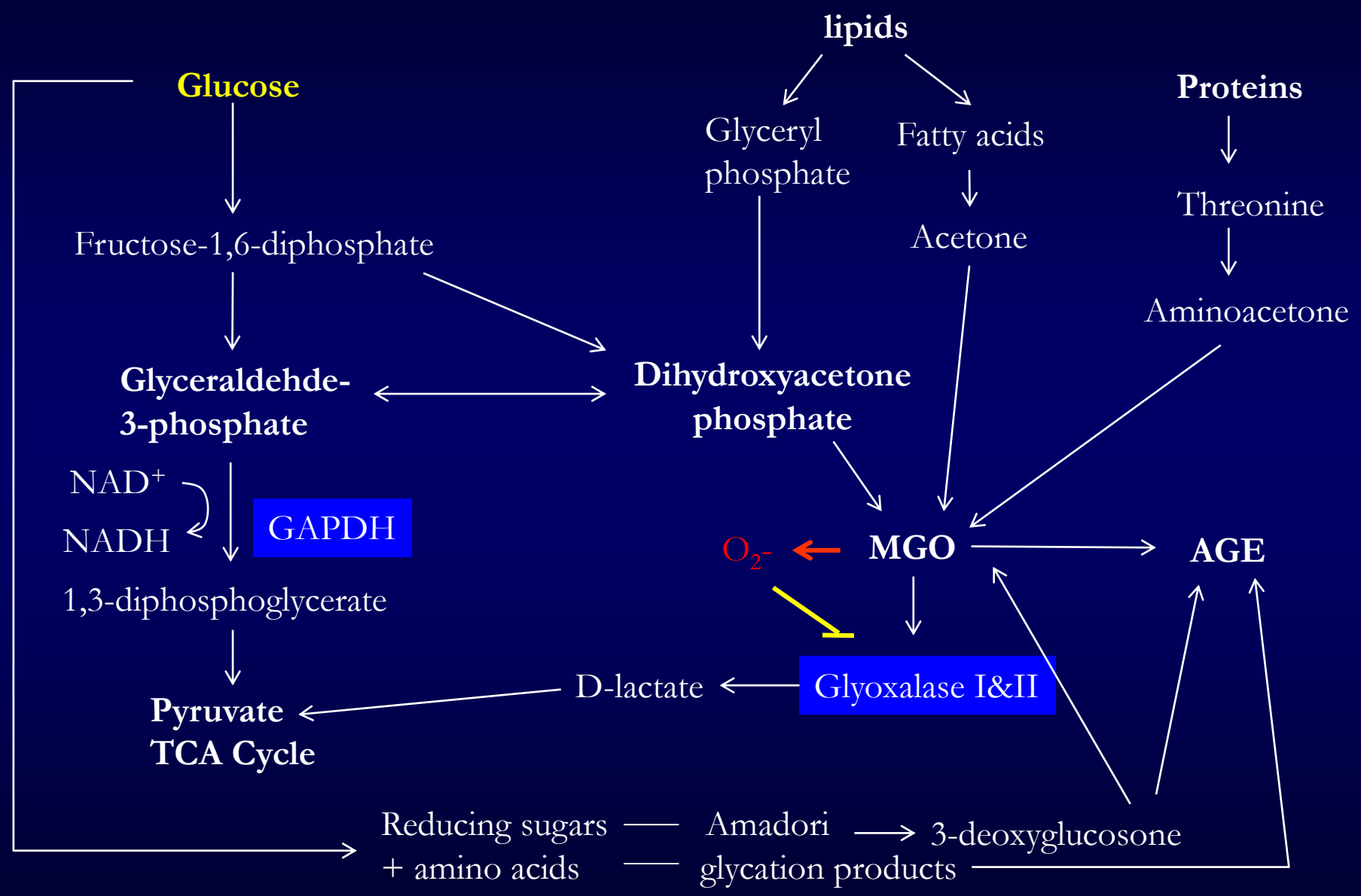
MGO is a very reactive substance
A new radical is produced by reacting with H_2O_2

ESR spectrum



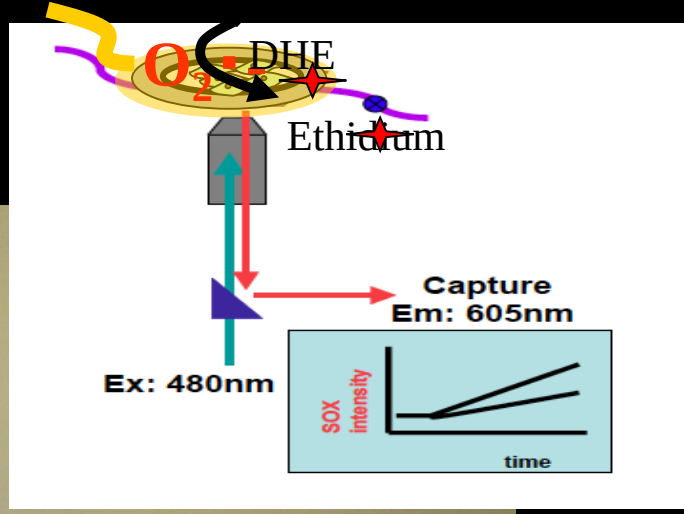
(Nakayama M, et al. Redox Rep 12; 125-133, 2007)

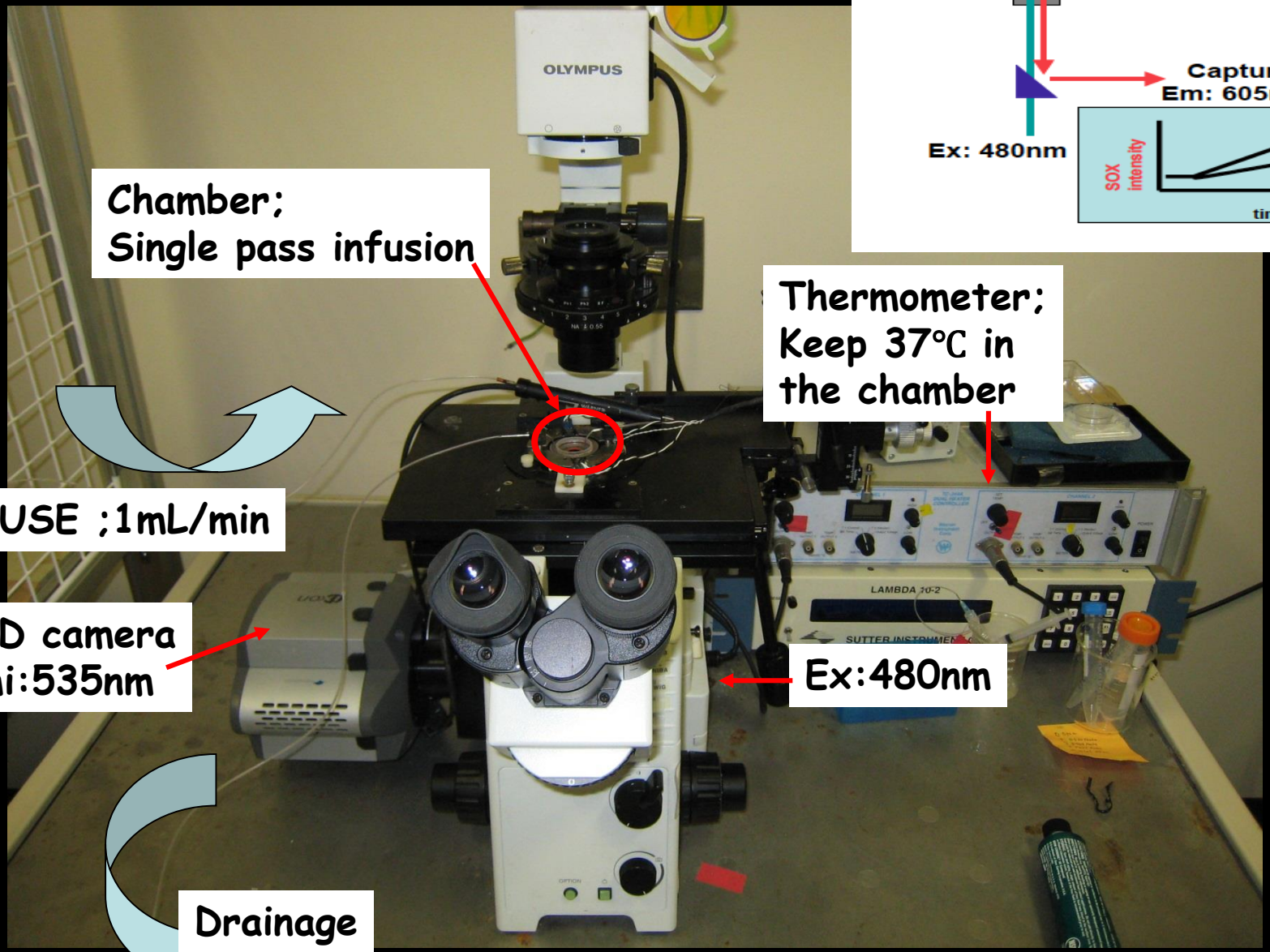
Metabolic pathways of MGO



(Price CL, et al: Trends in Endocrinology and Metabolism 20(7); 312-317, 2009)

REAL-TIME FLUORECSENT MICROSCOPY





Chamber;
Single pass infusion

Thermometer;
Keep 37℃ in
the chamber

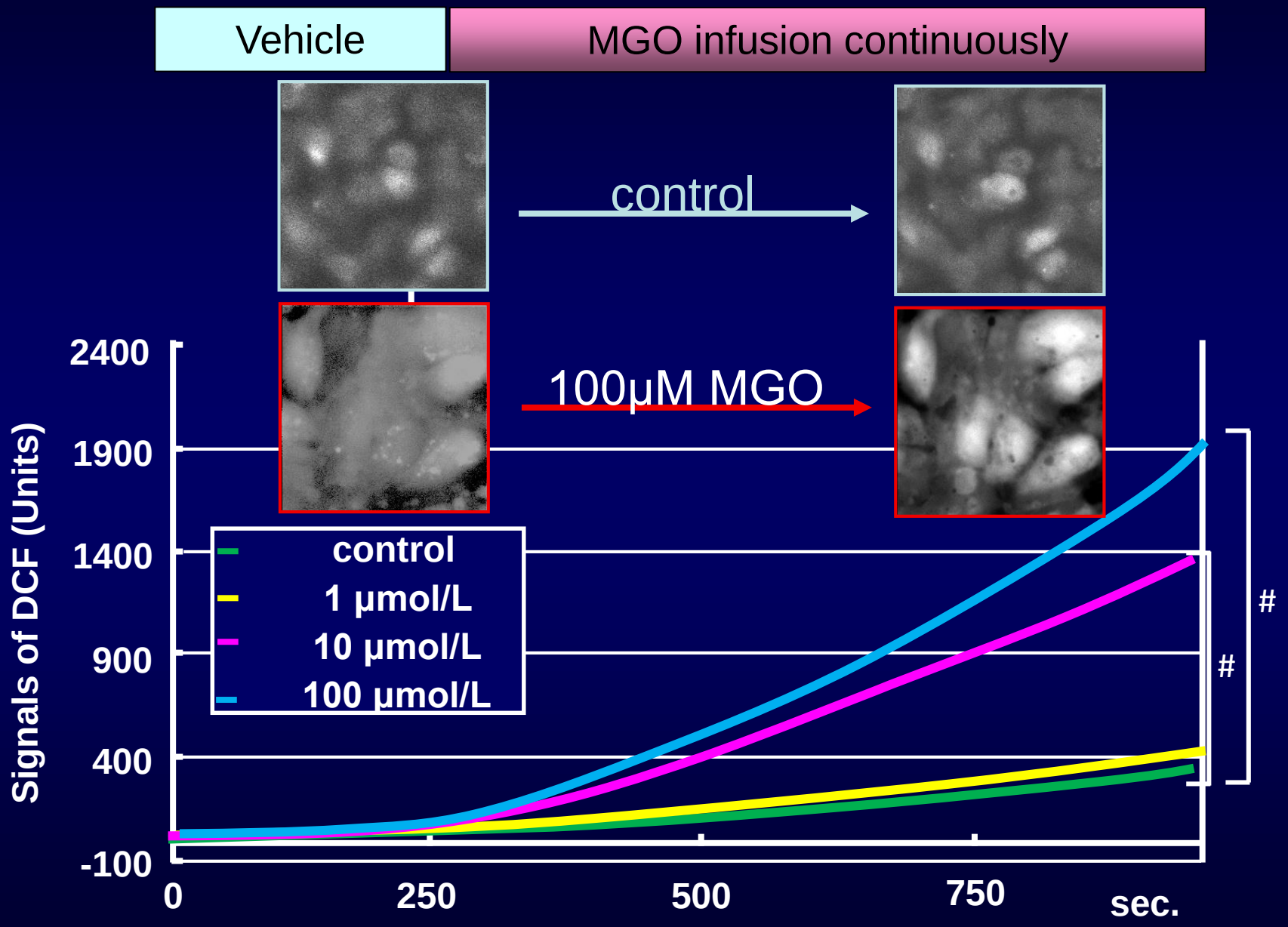
INFUSE ;1mL/min

CCD camera
Emi:535nm

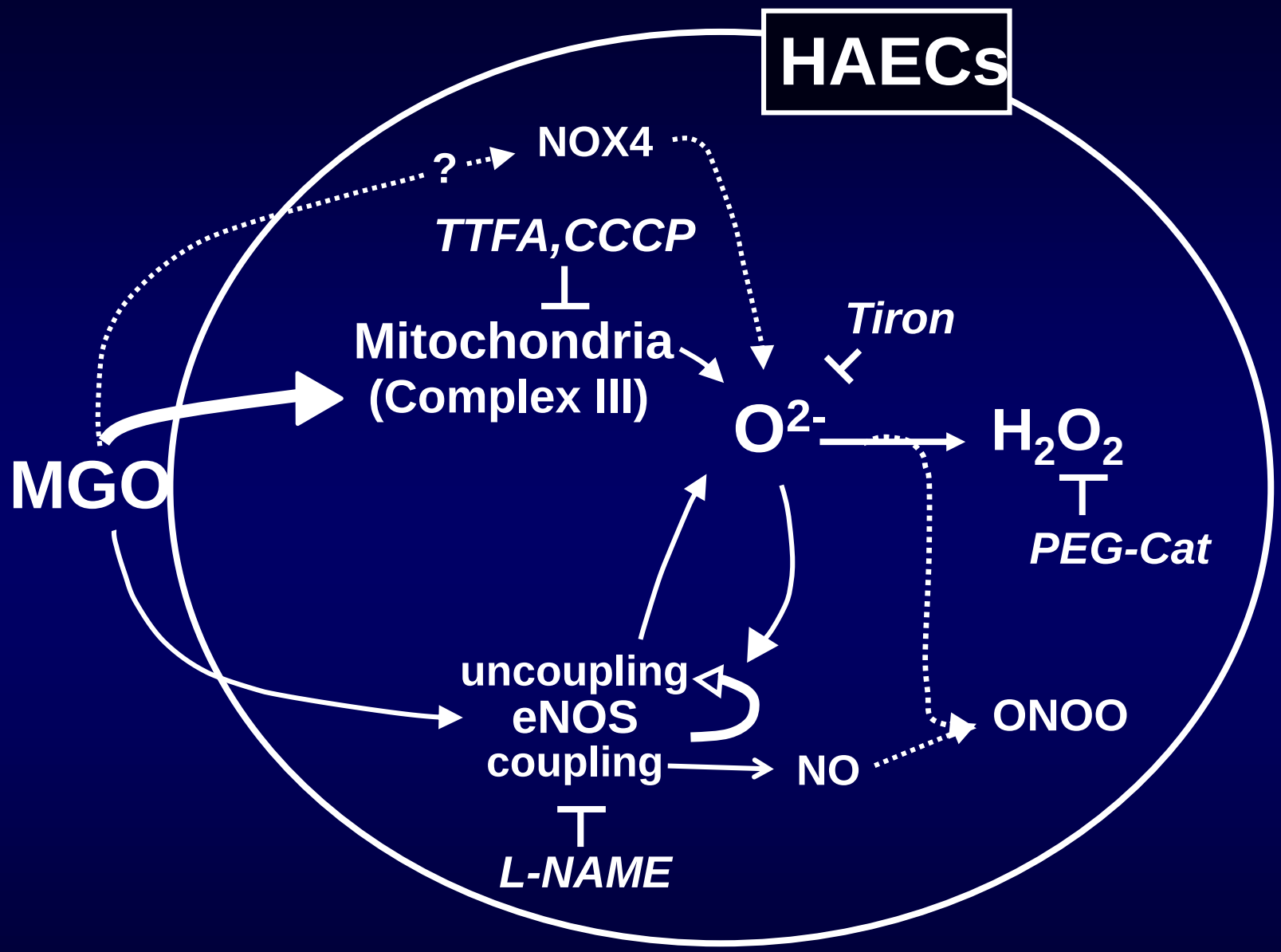
Ex:480nm

Drainage

MGO increases ROS in endothelial cells

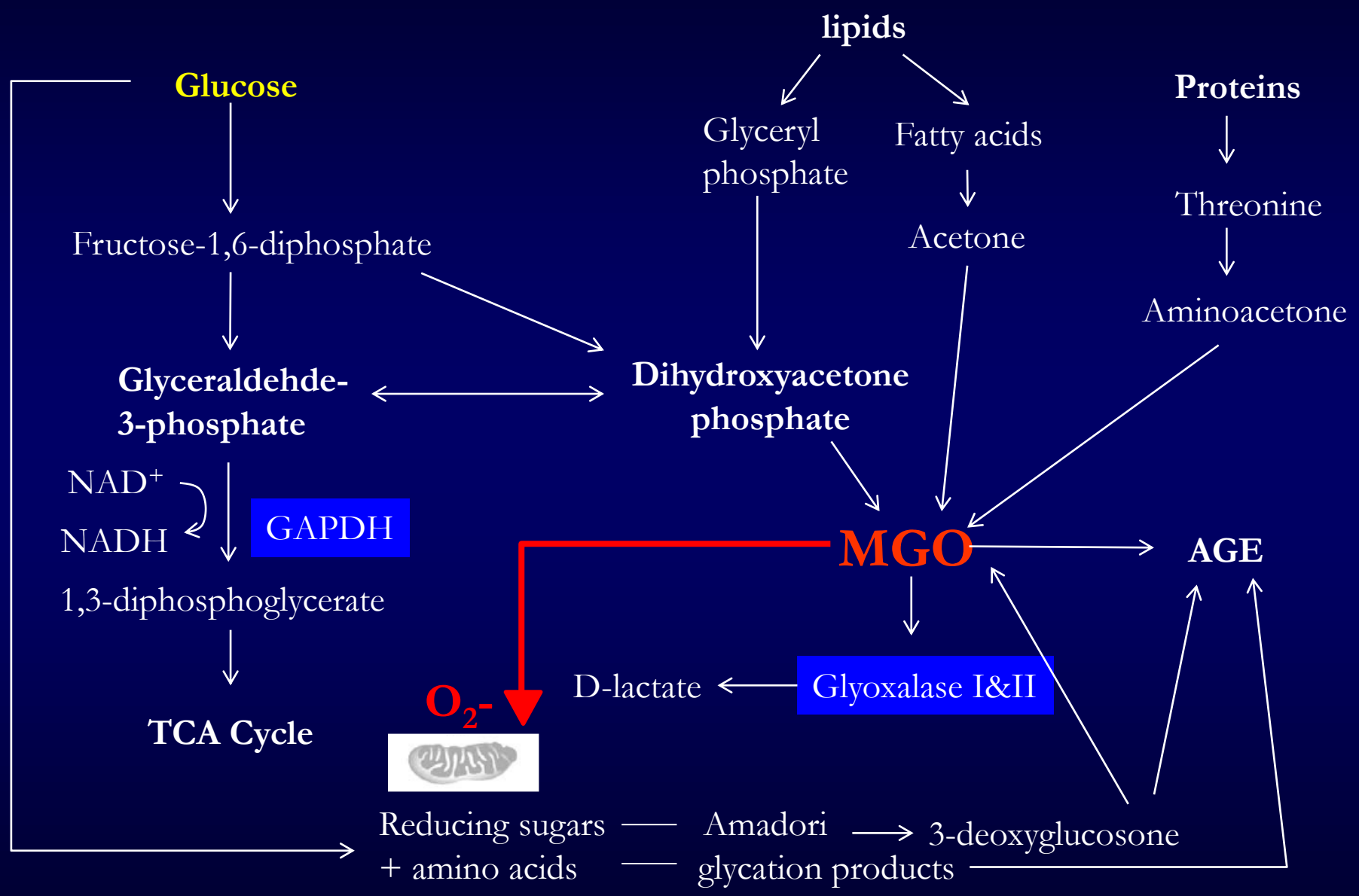


(Miyazawa N,et al. Free Radic Res 44:101-107.2010.)



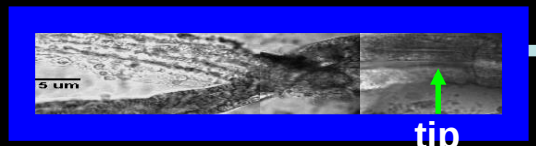
(Miyazawa N,et al. Free Radic Res 44:101-107.2010.)

Metabolic Pathways of MGO: DM (Hypothesis)



(Price CL, et al: Trends in Endocrinology and Metabolism 20(7); 312-317, 2009)

Microperfusion of mTAL
~measurement of Mit ROS~



Chamber;
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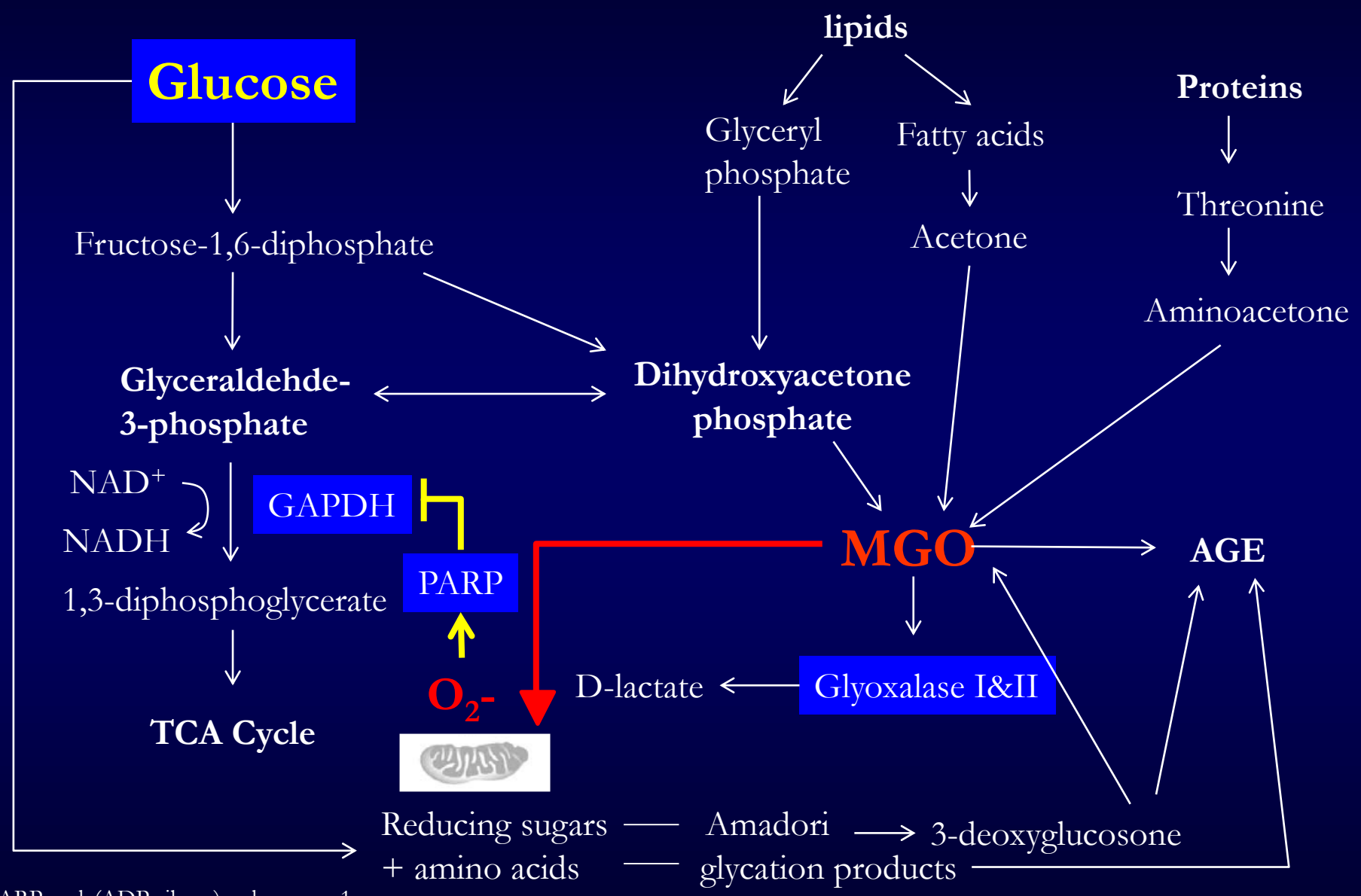
Metabolic Pathways of MGO: DM (Hypothesis)



RARP: poly(ADP-ribose) polymerase-1

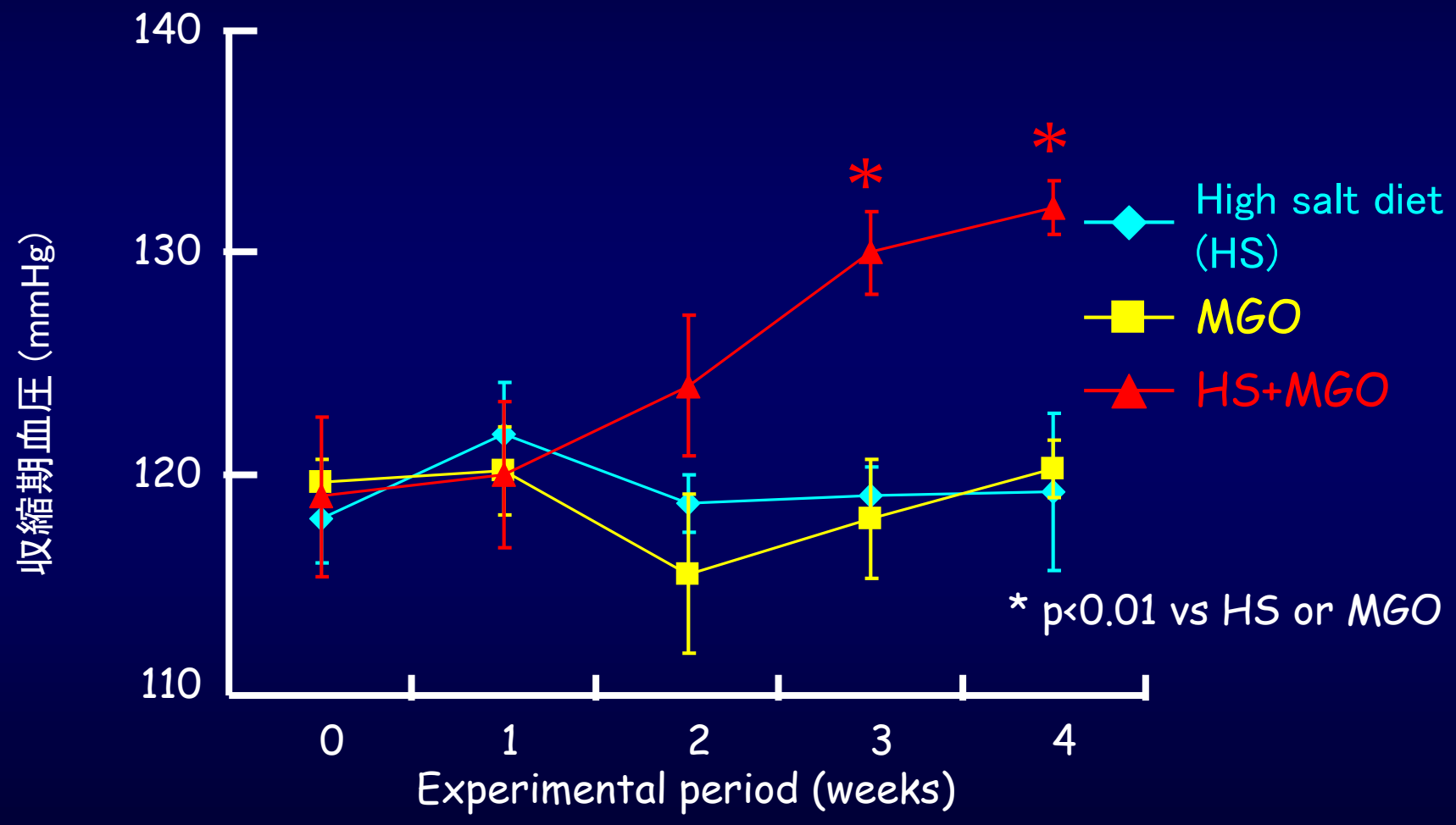
(Price CL, et al: Trends in Endocrinology and Metabolism 20(7); 312-317, 2009)

MGO causes

MGO is elevated in CKD

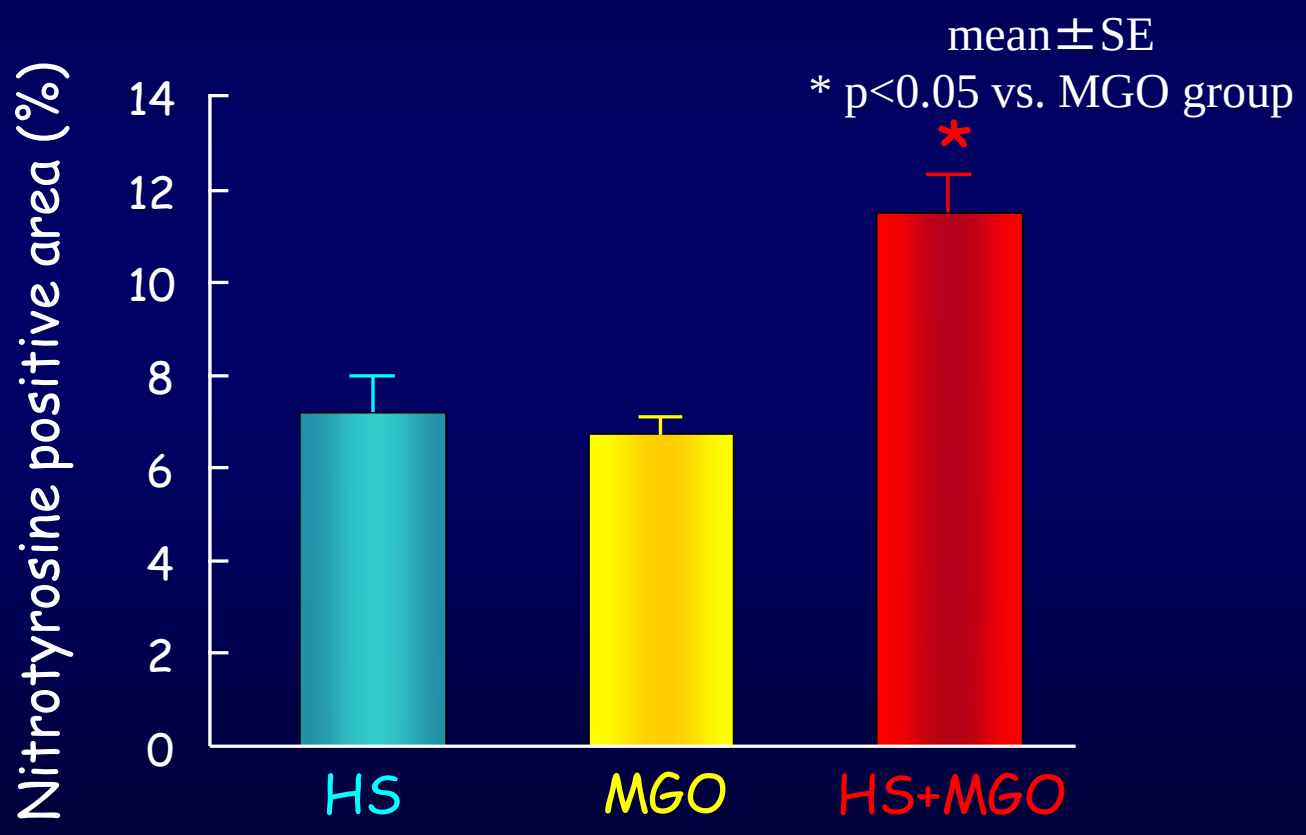
- Vascular injuries (heart, brain , kidney, eye)
- Inflammations, Oxidative stress
- Insulin resistance?
- Salt sensitive hypertension
- Immune dysfunctions
- Anemia (shortened life span)
- Cognitive dysfunction

MGO enhances salt sensitivity of BP in SD rats



(Guo Q, et al; J Hypertension 27; 1664-1671, 2009)

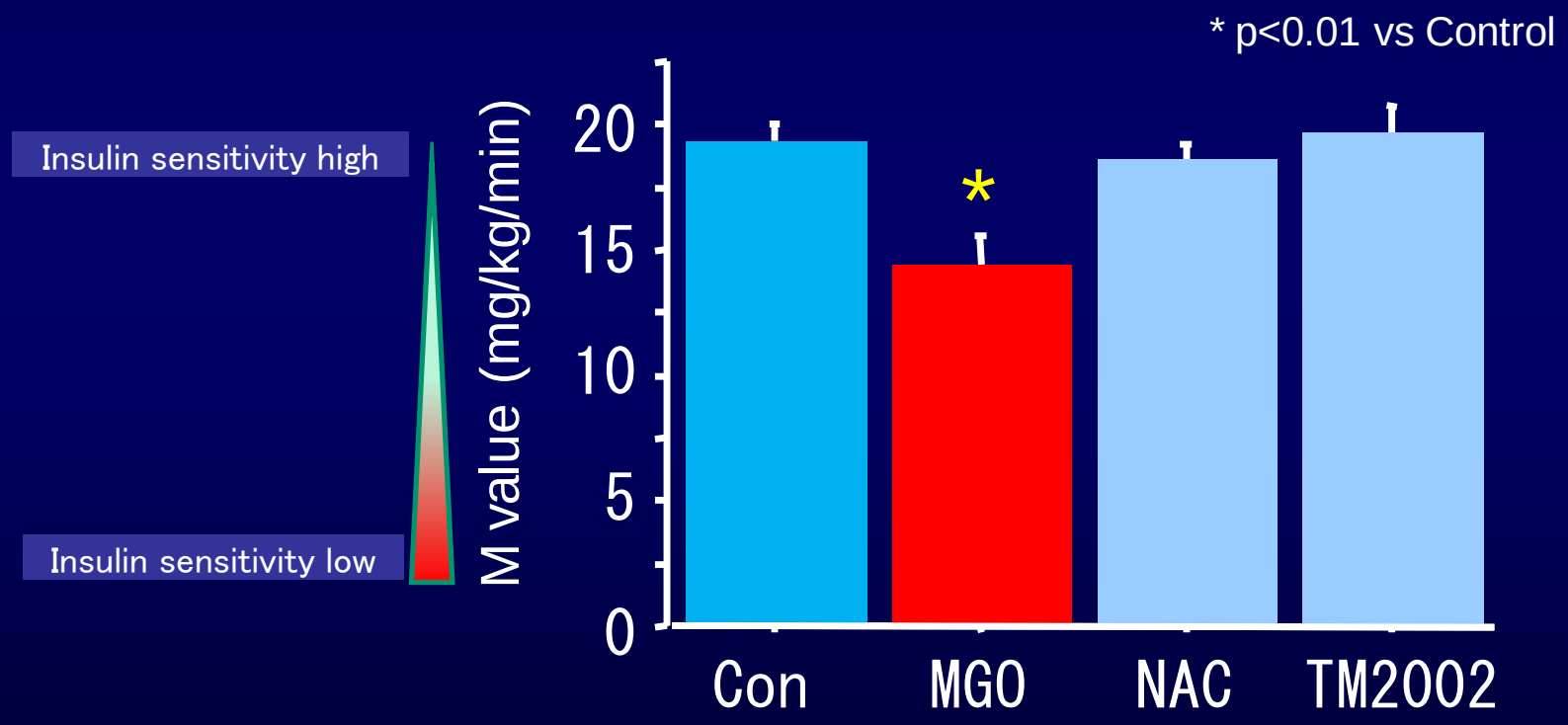
MGO increases ROS in the kidney



(Guo Q, et al; J Hypertension 27; 1664-1671, 2009)

MGO decreases insulin sensitivity
(M value: insulin sensitivity)

Glucose clamp in conscious rats



(Guo Q, et al; J Hypertension 27; 1664-1671, 2009)

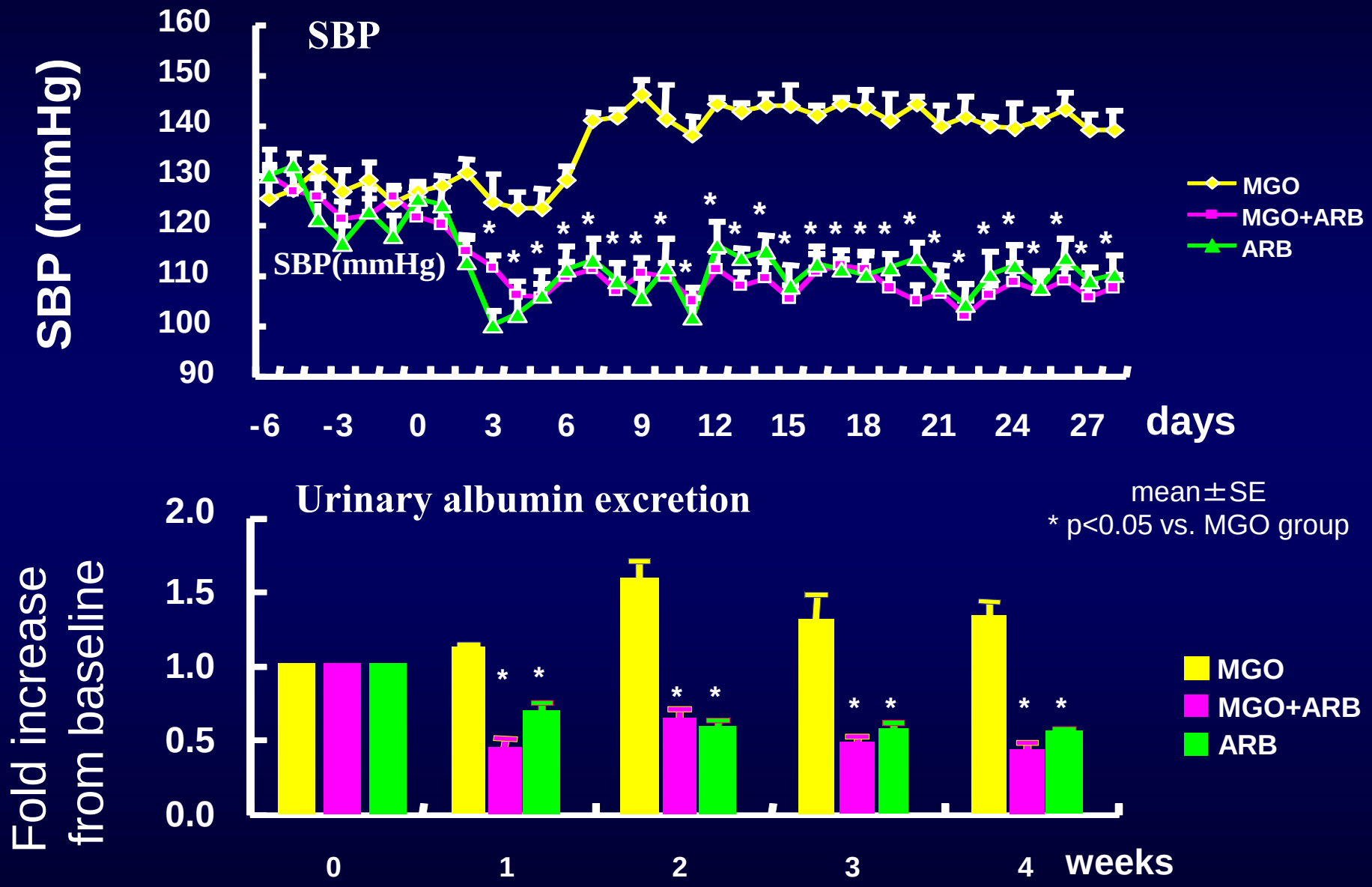
Dahl salt-sensitive rats

H_2O_2 is high even under low Na

H_2O_2 reacts with MGO

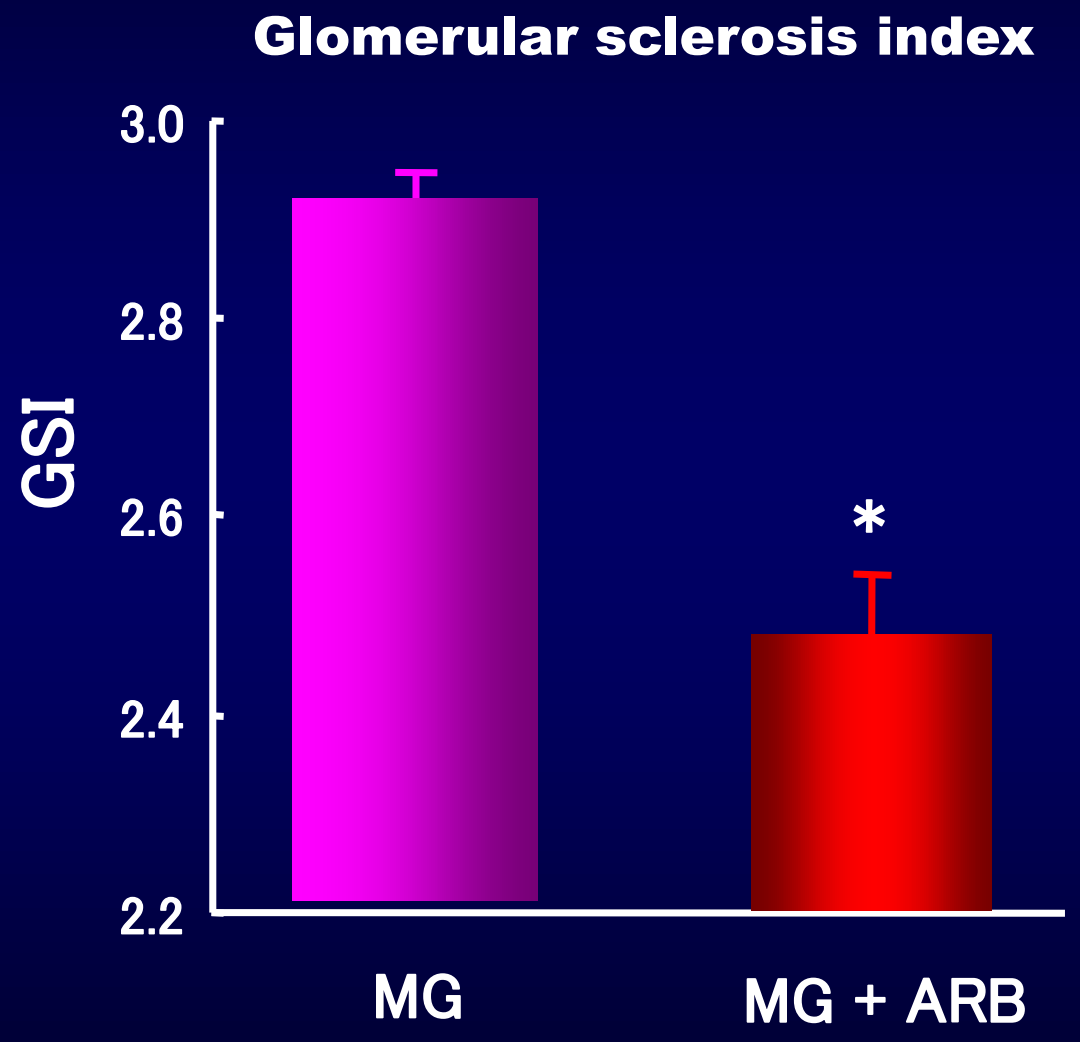
Chen. Hypertension Res: 2013 ;36:361-7

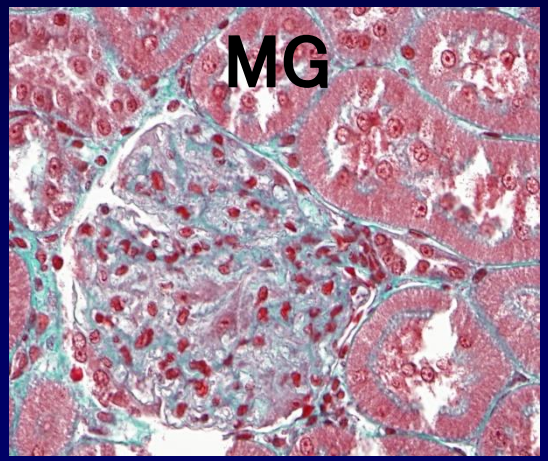
MGO increases BP in Dhal S fed low Na

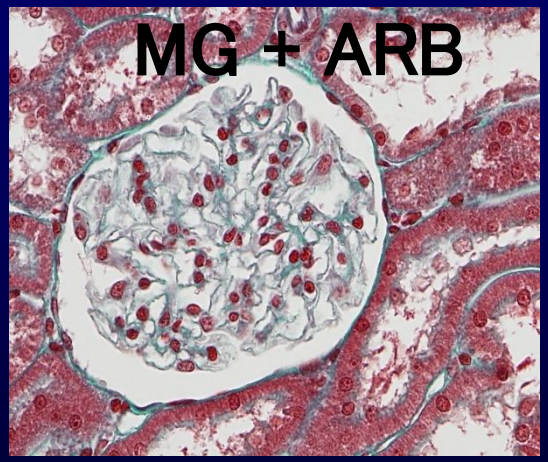


Chen . Hypertension Res: 2013 ;36:361-7

ARB improved MGO-induced damages



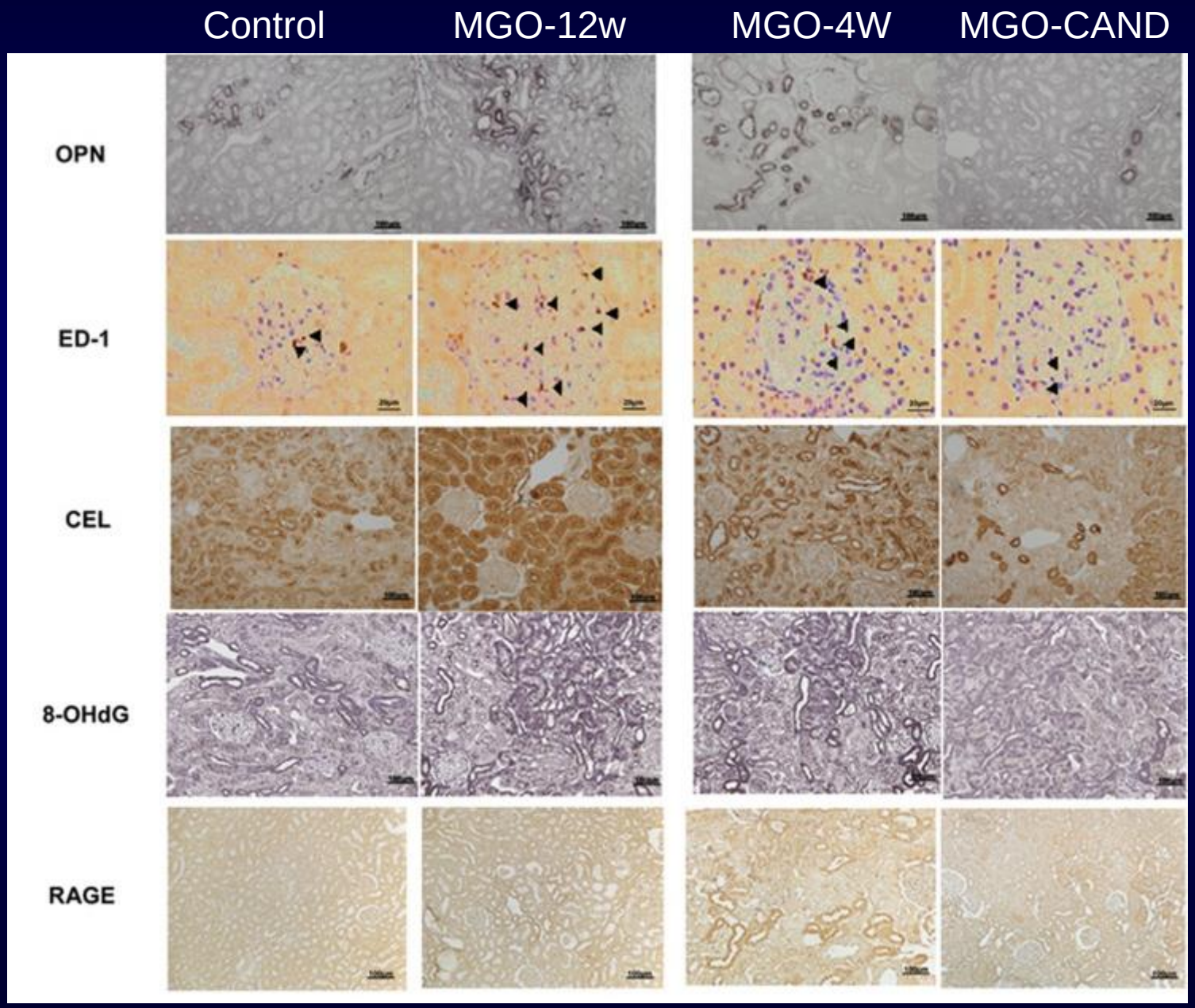




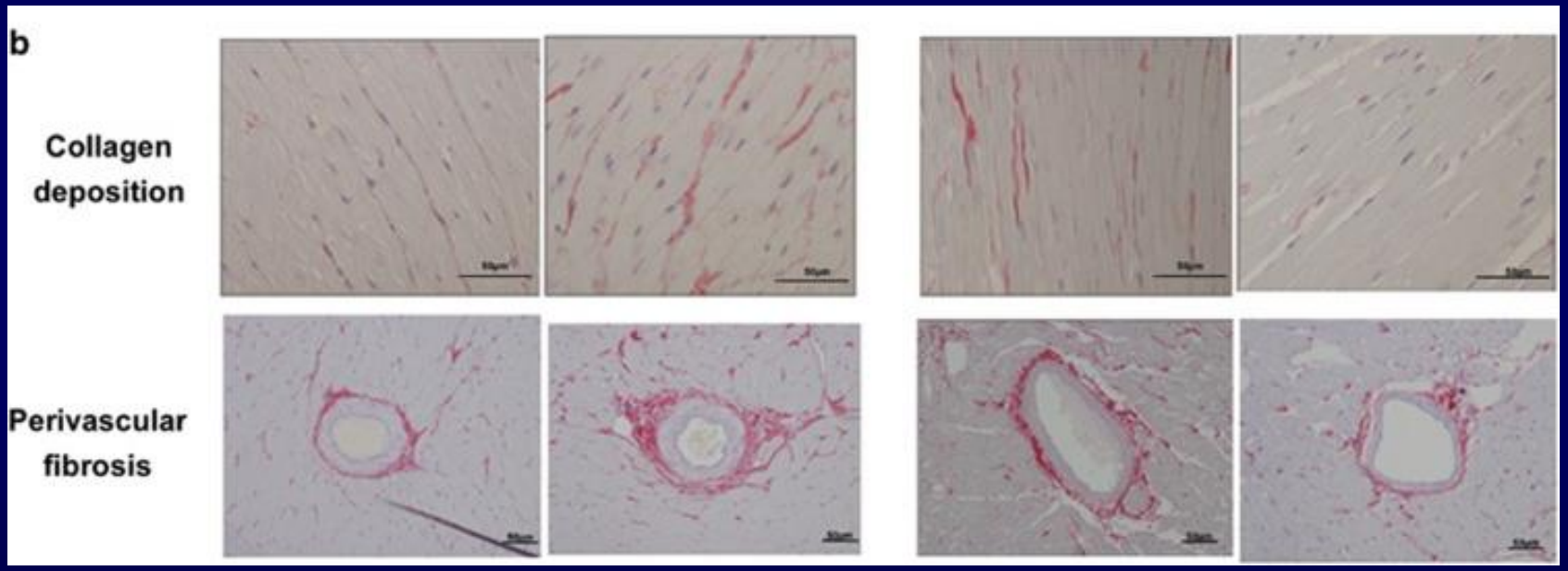
* $p<0.05$ vs. MGO group

Chen. Hypertension Res: 2013 ;36:361-7

Markers of oxidative stress and inflammation in the kidney

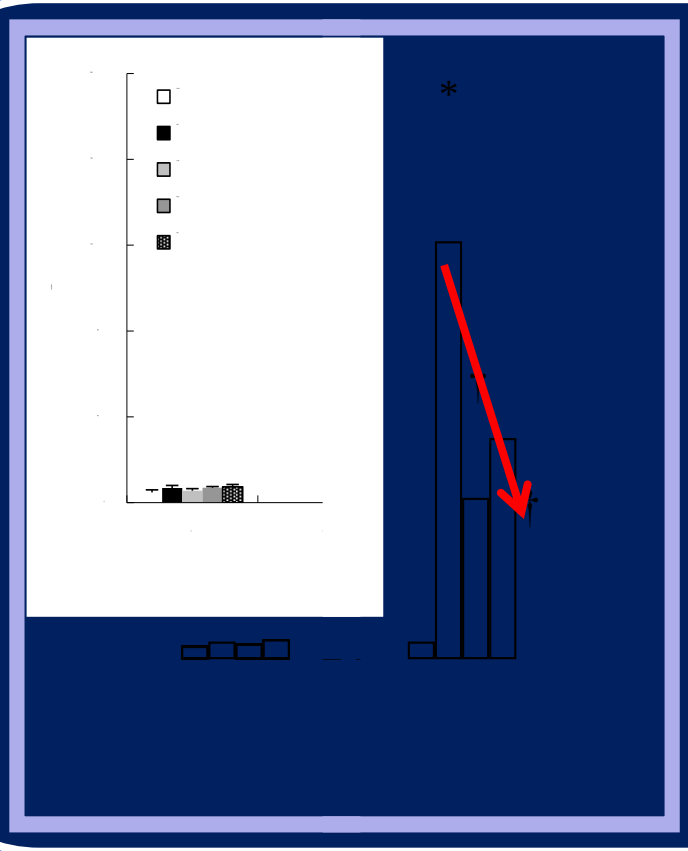


Collagen deposition and perivascular fibrosis in the heart



Chen. Hypertension Res: 2013 ;36:361-7

Pyridoxamine reduced albuminuria in Thy-1 nephritis



* P<0.05 vs CON,
† P<0.05 vs GN

MGO causes

Nephrol Dial Transplant (2008) 23: 3096–3102
doi: 10.1093/ndt/gfn218
Advance Access publication 28 April 2008

Original Article

Polymorphonuclear leukocyte injury by methylglyoxal and hydrogen peroxide: a possible pathological role for enhanced oxidative stress in chronic kidney disease

Masaaki Nakayama[1], Keisuke Nakayama[1], Wan-Jun Zhu[1], Yuko Shirota[2], Hiroyuki Terawaki[1], Toshinobu Sato[2], Masahiro Kohno[3] and Sadayoshi Ito[1,2]

[1]Research Division of Dialysis and Chronic Kidney Disease, Tohoku University Graduate School of Medicine, [2]Department of Blood Purification, Tohoku University Hospital and [3]Tohoku University, New Industry Creation Hatchery Center, Life Particle Interaction Engineering Creation, Sendai, Japan

Abstract pathology may be linked to enhanced oxidative stress in

- Cognitive dysfunction

MGO and Brain（Pubmed 116）

- Cognitive dysfunction in DM

  Brain Res. 21;1469:82-91.2012
- Alzheimer: high MGO in spinal fluid：

  (Ann N Y Acad Sci 1043; 211-216, 2005)
- MGO causes β-amyloid misfolding：

  (J Alzheimers Dis.30；63-73,2012. Neurochem 99; 1413-1424, 2006)
- MGO causes hipocampus damages：

  (Brain Research 1006; 157-167, 2004;Intern J Biochem & Cell Biol 40; 245-257, 2008)
- MGO-producing semicarbazaise-sensitive amine oxidase (SSAO) is high in serum and blood vessels in Alzheimer：

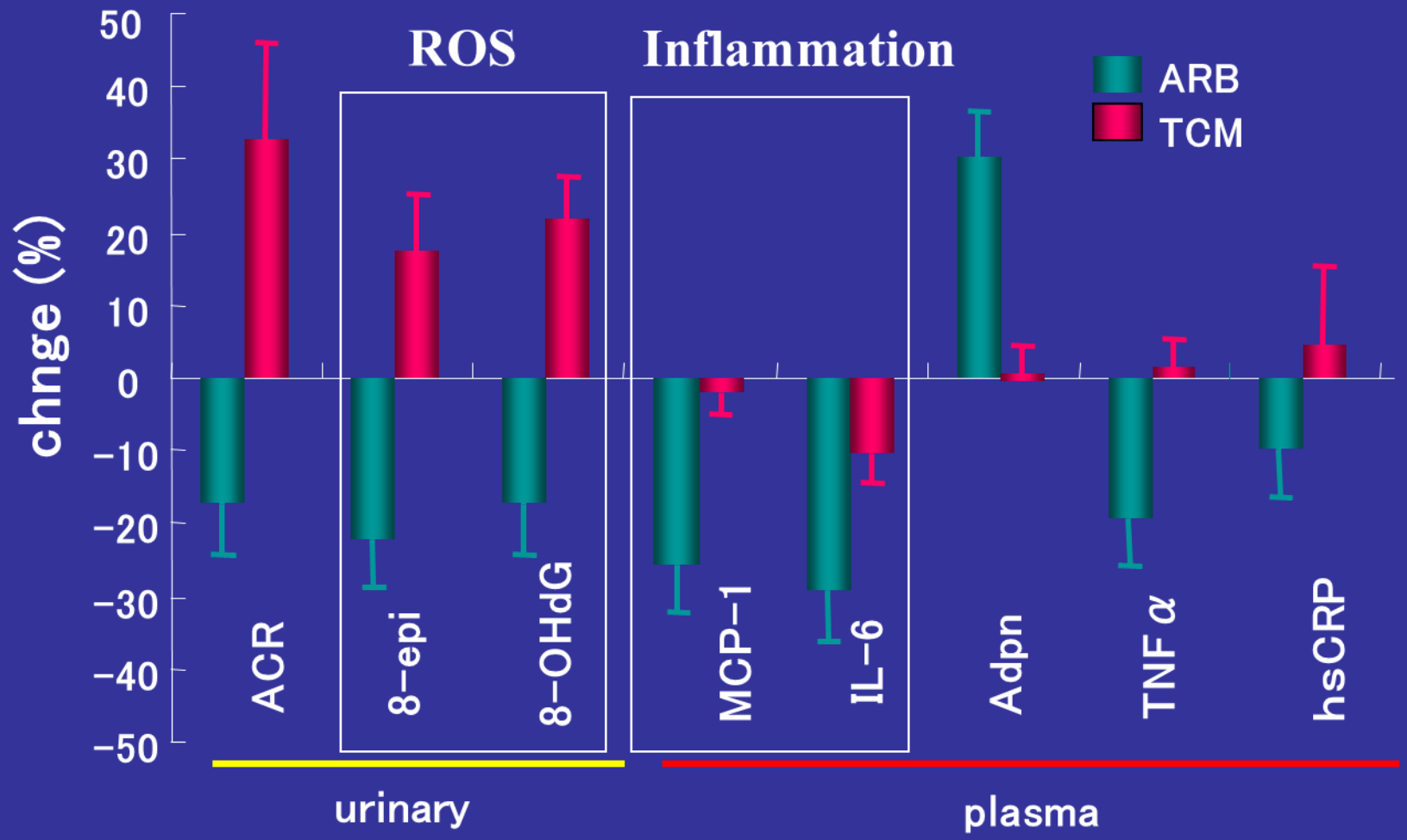
  (Neurosci Lett 321; 121-21, 2002:Neurosci Lett 384; 183-187, 2005)
- GLO-1 abnormality in some nervous diseases：

  (Neurosci Lett 438; 196-199, 2008)

Is it relevant in human?

ARB decreases ACR via inhibition of ROS

Ang II increase ROS via AT1R



S Ogawa et al. Hypertension 2006 ;47:699-705

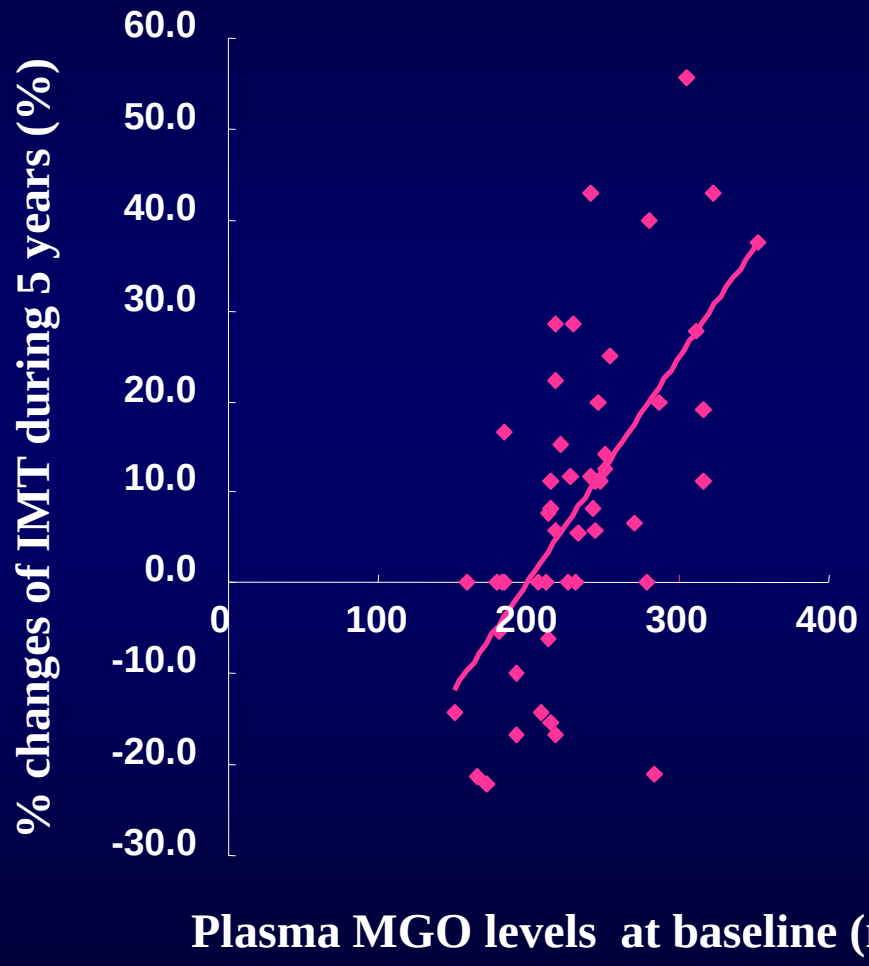
Baseline MGO and parameters

(Ogawa S, et al Hypertension 56: 471-476, 2010)

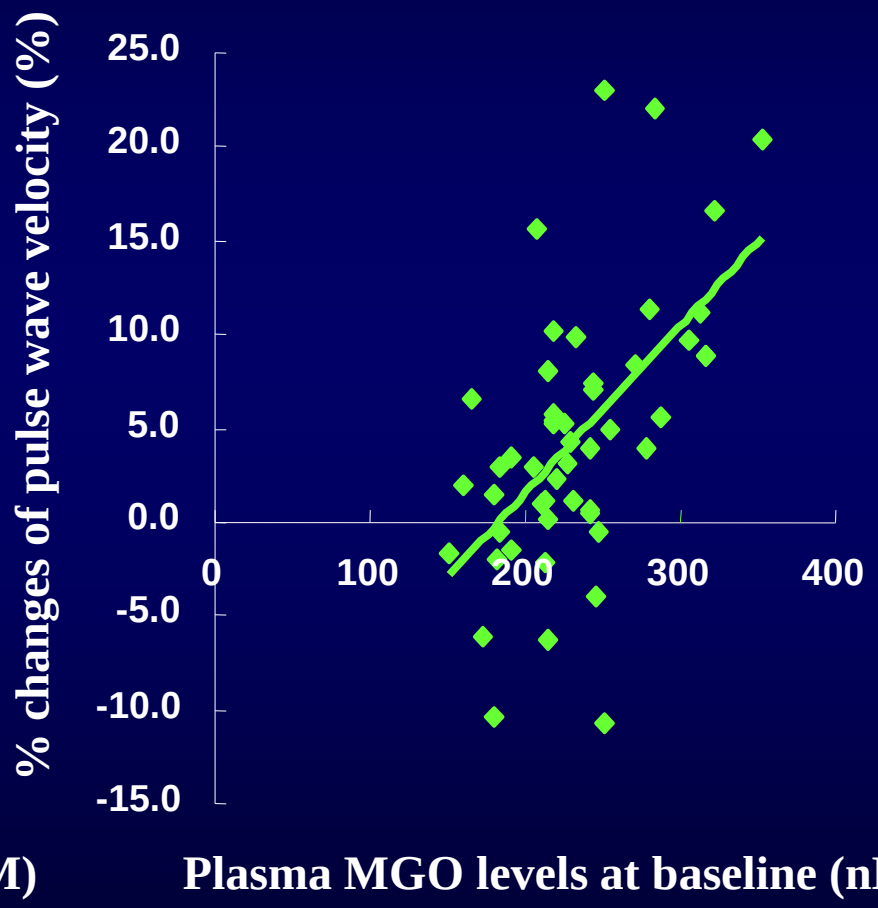
		R^2	r	p
3-DG	y = 0.7357x + 281.16	0.0365	0.191135254	< 0.05
Age	y = 0.0215x + 53.484	0.0063	0.079234755	n.s.
BMI	y = 0.0164x + 18.46	0.0405	0.20127173	< 0.05
SBP	y = 0.1037x + 101.11	0.0689	0.262565616	< 0.05
DBP	y = 0.0757x + 51.137	0.0891	0.298531428	< 0.05
HbA1c	y = -0.0002x + 6.8907	0.0000	-0.008184052	n.s.
creatinine	y = 0.0027x - 0.0461	0.0609	0.246790167	< 0.05
triglyceride	y = 0.4506x - 45.526	0.0838	0.289456466	< 0.05
T-cholesterol	y = 0.0895x + 152.12	0.022	0.148330033	0.096
HDL-C	y = -0.0089x + 56.015	0.001	-0.031056239	n.s.
ACR	y = -0.551x + 573.22	0.0018	-0.042905141	n.s.
IV-collagen	y = 0.006x + 3.3888	0.0087	0.093111815	0.080
pentosidine	y = 0.0283x + 38.455	0.0043	0.065476601	n.s.
8-OHdG	y = 0.0073x + 6.2963	0.0084	0.091913814	n.s.
8-epi-PGF	y = 0.3498x + 124.99	0.0158	0.125555919	0.062
Interleukin-6	y = -0.0022x + 2.3692	0.0011	-0.033323818	n.s.
Interleukin-18	y = -0.2737x + 372.95	0.0145	-0.120536309	n.s.
MCP-1	y = 0.2858x + 80.497	0.0347	0.186396425	0.052
hsCRP	y = 0.0006x - 0.051	0.0187	0.136734098	0.074
max IMT	y = 0.0029x + 0.4511	0.0283	0.168266674	0.054
PWV	y = 1.2589x + 1264.3	0.0305	0.174520132	0.053
ABI	y = 0.0003x + 1.0072	0.0191	0.13802653	0.077
VEGF	y = -0.0065x + 62.594	0.0000	-0.006709274	n.s.
Adiponectin	y = 0.0033x + 11.8	0.0003	0.016928384	n.s.
TNFα	y = 0.0046x + 0.0644	0.0178	0.13359534	0.084
ANP	y = -0.1346x + 93.385	0.0051	-0.071356329	n.s.
BNP	y = 0.0296x + 42.067	0.0005	0.021565371	n.s.

Plasma MGO and parameters after 5 years

IMT of Carotid



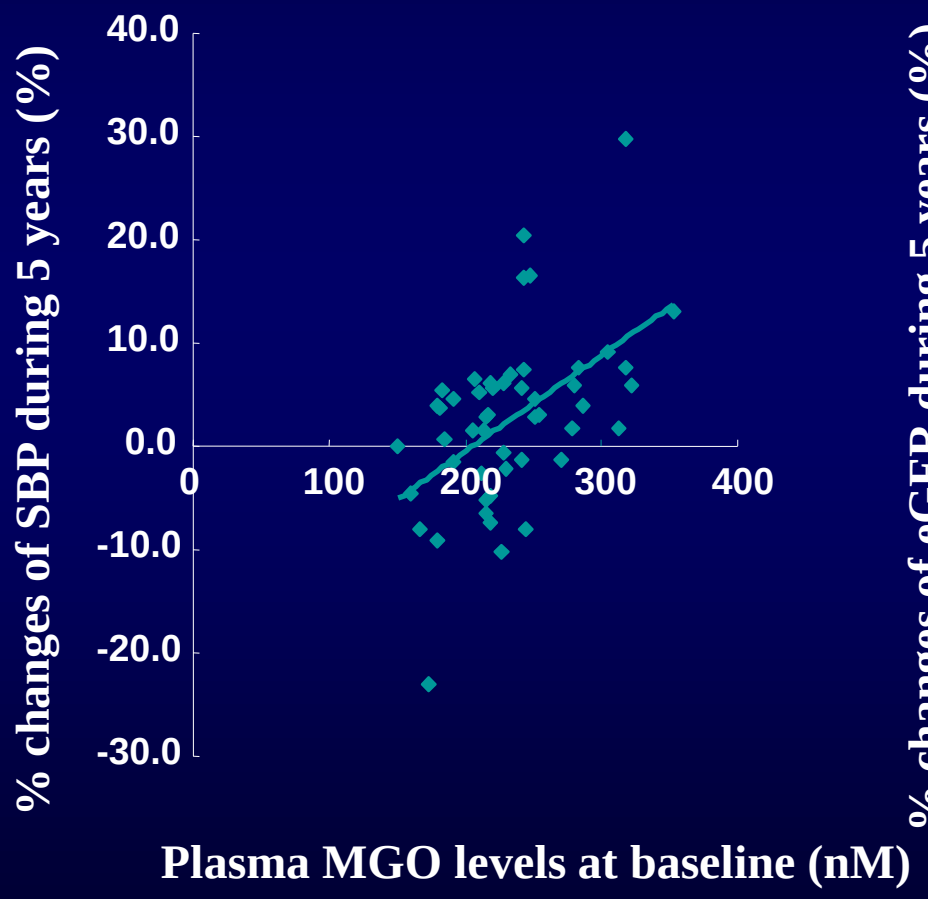
PWV



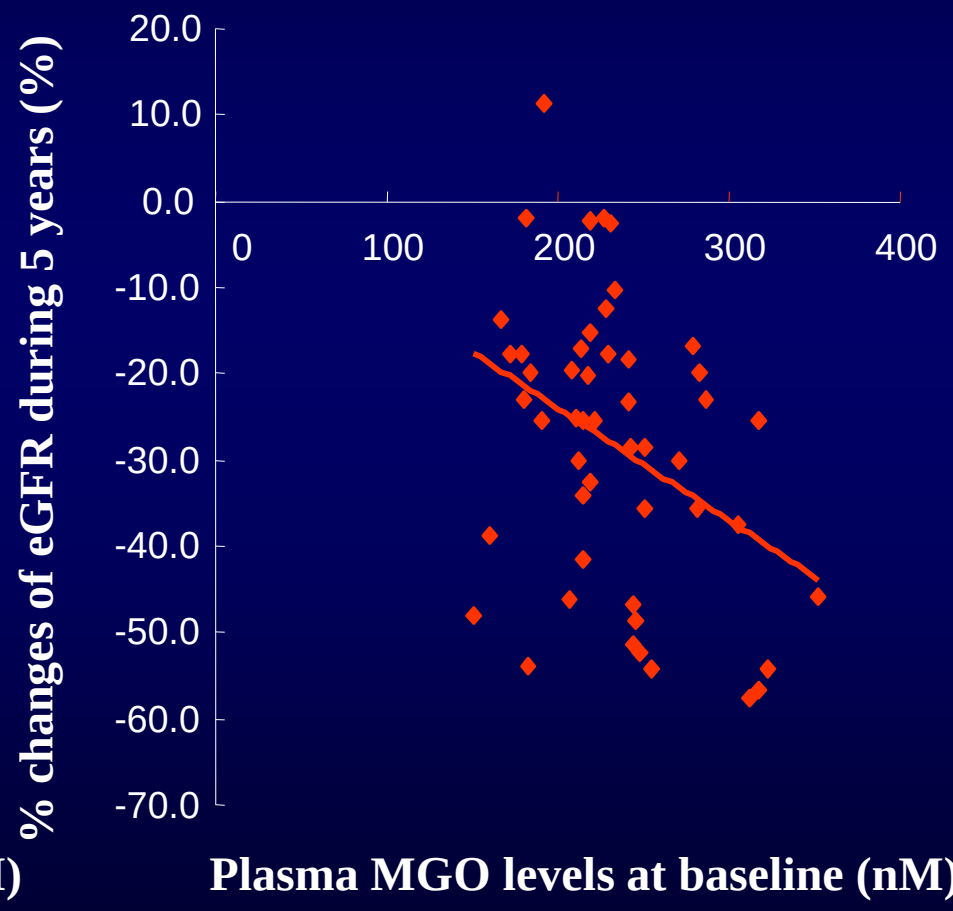
(Ogawa S, et al Hypertension 2010. 56: 471-476)

Plasma MGO and parameters after 5 years

Changes in BP

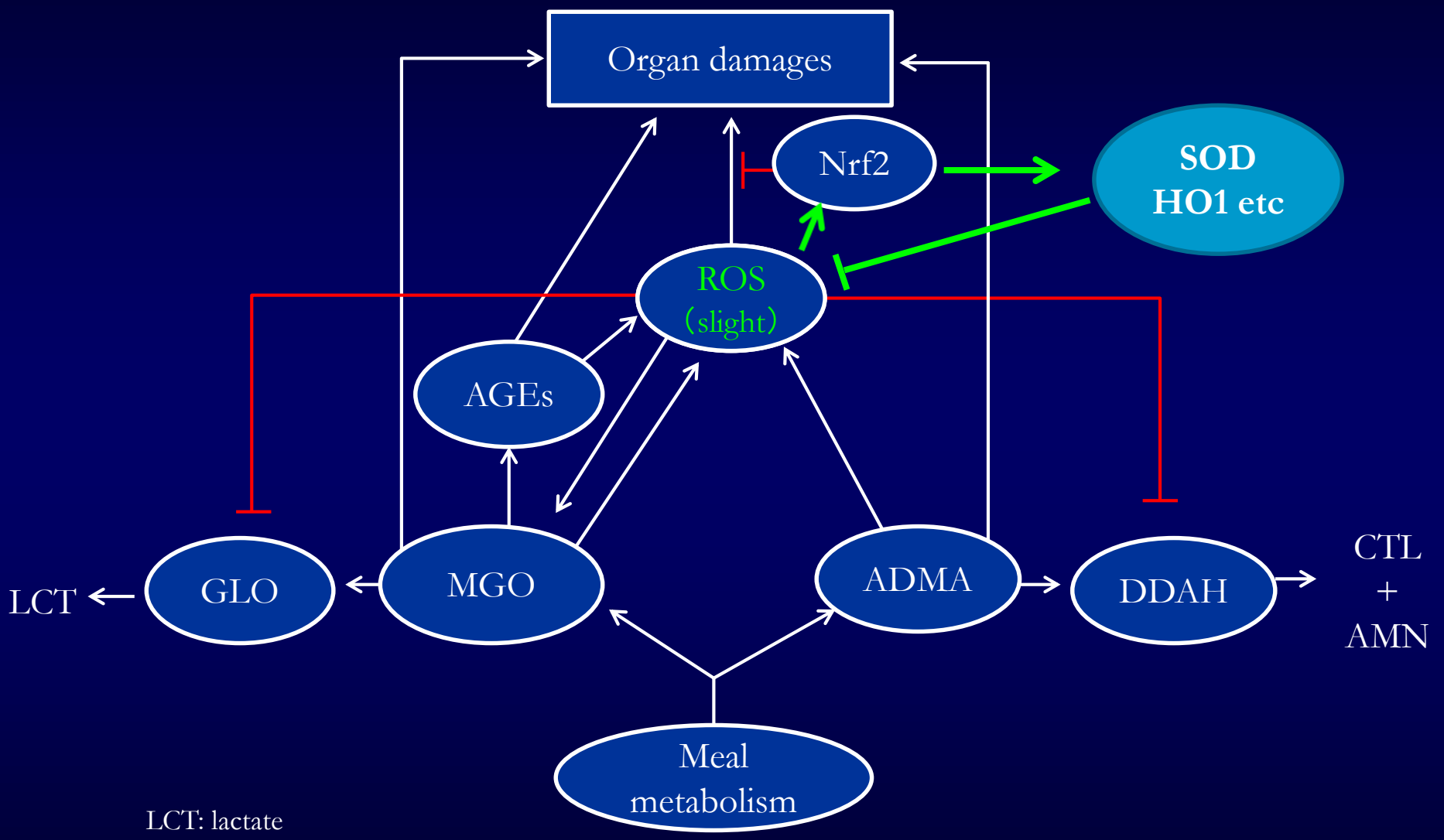


Changes in GFR



(Ogawa S,et al Hypertension 2010. 56: 471-476)

MGO、ADMA、Oxidative Stress



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DDAH: Dimethylarginine dimethylaminohydrolase
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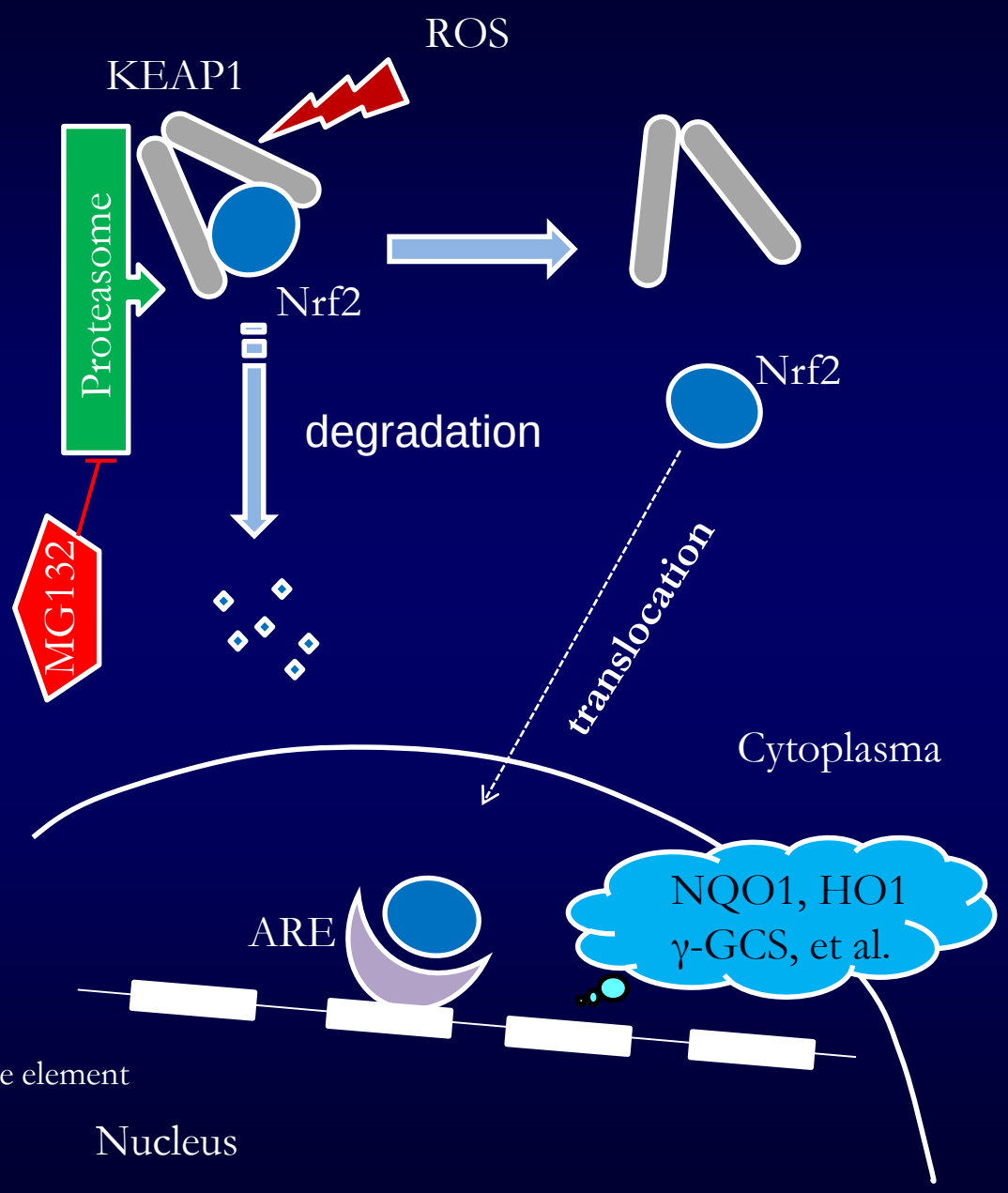
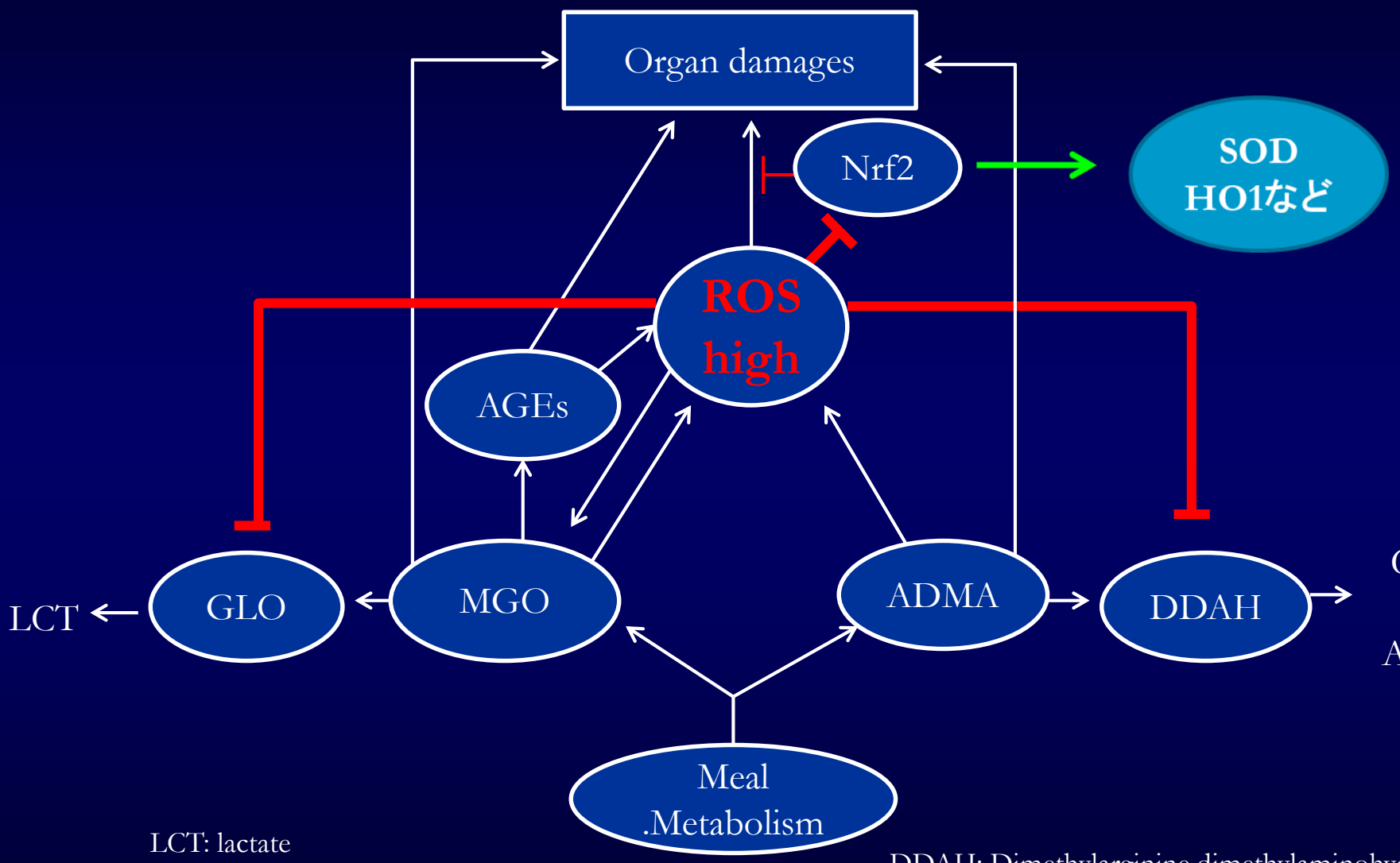
Stress responses by Nrf2 andKEAP1



ARE: antioxidant response element

(Li B, et al: Experimental Diabetes Research 2012(In Press))

MGO、ADMA、Oxidative Stress: advanced DN



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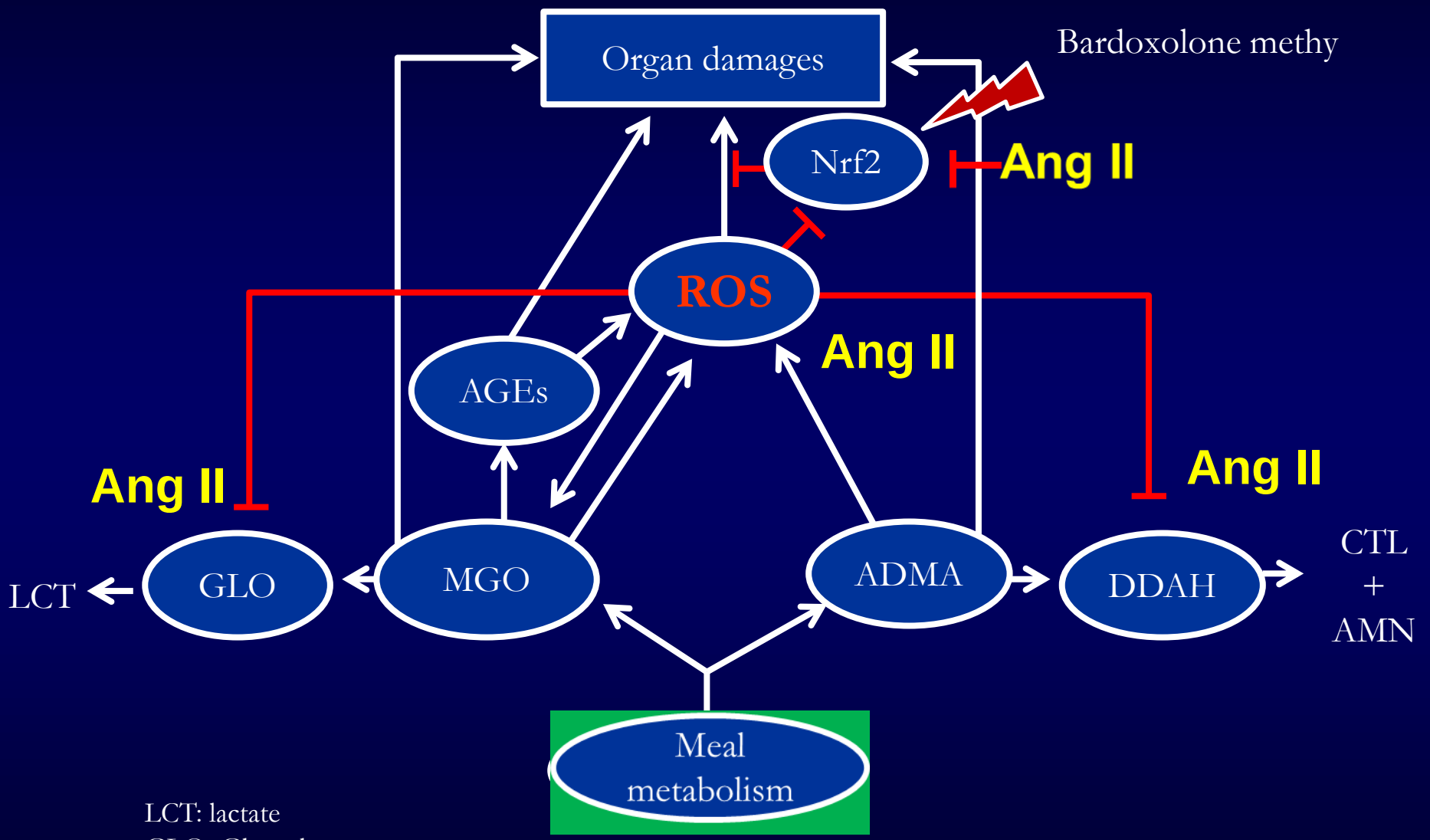
CTL: Citrulline
AMN: Amines

MGO、ADMA and ROS: advanced DN



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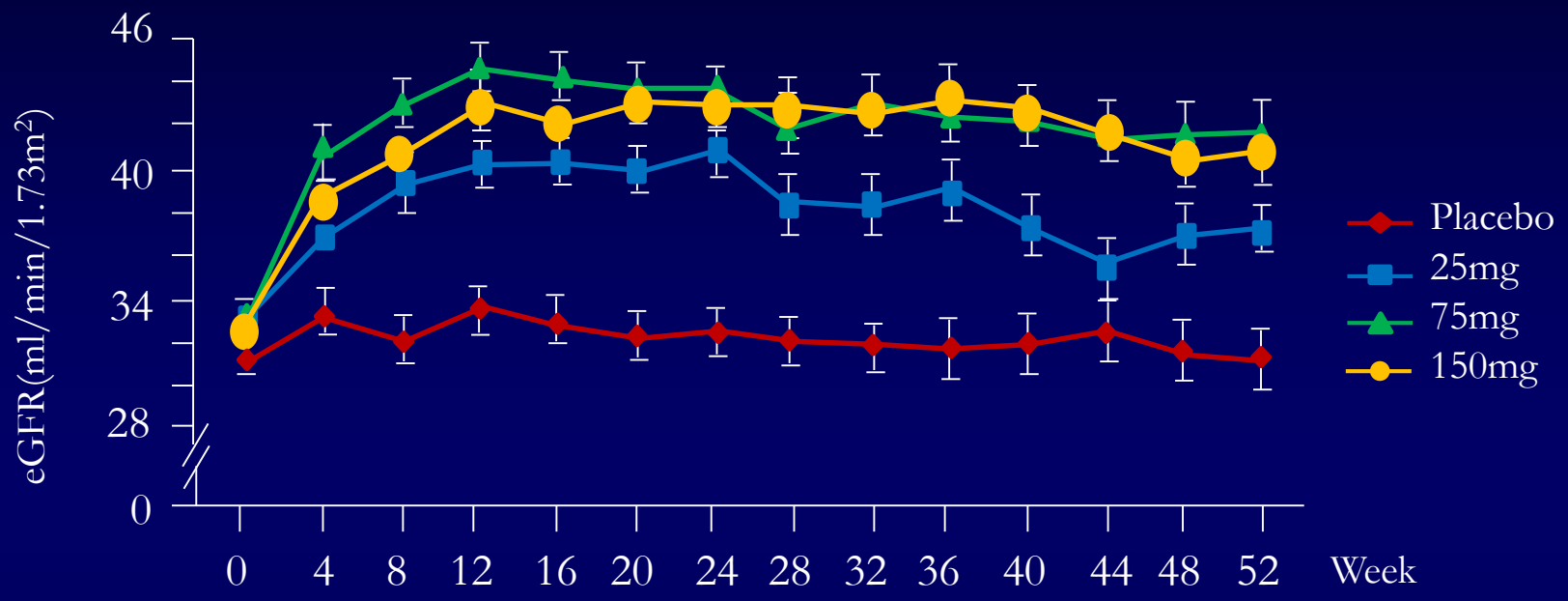
Changes in GFR



No. at Risk

Placebo	57	56	55	53	54	54	54	53	53	52	53	51	53	52
Bardoxolone methyl, 25mg	57	53	52	52	52	51	51	49	49	47	48	48	48	48
Bardoxolone methyl, 75mg	57	55	51	51	53	52	52	51	48	50	50	48	48	48
Bardoxolone methyl, 150mg	56	55	55	54	53	52	52	48	48	47	47	46	46	44

(Pergola PE, et al: N Engl J Med 365; 327-336, 2011)

Ongoing

~Inhibition of MGO at right phases~

- Oral pyridoxamine on peritoneal fluid MGO level in CAPD patients
- Oral pyridoxamine in schizophrenia
- Oral pyridoxamine in CKD patients

Tohoku University
~since 1907~

Thank you for your attention

100 year anniversary