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Artemisinin and Nitric Oxide

Mechanisms and Implications in Disease and Health

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Preface

Nitric oxide (NO), a physiologically important signaling molecule, was proclaimed "a molecule of the year" in 1992 by the *Science* magazine. The Nobel Prize in Physiology or Medicine in 1998 was awarded for the elucidation of NO's physiological roles. Artemisinin (ART), an effective antimalarial phytochemical monomer, is closely relevant to NO by inhibiting NO synthase (NOS). The discovery of ART led to the winning of the Lasker-DeBakey Clinical Medical Research Award in 2011.

This book introduces the dichotomies of beneficial and harmful effects of NO on human health and diseases in a dose-dependent manner, and also discusses the potential and multifaceted uses of ART in disease interventions and health maintenance. I not only explain why a steady-state relatively low NO level should be kept during development and aging, but also tell how to avoid an extremely high NO level triggered by inflammation. In general, an optimal NO level protects your health, but an extreme NO level hurts your body. So NO is often said to be a "double-edged sword"!

Based on my proposed "a uniform NO threshold theory in disease and health", I intend to reveal a millennium-long mystery of longevity, and also dedicate to decipher the puzzling secrets of aging and aging-associated diseases although they remain largely unknown. Except for the long-lived genetic background, what is the "fountain of youth"? I would say it is NO! Where is the "fountain of youth"? I would say it is hidden in mitochondria! What is the etiological cause of metabolic diseases, cardiovascular diseases, autoimmune diseases, neurodegenerative diseases, and cancer? The answer might be, among others, low-grade inflammation! Where is the origin of low-grade inflammation? The answer might be, at least, derived from the bacterial endotoxin lipopolysaccharide (LPS)!

NO is mainly biosynthesized by three isoforms of NOS in animals and human. A physiological low level of NO that would extend your lifespan is derived from endothelial NOS (eNOS) and neuronal NOS (nNOS), but the pathological high level of NO that might worsen your health is originated from proinflammatory cytokine inducible NOS (iNOS), although it is also responsible for killing the invaded pathogens. A person addicting high-fat diets (HFD) has a raised risk of

developing insulin resistance, type II diabetes, fatty liver, and even liver cancer because his/her iNOS is always activated by low-grade inflammation. In contrast, a person obeying calorie restriction (CR) has a great probability of becoming a centenarian because his/her eNOS and nNOS are higher enough to activate an antioxidative network for scavenging reactive oxygen species (ROS). So iNOS and eNOS/nNOS represent the pivotal targets for improvement of human health!

Why people become obese remains obscure, but obese or lean is most likely modulated by an interaction of nutrients with gut microbiota. A fat-rich food can nurse "meat-addicted microbes" and impede the growth of "fiber-degraded microbes", thereby leading to adipose depots and overweight/obesity. Concisely, while obesity is switched by turning on iNOS for adipogenesis, weight loss is switched by turning on eNOS for adipolysis. Whether obesity is a disease is currently a debating issue. In my opinion, obese persons without chronic inflammation should be healthy and exhibit insulin sensitivity, whereas obese persons with chronic inflammation should be unhealthy and show insulin tolerance and even develop type II diabetes. In an obese person with gastrointestinal dysbiosis due to an overgrowth of Gram-negative bacteria, especially gut mucin-degrading bacteria, LPS within the gut would leak into the bloodstream and trigger a systemic inflammatory response, hence inducing inflammatory diseases. So it could be said that gut bacterial dysbiosis cause LPS leakage, LPS leads to inflammation, and inflammation results in metabolic diseases.

This book was written for medical researchers and students, clinicians, biologists, and other people interested in NO-involved biology and medicine. Mainly based on our own analytic data and the most cited references on ART, NO, and heme-containing proteins, this seven-chapter book has attempted to reconcile the interaction of ART with cytosolic NOS and mitochondrial cytochrome *c* oxidase (COX), and also discuss the current achievements of ART applying in the cutting-edge innovation for antitumor, antibacterial infection, anti-inflammation, and antiaging. As prospects, iNOS and eNOS/nNOS deem the vital targets in drug discovery for disease interventions.

At the very end, I have to say that ART is really an elixir!

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Contents

Abbreviations

3NT	3-Nitrotyrosine
AMP	Ampicillin
AMPK	Adenosine monophosphate-activated protein kinase
ARG	L-arginine
ASC	Artemisinin-sensitizing compound
AT	Aminotriazole
ATP	Adenosine triphosphate
BAT	Brown adipose tissue
BIA	Bacteria-induced arthritis
BLA	Betulilic acid
BMI	Body mass index
CII	Collagen type II
CAT	Catalase
CEF	Cefotaxime
CFA	Complete Freund's adjuvant
CIA	Collagen-induced arthritis
CIAA	Complete Freund's adjuvant-induced acute arthritis
CICA	Collagen type II-complete Freund's adjuvant-induced chronic arthritis
CO	Carbon monoxide
COX	Cytochrome *c* oxidase
CR	Calorie restriction
CSC	Cancer stem cell
DM	Diethyl maleate
DNMT	DNA methyltransferase
DNP	2,4-dinitrophenol
DTT	Dithiothreitol
eNOS	Endothelial nitric oxide synthase
EPO	Erythropoietin
G^-	Gram-negative bacteria

G^+	Gram-positive bacteria
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GC	Gualylate cyclase
GLUT	Glucose transporter
GSH	Glutathione (reduced)
HFD	High-fat diet
HIF-1α	Hypoxia inducible factor alpha
HO-1	Heme oxygenase 1
IGF	Insulin-like growth factor
IL	Interleukin
iNOS	Inducible nitric oxide synthase
KEGG	Kyoto Encyclopedia of Genes and Genomes
LA	Lactic acid
LFD	Low-fat diet
LIAA	Lipopolysaccharide-induced acute arthritis
L-NMMA	N^G-monomethyl-L-arginine monoacetate
LPS	Lipopolysaccharide
MA	Mercaptosuccinic acid
ME	Mitochondrial enhancement
mtNOS	Mitochondrial nitric oxide synthase
mTOR	Mammalian target of rapamycin
NAD^+	Oxidized nicotinamide adenine dinucleotide
$NADH+H^+$	Reduced nicotinamide adenine dinucleotide
$NADP^+$	Oxidized nicotinamide adenine dinucleotide phosphate
$NADPH+H^+$	Reduced nicotinamide adenine dinucleotide phosphate
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NG	Nitroglycerine
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
NT	Nitroglycerin
PGC-1α	Peroxisome proliferator-activated receptor γ coactivator 1 alpha
PME	Post-mitochondrial enhancement
POX	Peroxidase
RA	Rheumatoid arthritis
RAP	Rapamycin
RIF	Rifampicin
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SAT	Subcutaneous adipose tissue
SCFA	Short-chain fatty acid
SIRT1	Sirtuin 1
SNP	Sodium nitroprusside

SOD	Superoxide dismutase
SpO_2	Saturation percentages of O_2
TERT	Telomerase reverse transcriptase
TLR4	Toll-like receptor 4
TNFα	Tumor necrosis factor alpha
TRF	Telomere restriction fragment
VAT	Visceral adipose tissue
VEGF	Vascular endothelial growth factor
WAT	White adipose tissue