Christian Doppler Laboratory for Cardiac and Thoracic Diagnosis & Regeneration

MEDIZINISCHE UNIVERSITÄT WIEN

Nobel Prize in Medicine/Physiology 1998

"….for their discoveries concerning

nitric oxide as a signalling molecule

in the cardiovascular system."

Christian Doppler Laboratory for Cardiac and Thoracic Diagnosis & Regeneration

MEDIZINISCHE UNIVERSITÄT WIEN

Background

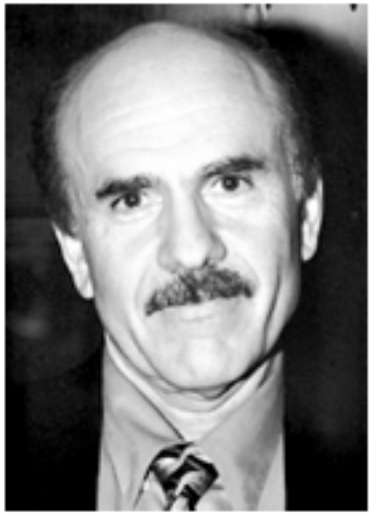
- Mechanism of action of nitroglycerin unknown until 1970s
- Acetylcholine as vasodilatator *in vivo*, but vasoconstrictor *in vitro*

Robert F. Furchgott

Born: 4 June 1916, Charleston, SC, USA

Died: 19 May 2009, Seattle, WA, USA

Affiliation at the time of the award: SUNY Health Science Center, Brooklyn, NY, USA



Louis J. Ignarro

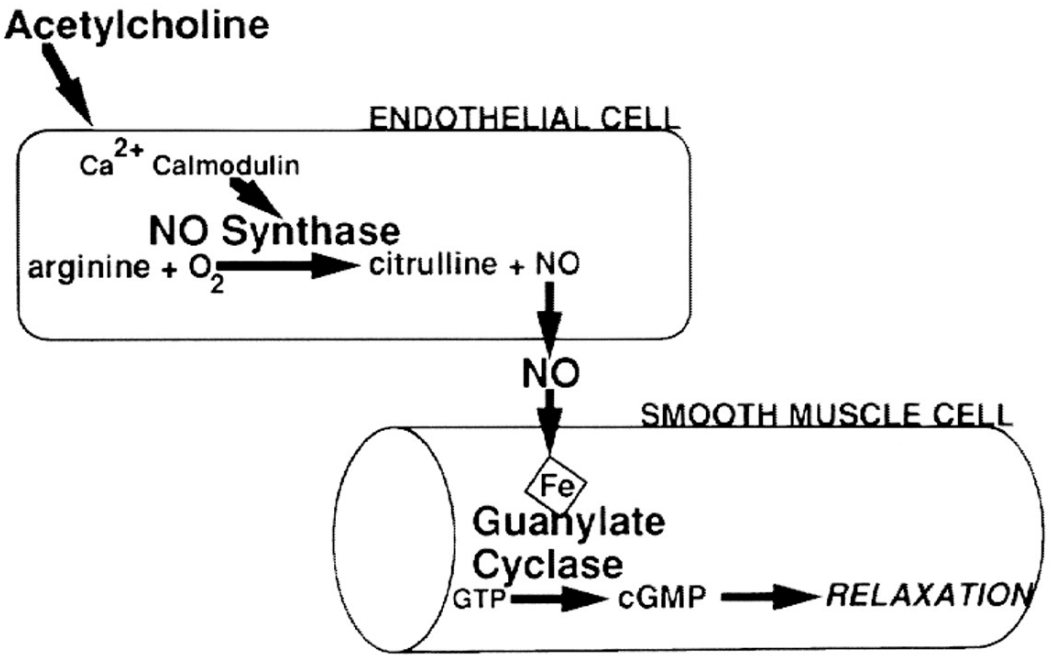
Born: 31 May 1941, Brooklyn, NY, USA

Affiliation at the time of the award: University of California School of Medicine, Los Angeles, CA, USA

Ferid Murad

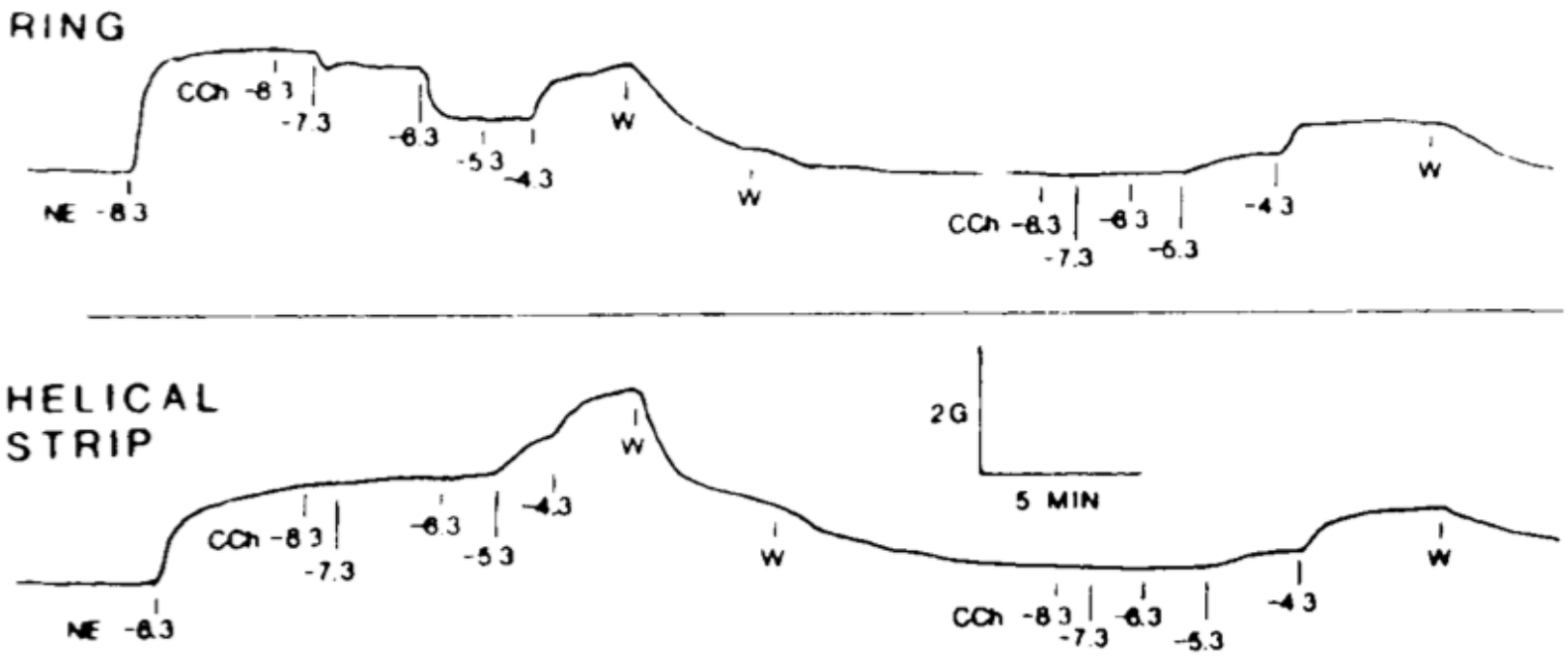
Born: 14 September 1936, Whiting, IN, USA

Affiliation at the time of the award: University of Texas Medical School at Houston, Houston, TX, USA

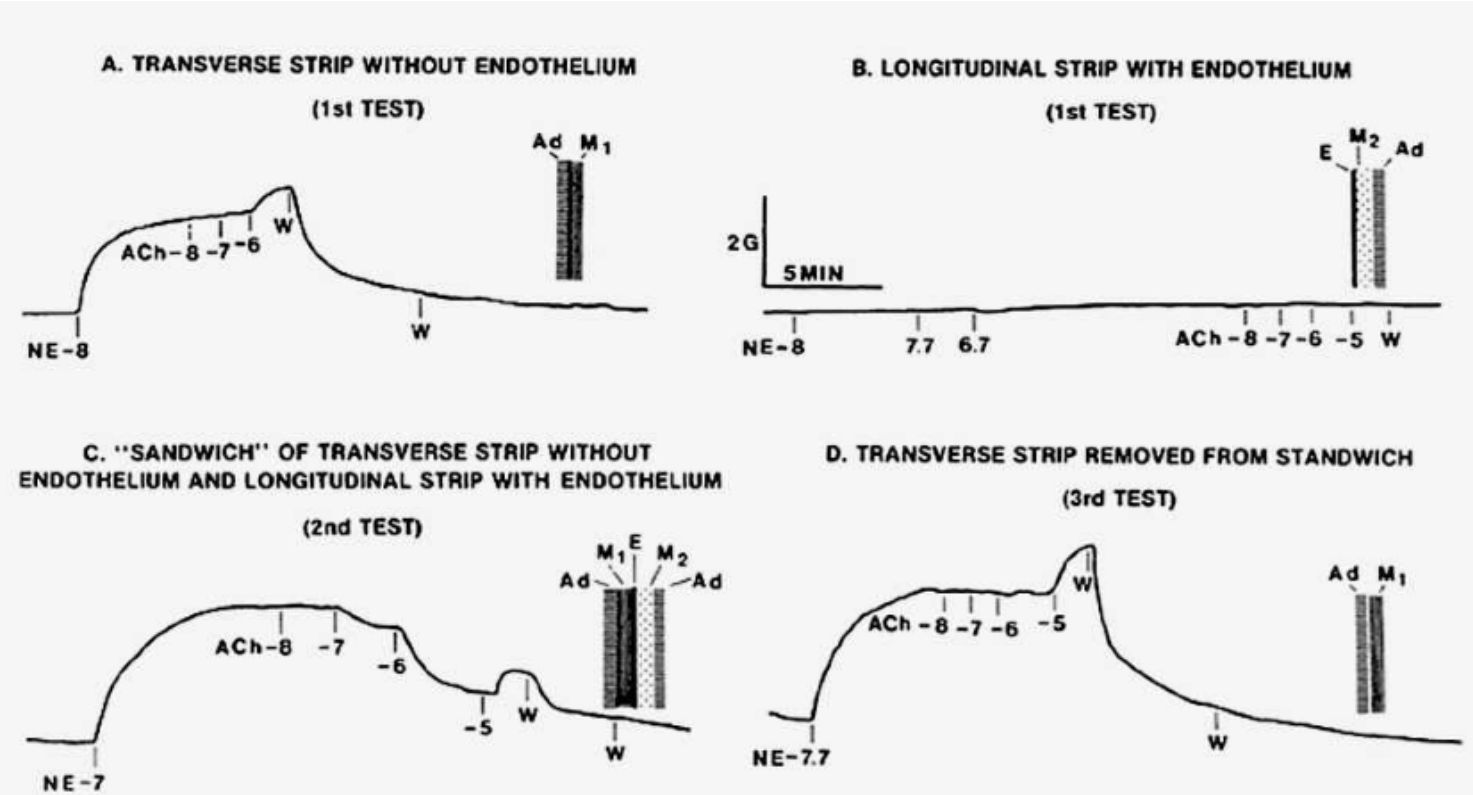

Acetylcholine
ENDOTHELIAL CELL
Ca2+ Calmodulin
NO Synthase
arginine + O2
citrulline + NO
NO
SMOOTH MUSCLE CELL
Fe
Guanylate Cyclase
GTP
cGMP
RELAXATION

Robert F. Furchgott

Key findings



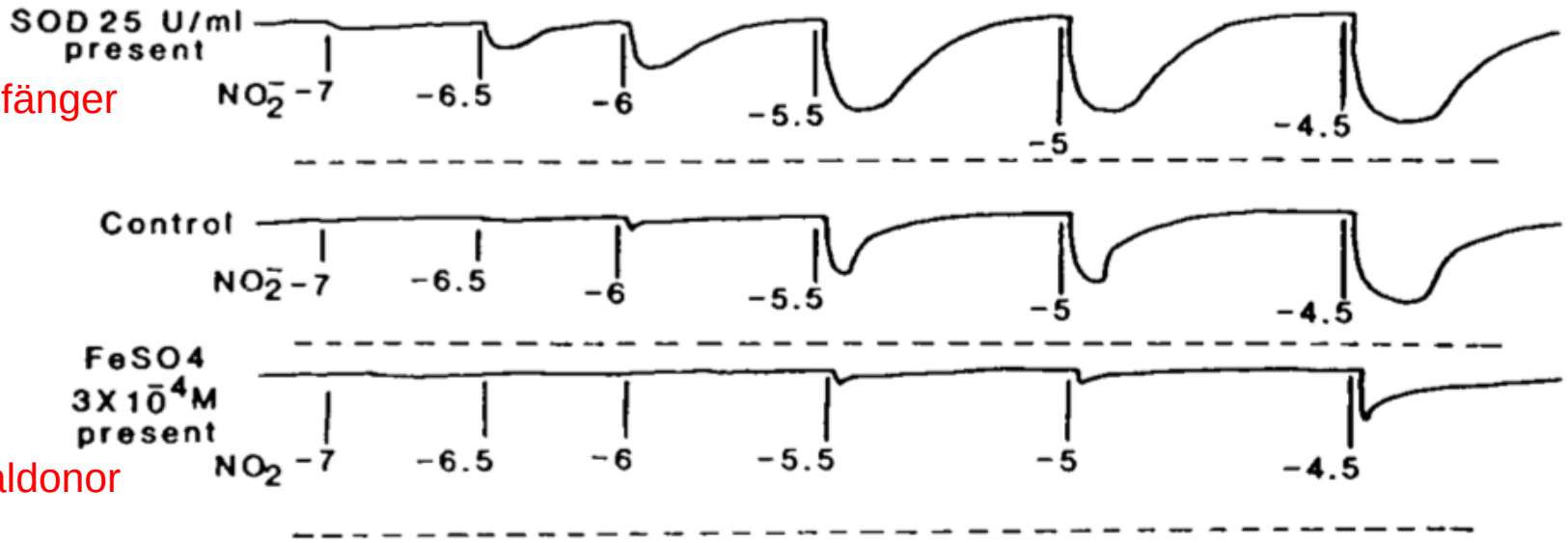
CCh = Carbachol (similar to Ach)



-> „endothelium-derived relaxing factor“ (EDRF)

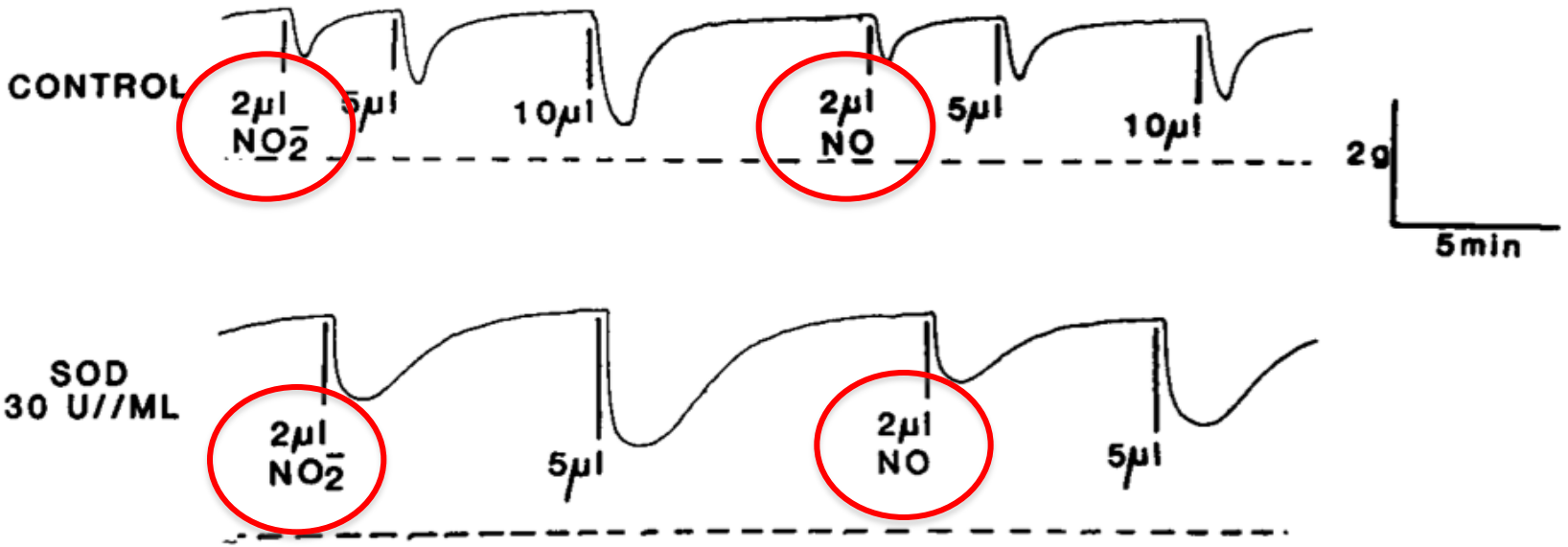
R Furchgott, Nobel lecture 1998

Radikalfänger

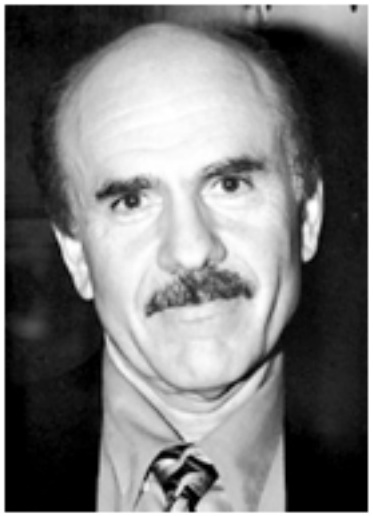


Radikaldonor

R Furchgott, Nobel lecture 1998

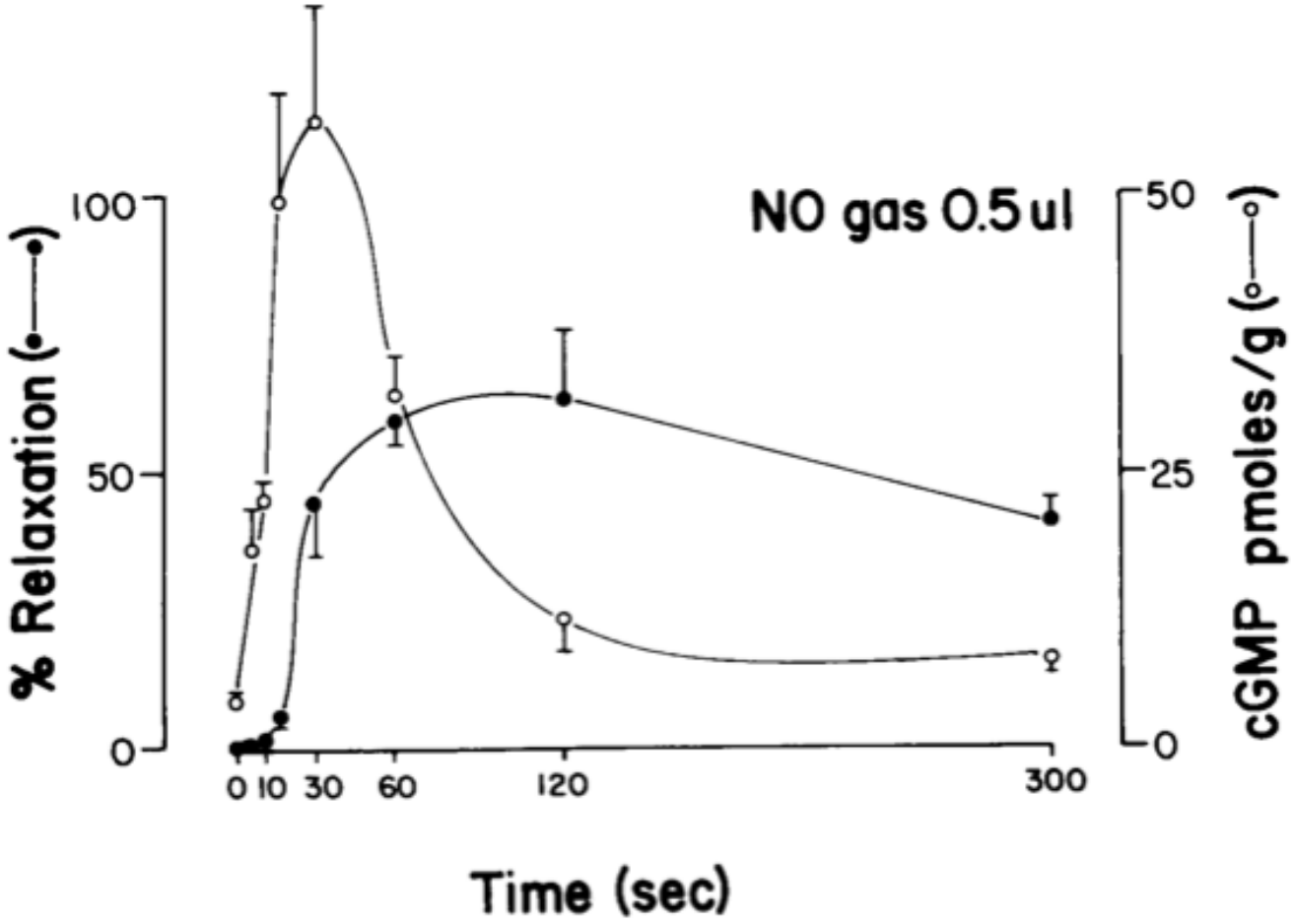


R Furchgott, Nobel lecture 1998

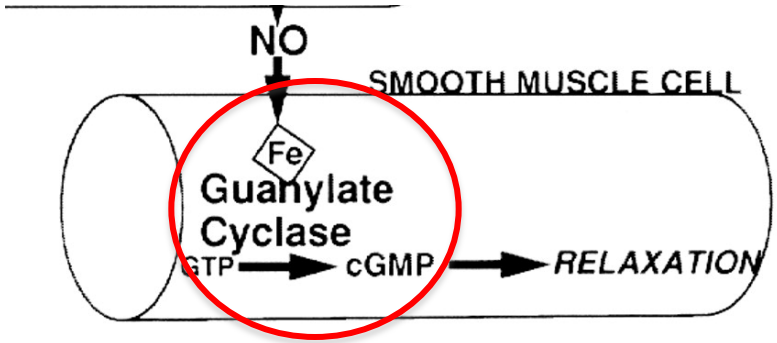


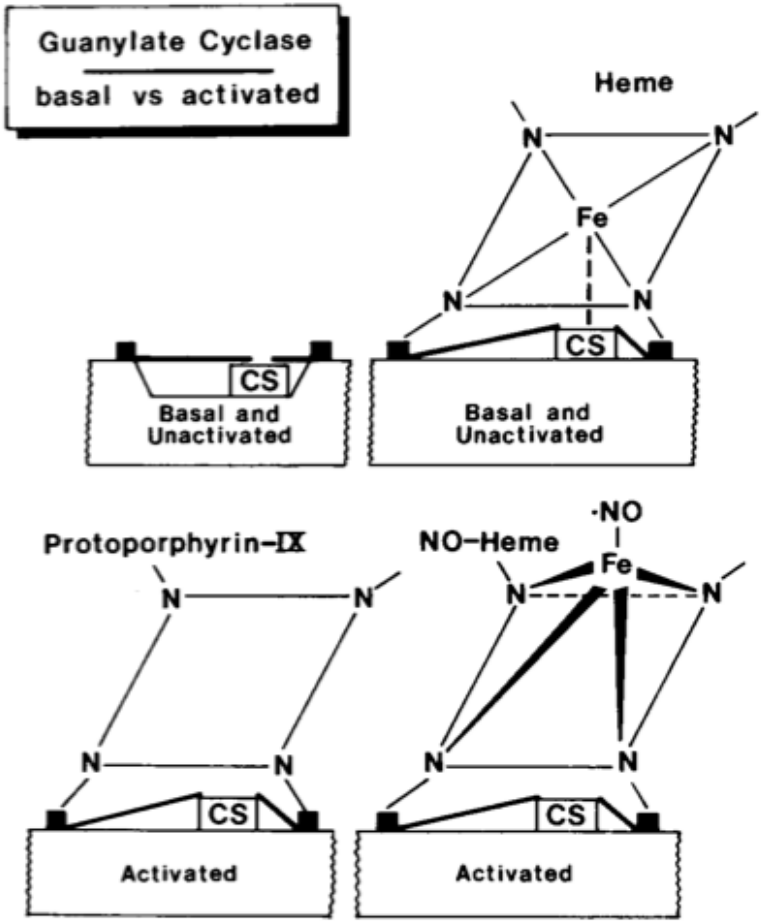
Louis J. Ignarro

Key findings

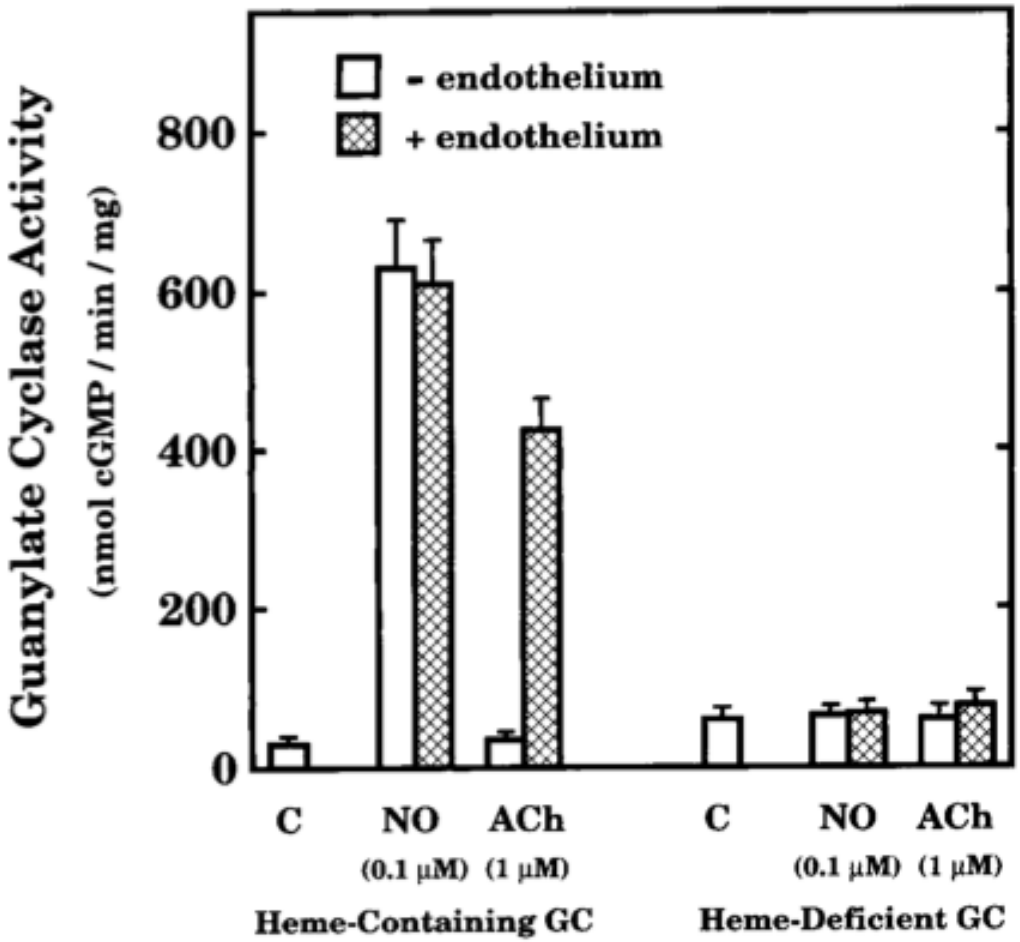


L Ignarro, Nobel lecture 1998



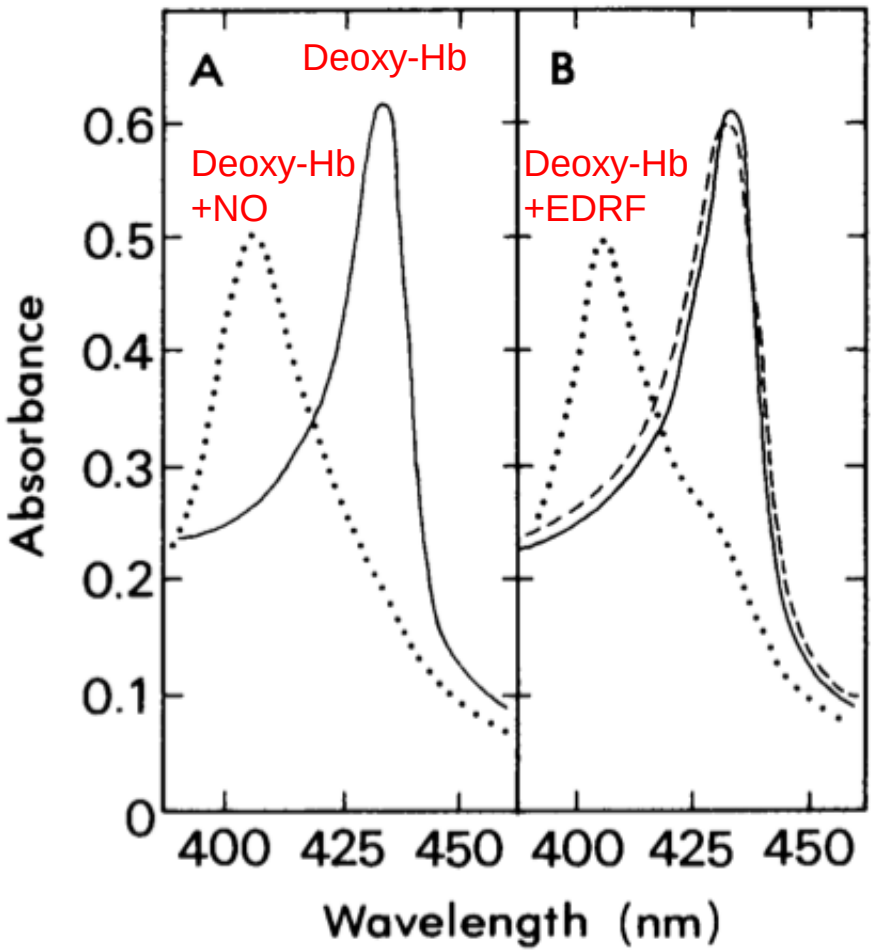


L Ignarro, Nobel lecture 1998



L Ignarro, Nobel lecture 1998

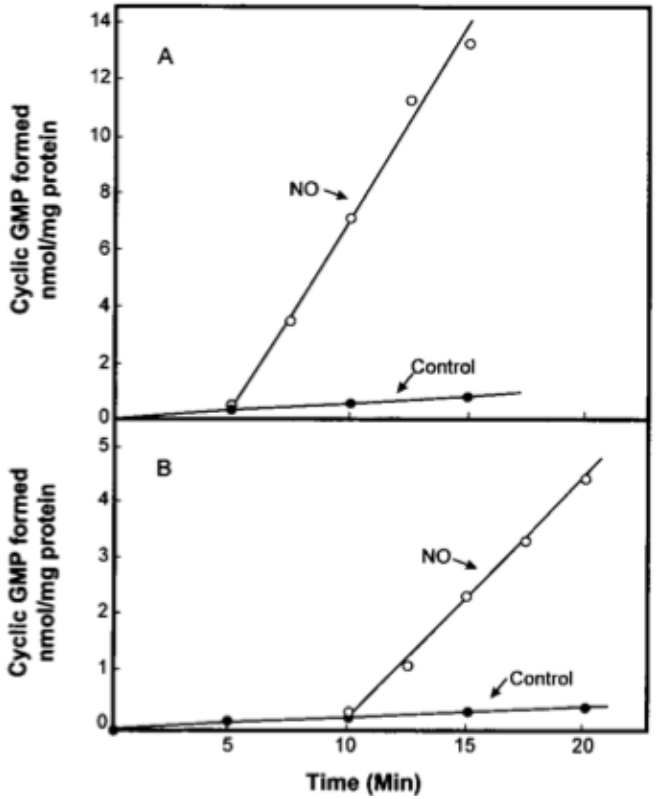
NO & EDRF



L Ignarro, Nobel lecture 1998

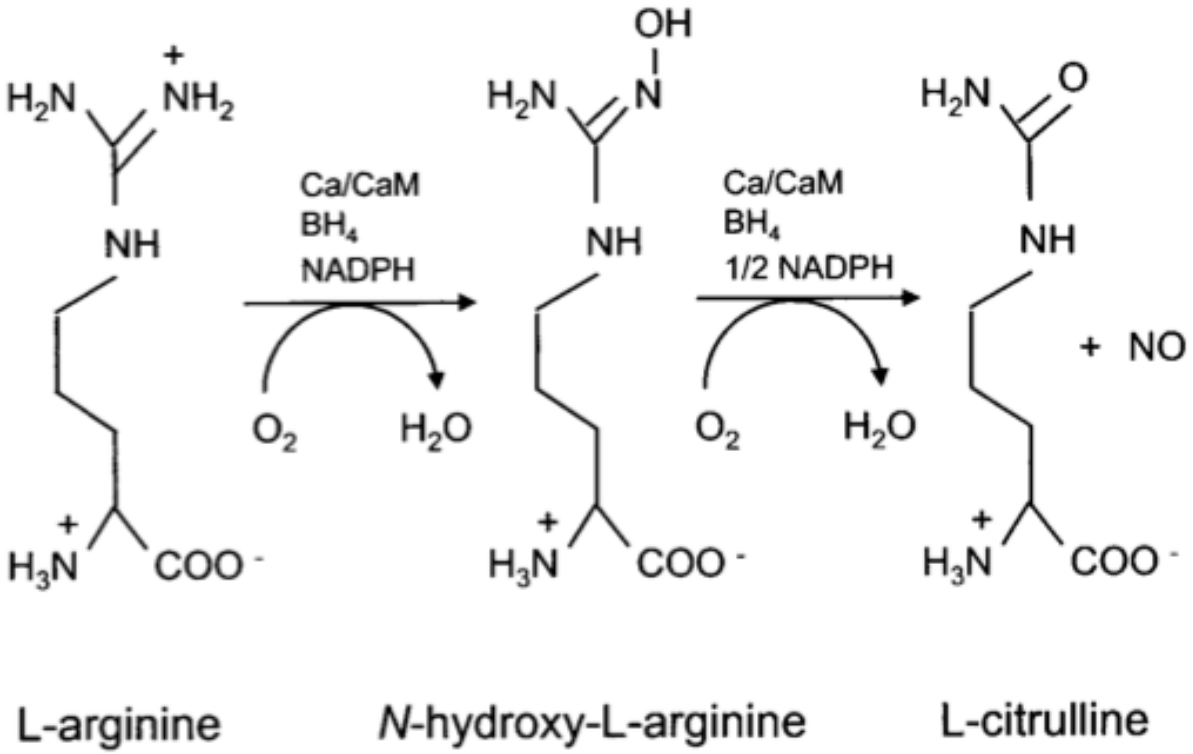
Ferid Murad

Key findings

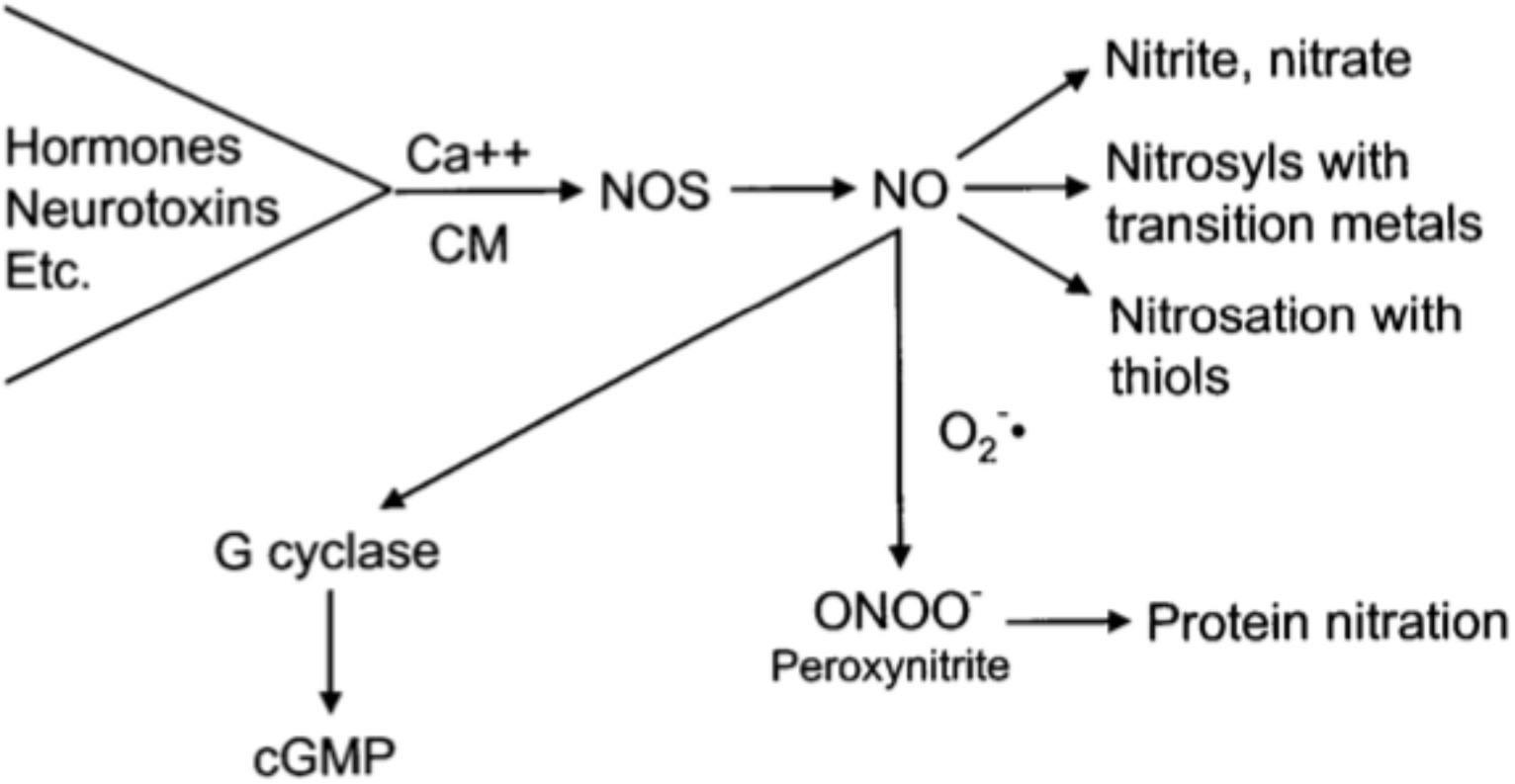


NOS-1 (155kD)	neuronal, brain, Type I-NOS; central and peripheral neurons, NANC neurons, islets, endometrium, skeletal muscle, etc.
NOS-2 (125kD)	inducible, Type II-NOS; macrophage, liver, smooth muscle, endothelium, heart, etc; effects of LPS, cytokines and glucocorticoids
NOS-3 (135kD)	endothelial, Type III-NOS; endothelium, brain, heart, etc.; acylation, phosphorylation

F Murad, Nobel lecture 1998



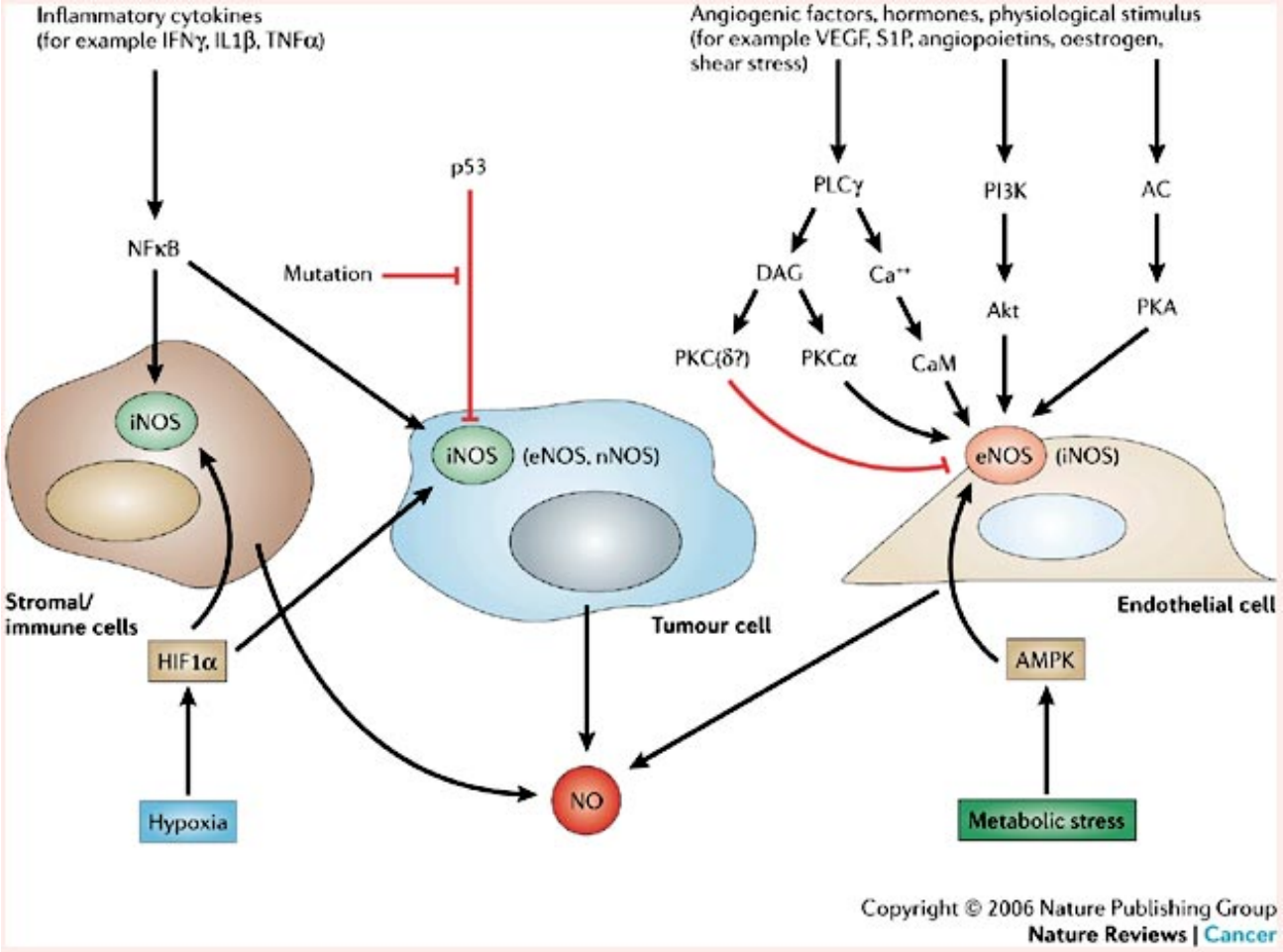
F Murad, Nobel lecture 1998



F Murad, Nobel lecture 1998

Relevance

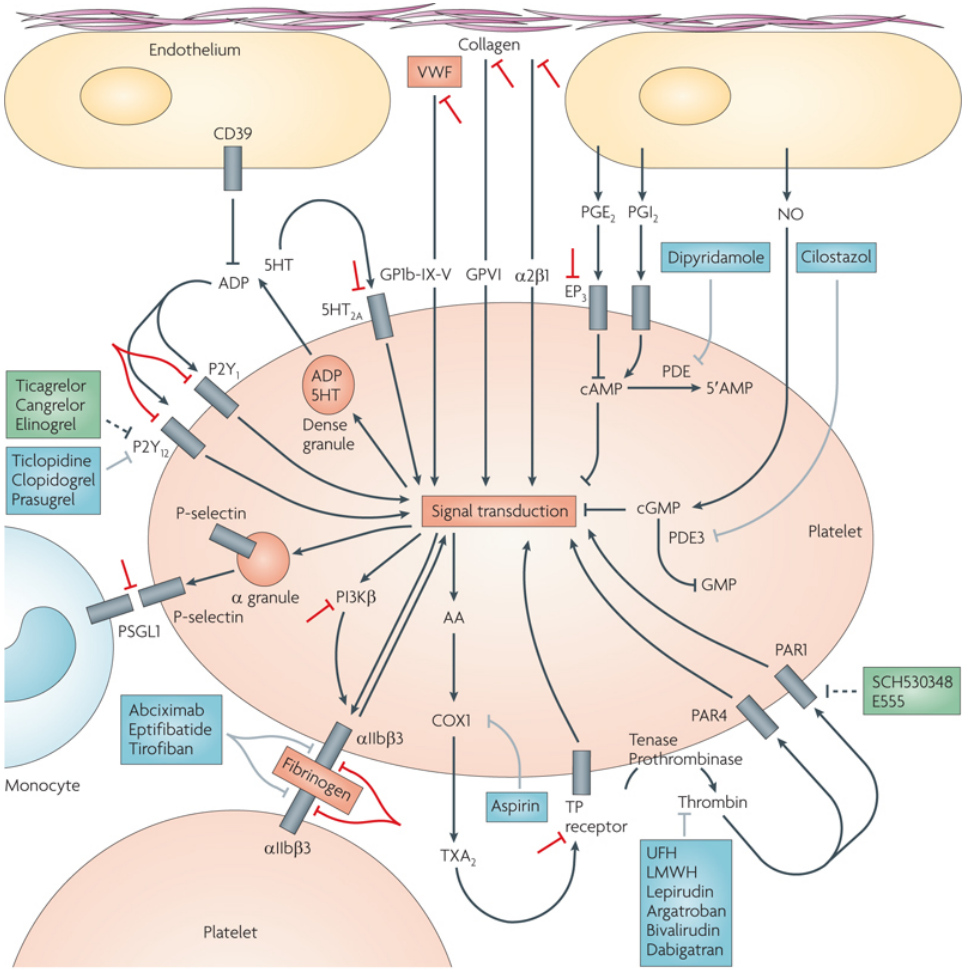
Oncology


Inflammatory cytokines
(for example IFNγ, IL1β, TNFα)
Angiogenic factors, hormones, physiological stimulus
(for example VEGF, S1P, angiopoietins, oestrogen,
shear stress)
p53
NFκB
Mutation
PLCγ
PI3K
AC
DAG
Ca++
Akt
PKA
PKC(δ?)
PKCα
CaM
iNOS
iNOS (eNOS, nNOS)
eNOS (iNOS)
Stromal/
immune cells
Tumour cell
Endothelial cell
HIF1α
AMPK
NO
Hypoxia
Metabolic stress
Copyright © 2006 Nature Publishing Group
Nature Reviews | Cancer

Christian Doppler Laboratory for Cardiac and Thoracic Diagnosis & Regeneration

MEDIZINISCHE UNIVERSITÄT WIEN

Platelet function



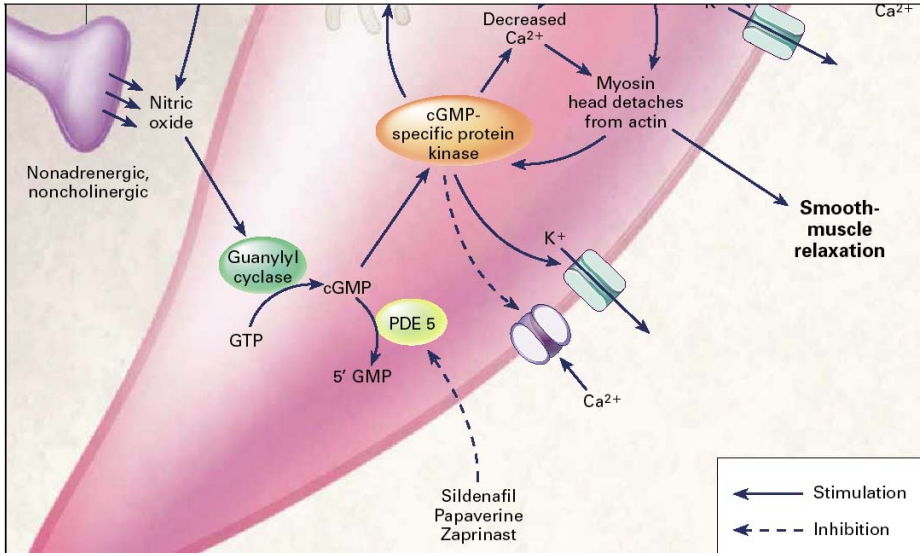
Nature Reviews | Drug Discovery

Erectile dyfunction/Pulmonary hypertension

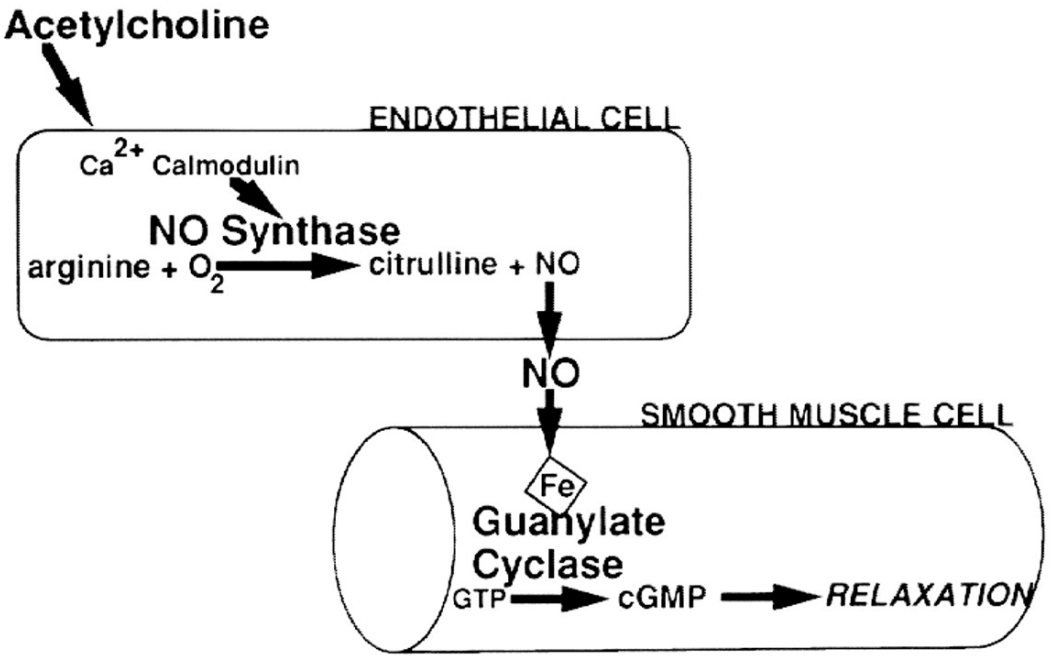
90 THE NEW ENGLAND JOURNAL OF MEDICINE Jan. 9, 1992

NITRIC OXIDE AS A MEDIATOR OF RELAXATION OF THE CORPUS CAVERNOSUM IN RESPONSE TO NONADRENERGIC, NONCHOLINERGIC NEUROTRANSMISSION

JACOB RAJFER, M.D., WILLIAM J. ARONSON, M.D., PEGGY A. BUSH, B.S., FREDERICK J. DOREY, PH.D., AND LOUIS J. IGNARRO, PH.D.



T.Lue, NEJM 342:1802, 2000


Acetylcholine
ENDOTHELIAL CELL
Ca2+ Calmodulin
NO Synthase
arginine + O2
citrulline + NO
NO
SMOOTH MUSCLE CELL
Fe
Guanylate Cyclase
GTP
cGMP
RELAXATION