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CardioVascular

G.I.

CNS

Pulmonary

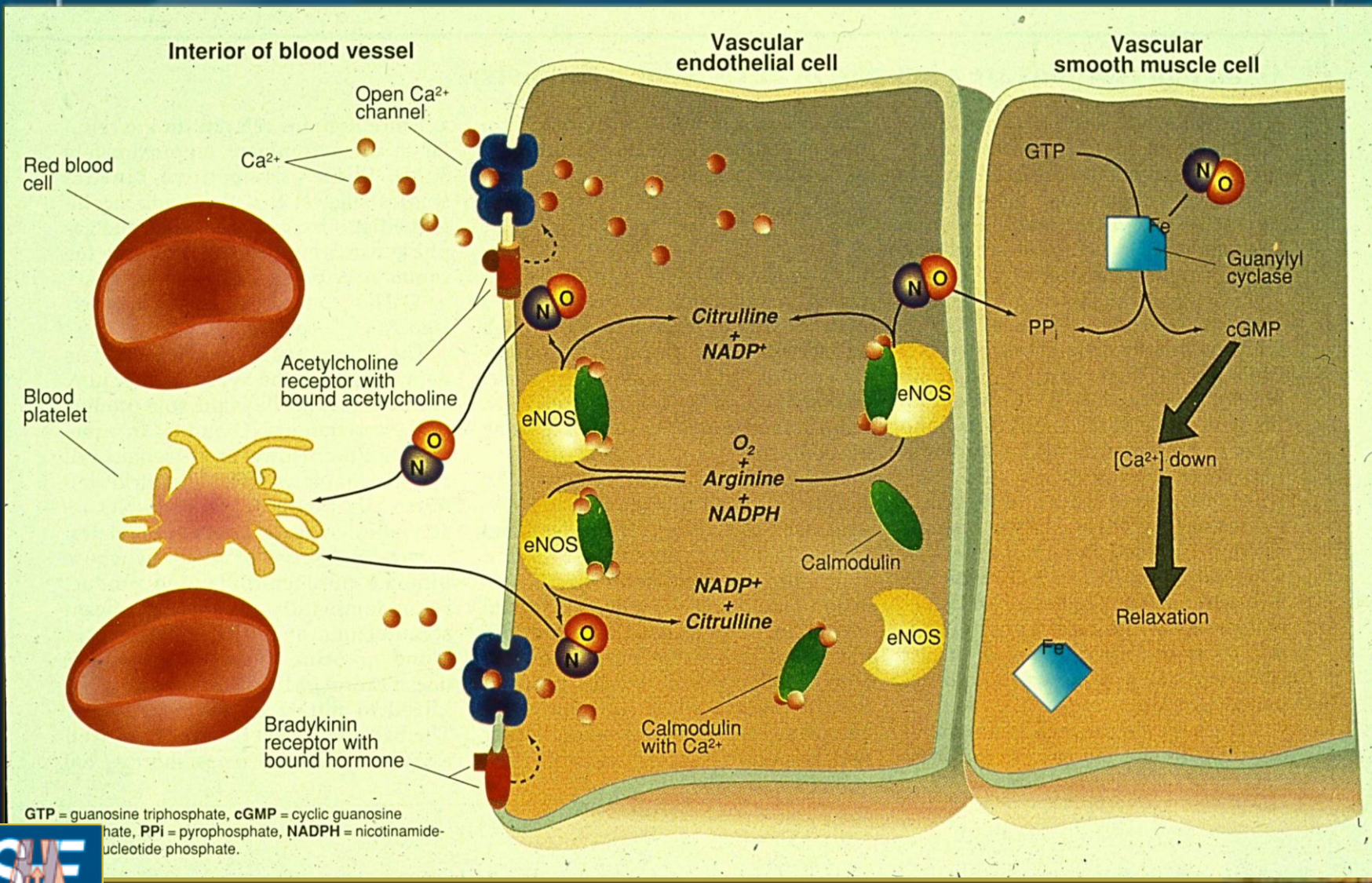
NO

Anti-Inflammatory

G.U.

Host Defense

Many Others



GTP = guanosine triphosphate, cGMP = cyclic guanosine triphosphate, PP_i = pyrophosphate, NADPH = nicotinamide nucleotide phosphate.



NEBIVOLOL

*A Unique Highly CardioSelective
Beta-Adrenergic Receptor Blocker
with Vasodilator Properties
Attributed to Nitric Oxide*

VASODILATION

- ✓ Partly endothelium-dependent:

Mechanism = \uparrow eNOS \rightarrow \uparrow NO

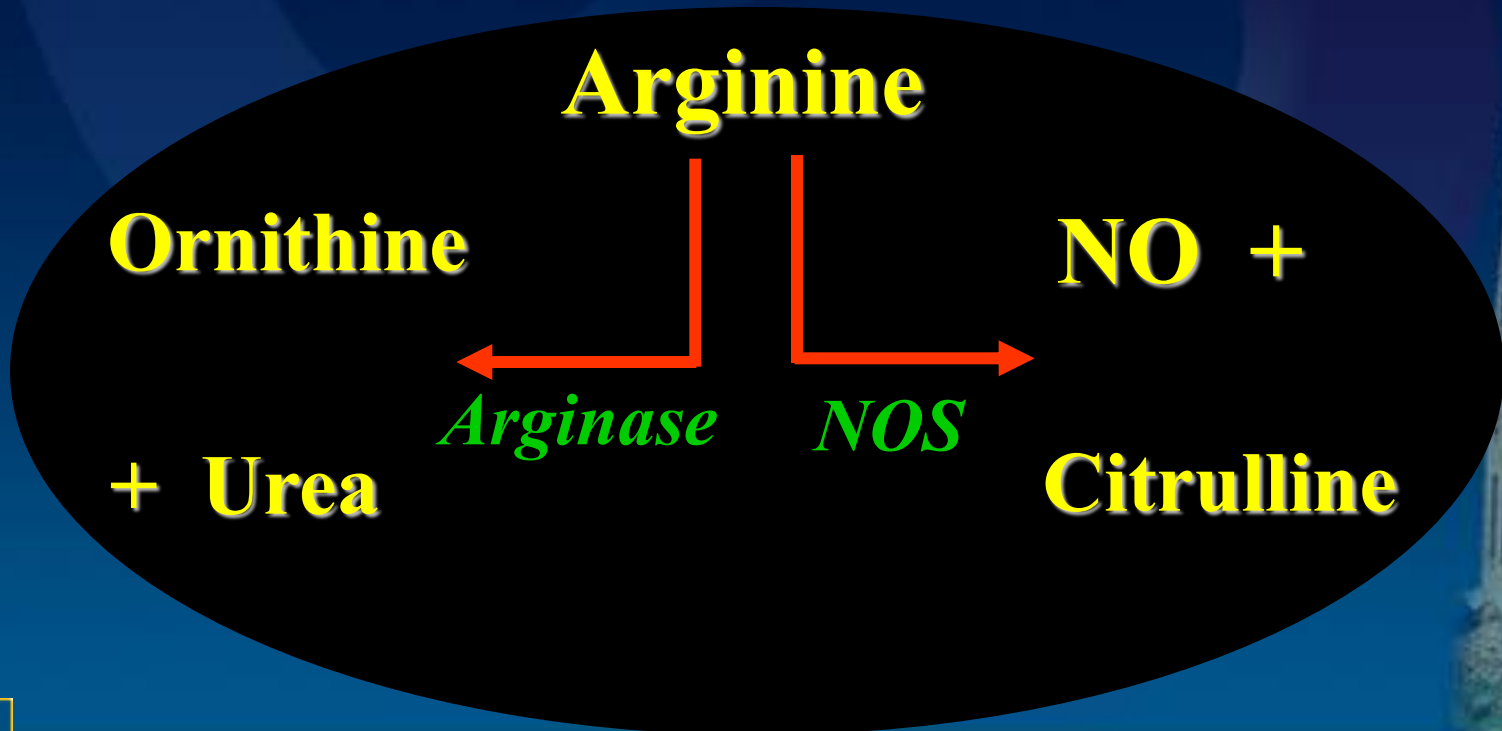
- ✓ Partly direct action on vascular smooth muscle \rightarrow \uparrow NO

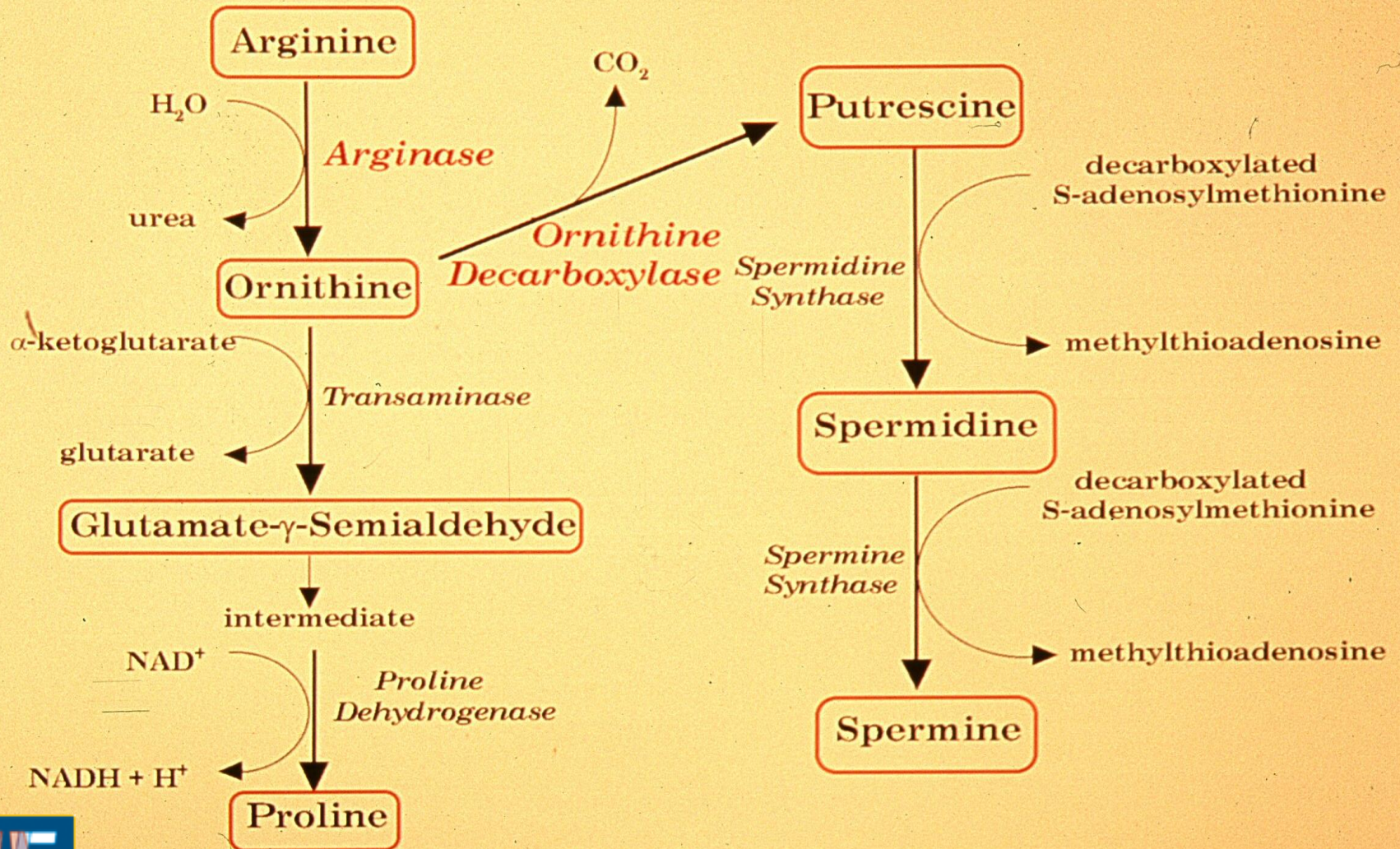
Nebivolol Inhibits the Growth of Vascular Smooth Muscle

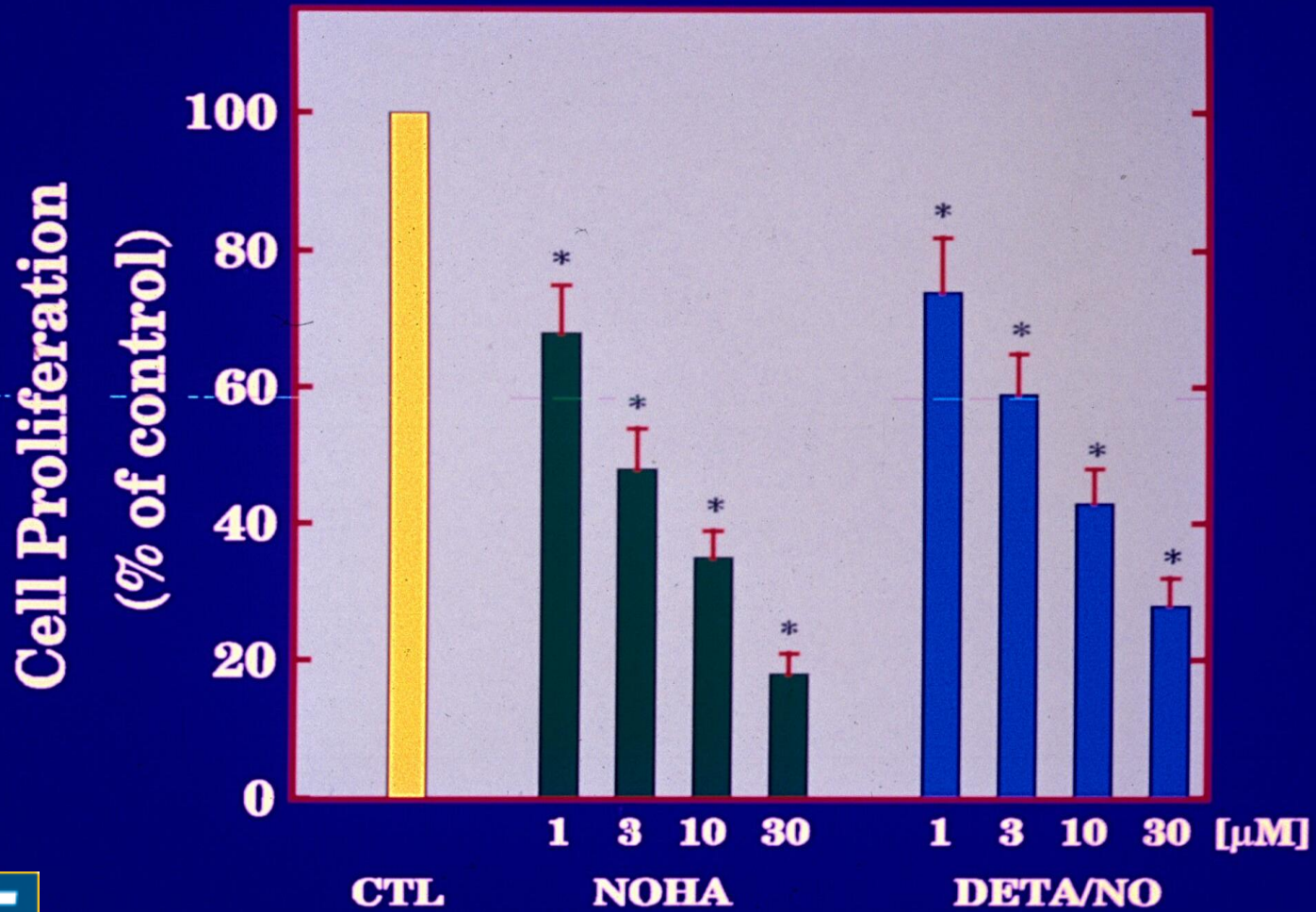
Rat aortic smooth muscle cells

RASMC in cell culture

NO Synthase and Arginase Utilize a Common Substrate - Arginine







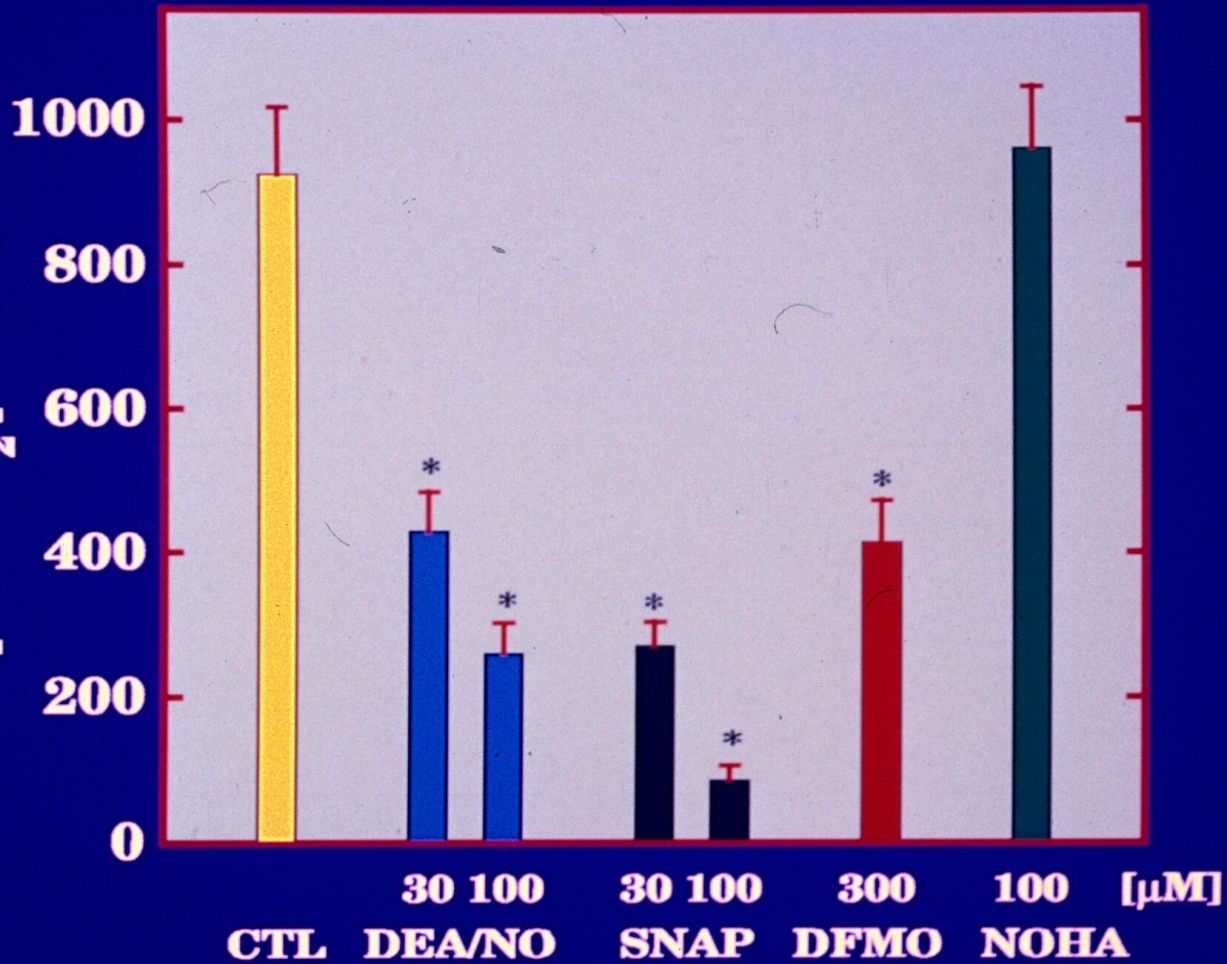
N-Hydroxyarginine (NOHA)

- ✓ *NOHA is an intermediate in the oxidation of L-arginine to NO + L-citrulline by NO synthase*
- *NOHA is a potent inhibitor of arginase activity*

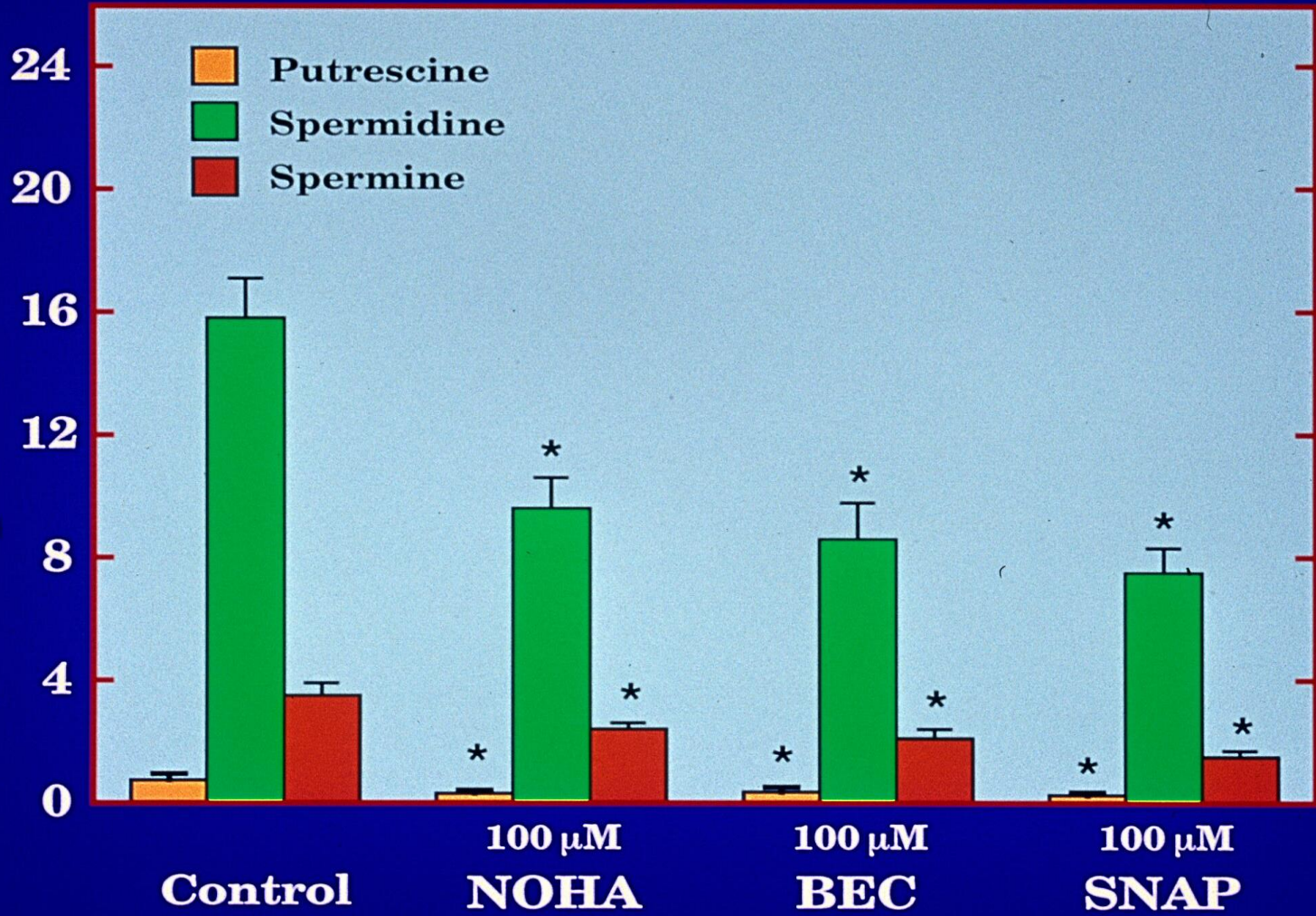
What is the Mechanism of Cytostasis of NO?

Ornithine Decarboxylase Activity

(pmol CO₂ per min)



Polyamine Concentrations
(nmol per 6×10^6 cells)



NO is a Potent Inhibitor of ODC

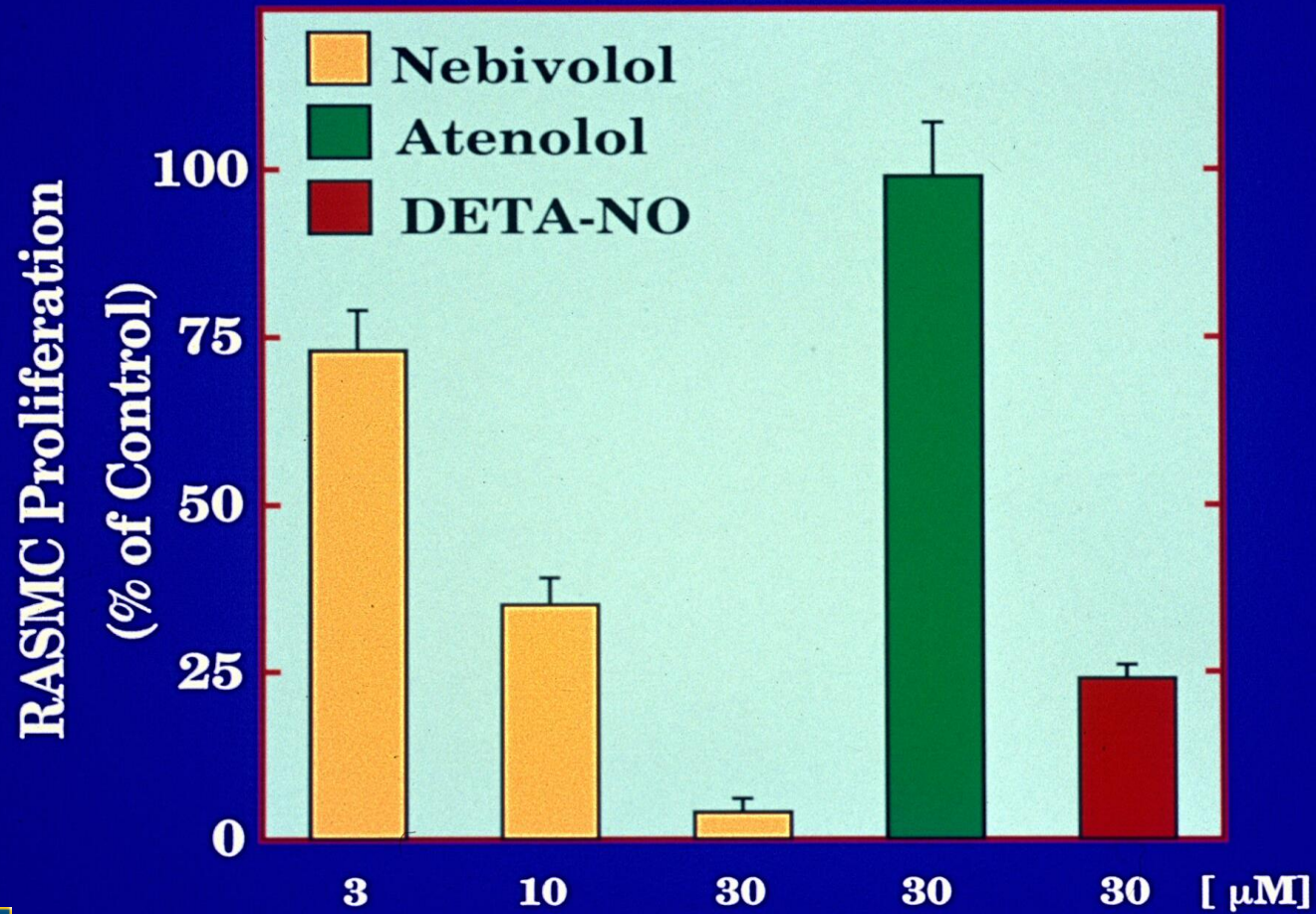
- *Mechanism of action: S-nitrosylation of cysteine-360 SH at catalytic site of ODC*
- *Cytostatic action of NO does not involve cyclic GMP in many cell types*

Nebivolol Inhibits the Growth of Vascular Smooth Muscle

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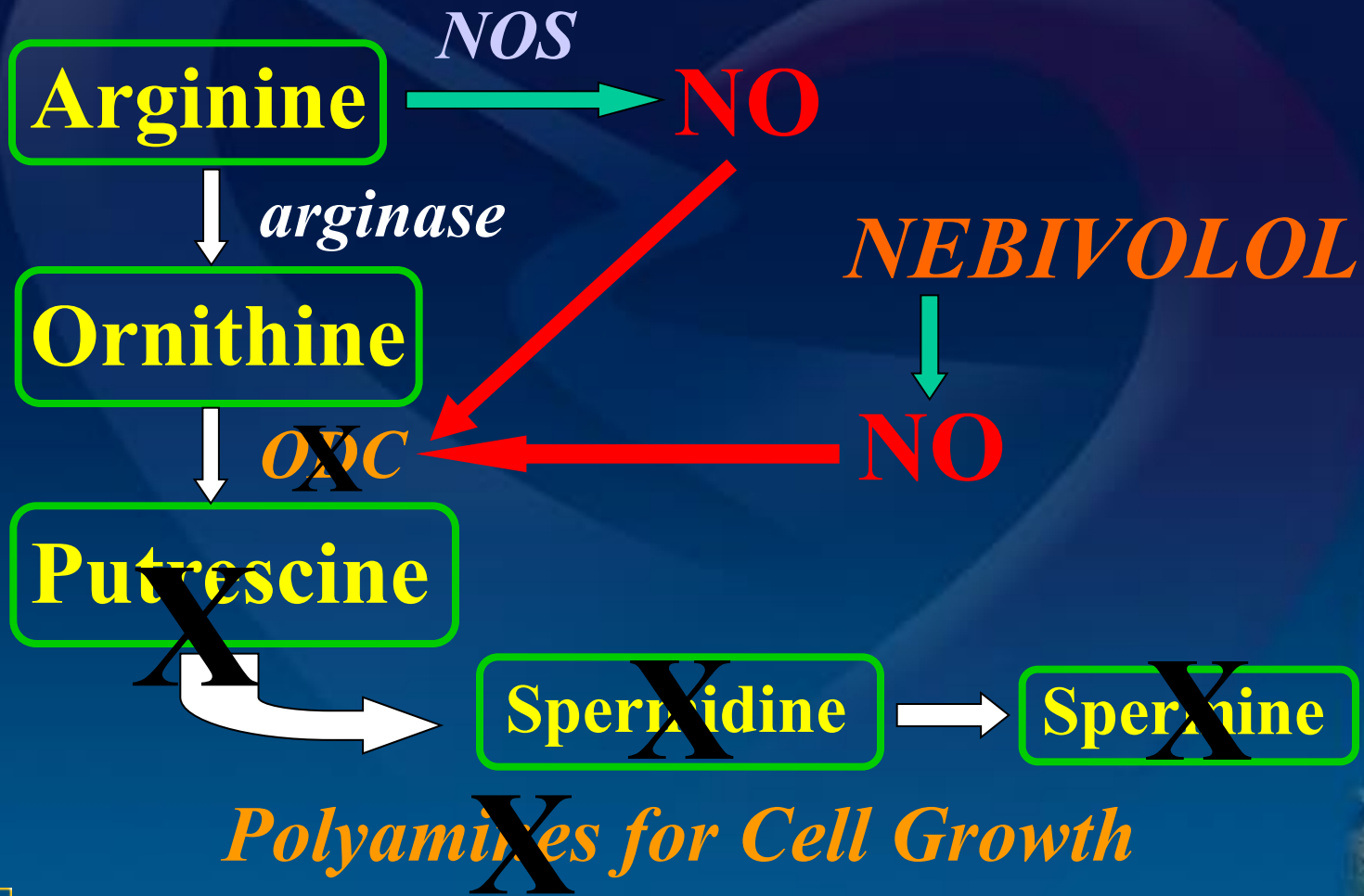
RASMC Proliferation



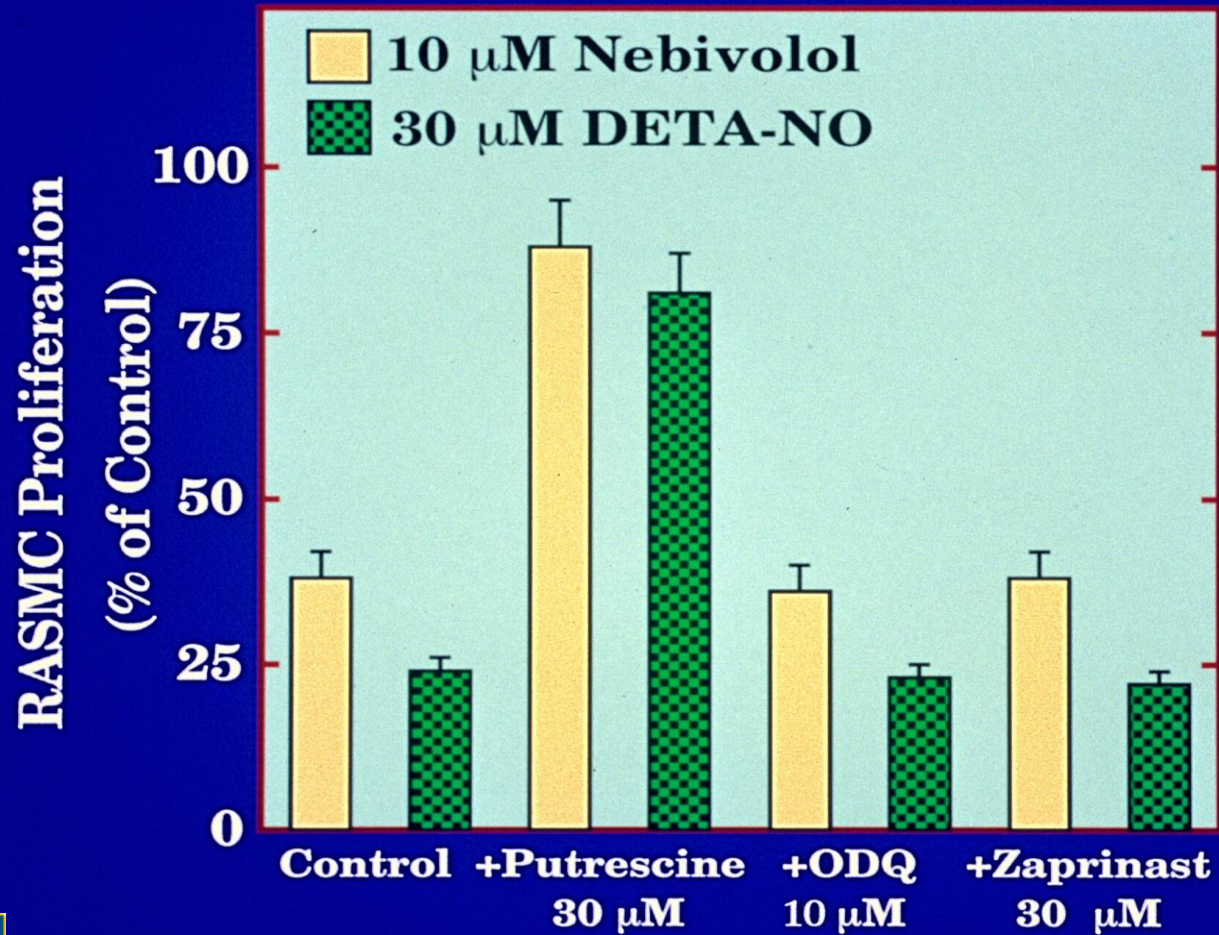
Inhibition of Vascular Smooth Muscle Proliferation by Mechanisms Similar to NO

*Mechanism = NO-dependent but
Cyclic GMP-independent*

Mechanism of Nebivolol

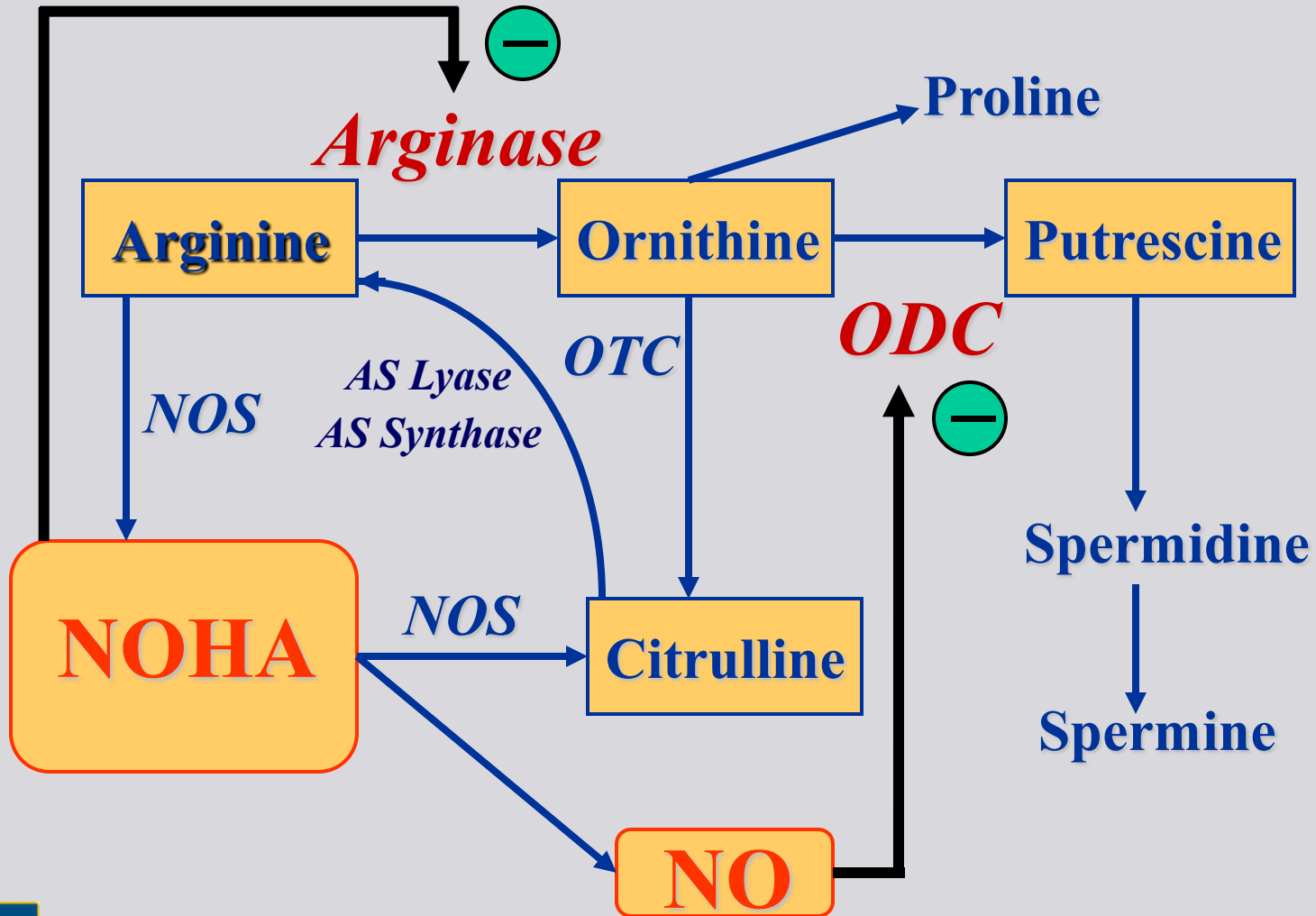


RASMC Proliferation



Unique Role of NO Synthase in Regulating Cell Growth

Two products of the NO synthase pathway inhibit two sequential steps in the arginine-polyamine pathway thereby leading to arrest of cell proliferation



Unique Properties

- ✓ *NO-mediated decrease in B.P. plus β_1 -blockade to protect the heart*
- ✓ *NO-mediated protection against thrombosis*
- ✓ *NO-mediated protection against atherosclerosis*