Center for Environmental and Smoking Induced Diseases (CESID)

1-Molecular mechanisms of smoking induced pulmonary and cardiovascular disease

-Free radicals and nitric oxide research
-EPR and MRI facility
-CV physiology and cardiac ischemia reperfusion research

2-Proteomic research aiming to discover new markers for early detection and, therefore prevention of smoking induced pulmonary and CVD

The Dorothy M. Davis
Heart & Lung Research Institute
The Ohio State University

Jay Zweier, MD, Director

Molecular Mechanism of Smoking Induced Endothelial Dysfunction

1- Role of tetrahydrobioptrin (BH4) and reactive oxygen species (ROS)

2- Role of cytoglobin

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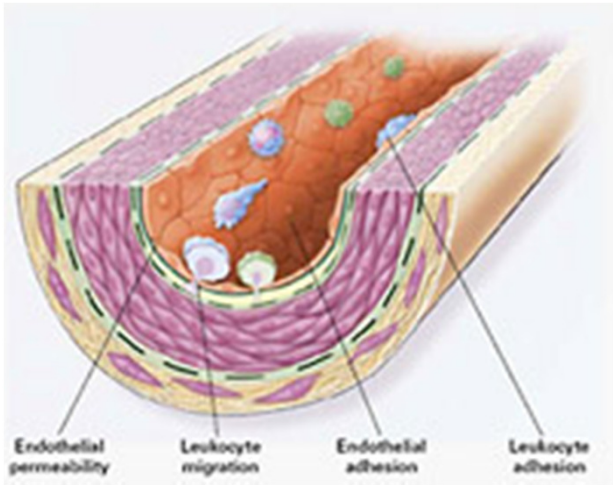
Healthy Endothelium

The endothelium is the thin layer of cells that lines the interior surface of blood vessels, forming an interface between circulating blood in the lumen and the rest of the vessel wall

The endothelium regulates:
- Homeostasis
- Blood cell trafficking
- Permeability and proliferation

More importantly vasomotor tone



Endothelial Cells and Vasomotor Tone Control

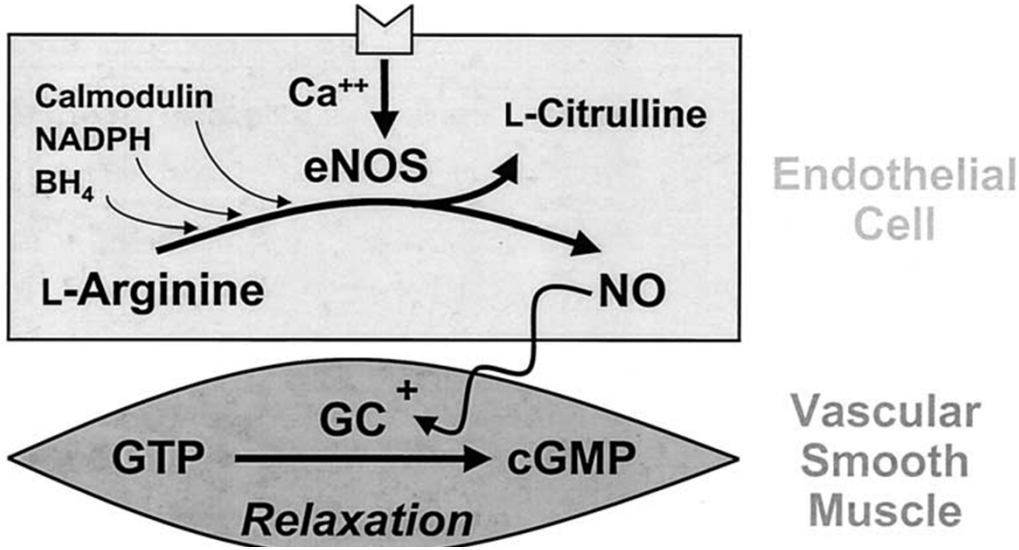
Endothelial cells produce both vasoconstrictive and vasodilating substances

-Endothelium-dependent relaxing factors
-Endothelium-dependent hyperpolarizing factors
-Endothelium-dependent contracting factors

A critical balance between these factors maintains the physiological functions of the endothelium and vascular homeostasis

Nitric Oxide Production in EC

NO is one of the most important regulatory and vasoactive substances ECs produce to maintain the physiological functions of the endothelium and vascular homeostasis



Nitric Oxide: a Key Mediator of the EC

NO exerts antiathersclerotic properties:

-Regulation of vasomotor tone and vessel wall permeability
-Suppression of leucocytes adhesion to endothelial surface
-Inhibition of platelet aggregation
-Inhibition of inflammation,
-Inhibition of VSMC proliferation

NO opposes the actions of potent endothelium-derived contracting factors such as angiotensin II and endothelin-1

Physiological production of NO=Healthy Endothelium

What is Endothelial Dysfunction?

Blunting of the NO-dependent vasodilatory effect of acetylcholine

Proinflamatory and prothrombotic state characterized by predisposion of the vasculature to:
-Vasoconstriction
-Leukocyte adherence
-Platelet activation
-Pro-oxidation
-Thrombosis
-Impaired coagulation
-Vascular inflammation and atherosclerosis

Endothelial Dysfunction in Pathological Conditions

ED has been shown to precede the development of the clinical manifistations of many of cardiovascular and metabolic disorders:

Hypertension
Coronary heart disease
Dyslipidemia
Diabetes

Smoking and Endothelial Dysfunction

-Epidemiological studies have established strong relationships between cigarette smoking, atherosclerosis burden, and cardiovascular disease states

-Approximately one-third of smoking-related premature deaths are due to CVD

-Significant CVD risk reduction and mortality benefits are associated with smoking cessation

Despite the overwhelming epidemiological studies, the precise mechanisms are not elucidated

Aim of the Work

To study in depth the molecular mechanisms involved in vascular dysfunction associated to cigarette smoking

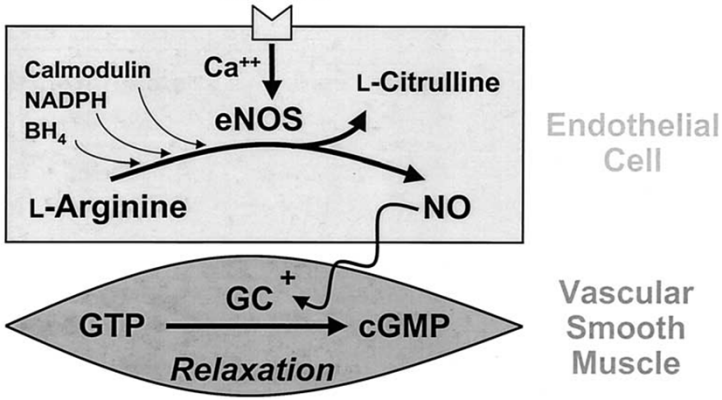
Understanding the extent and nature of the problem may potentially develop strategies to attenuate the effect of smoking on the vasculature, preserve the quality of life, and alleviate cardiovascular diseases in smoker population

NO Bioavailability

Physiological production of NO=Healthy Endothelium

In vivo NO bioactivity is determined by:

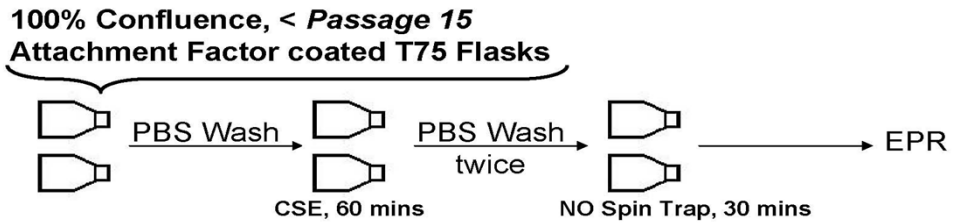
1-NO biosynthesis

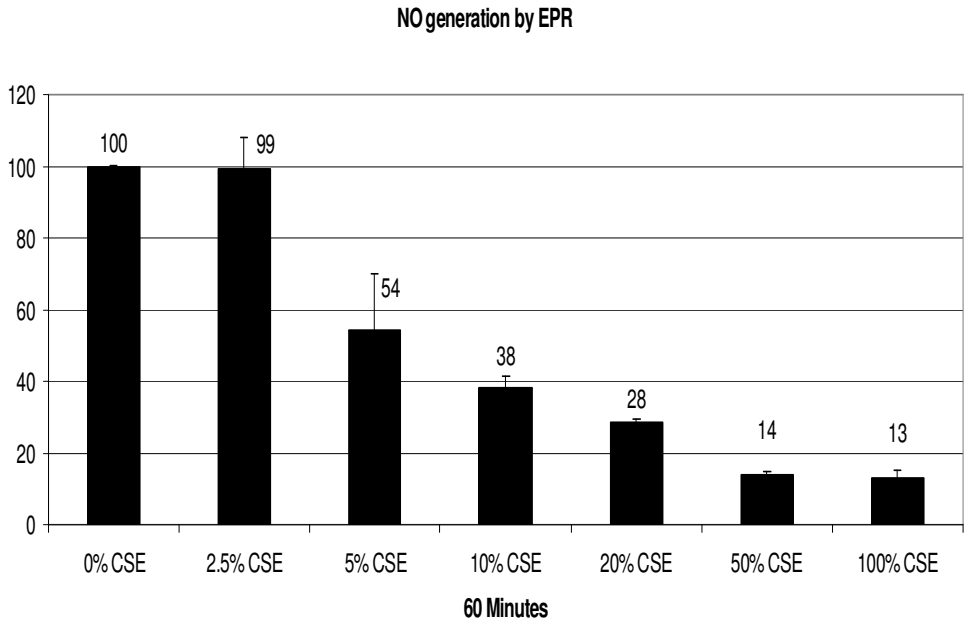


2-NO degradation

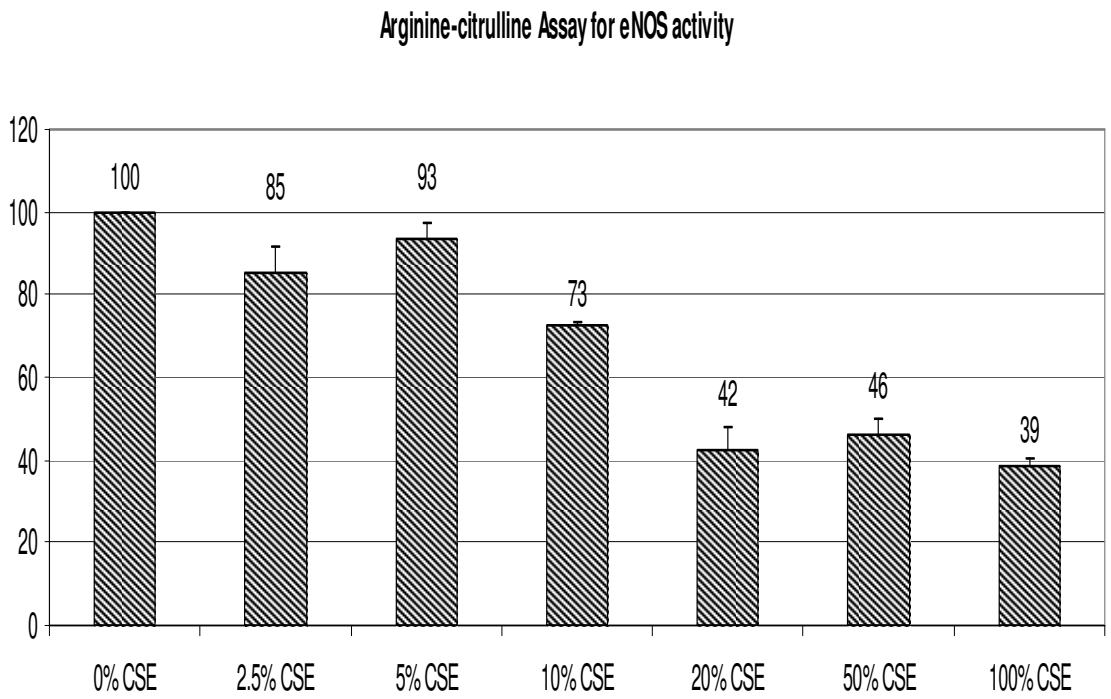
-Reaction with superoxide anion
-Reaction with globins:

CSE Inhibits NO Generation

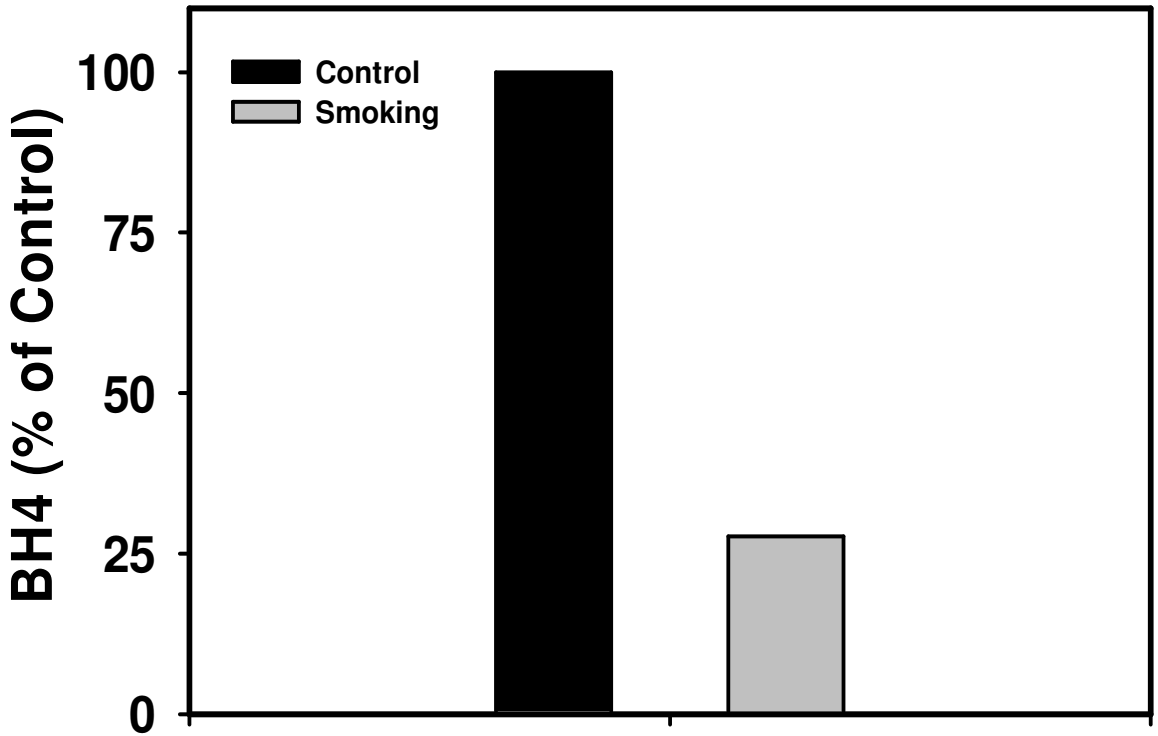




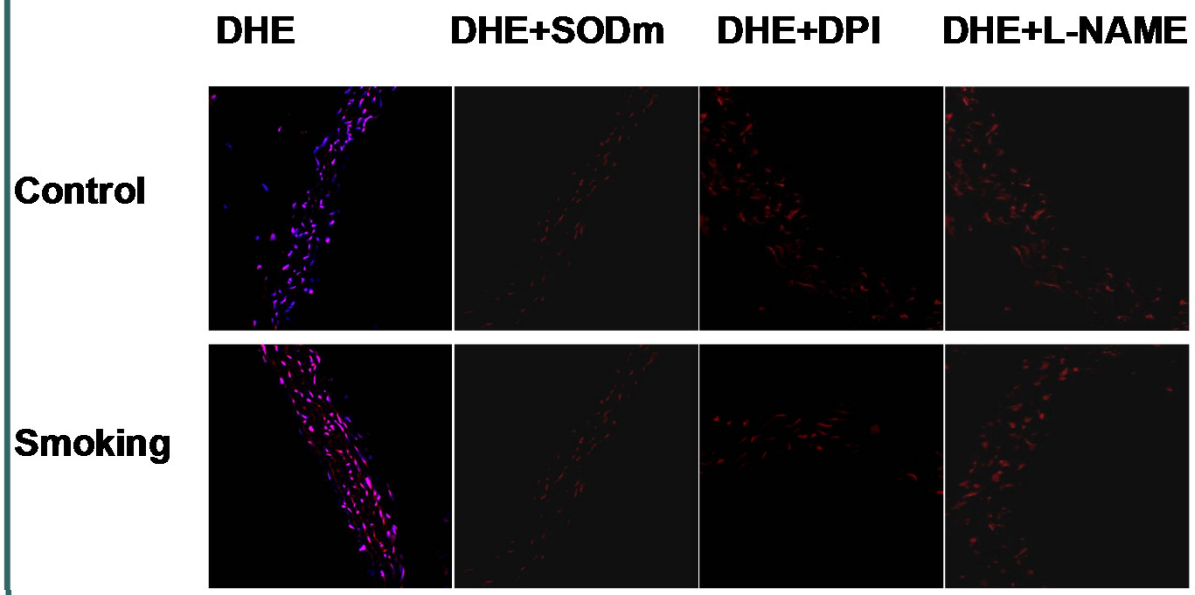
CSE Inhibits eNOS Activity

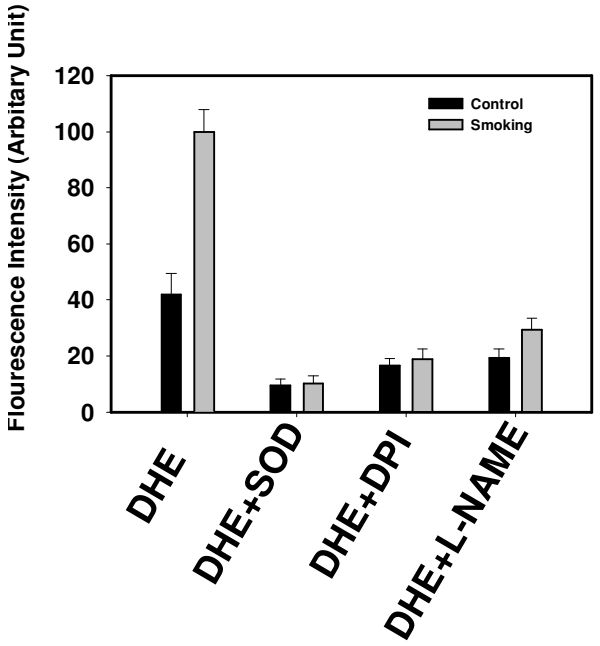


Smoking Reduces BH4

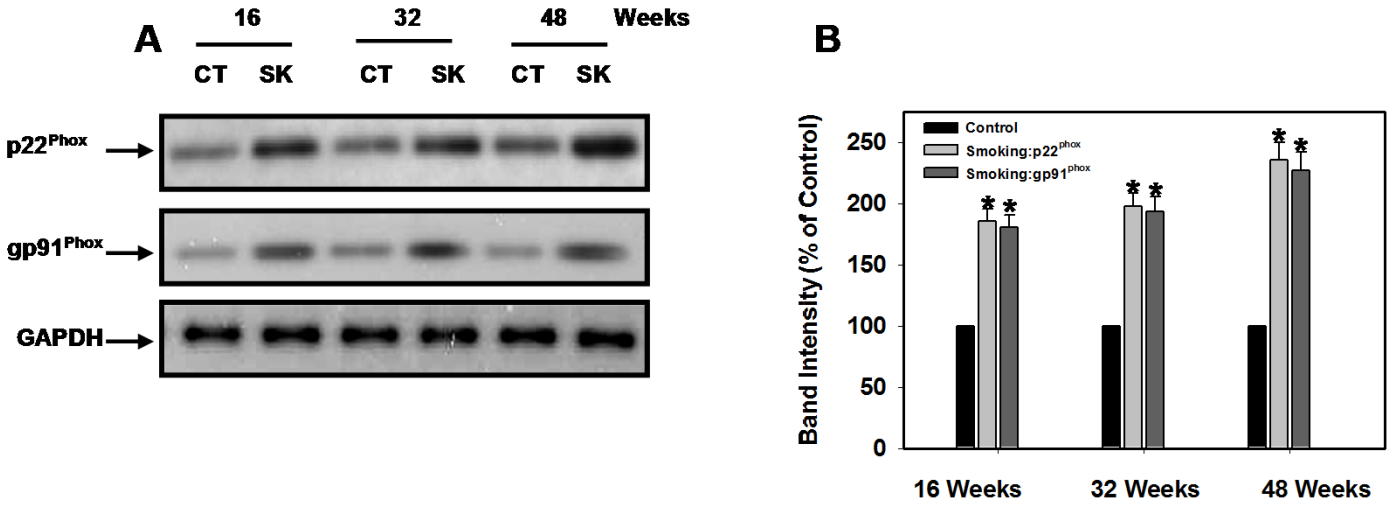


Smoking Induces ROS

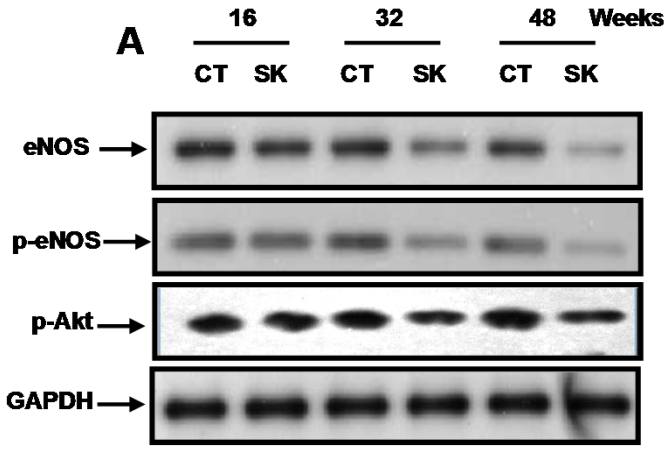


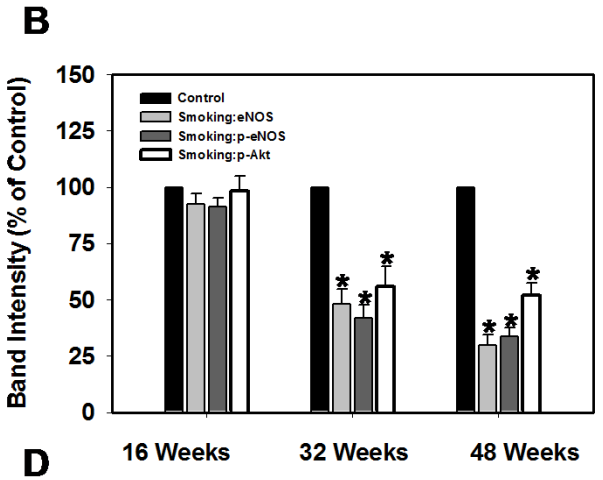


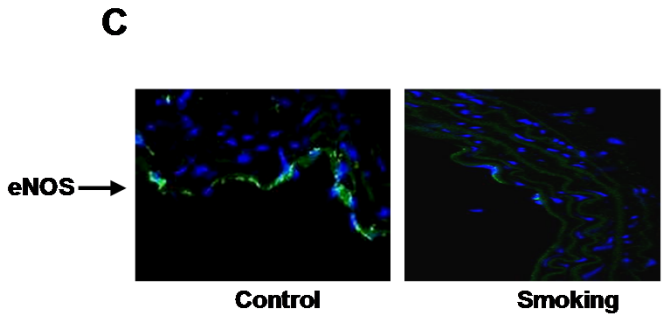
Smoking Upregulates NADPH Oxidase

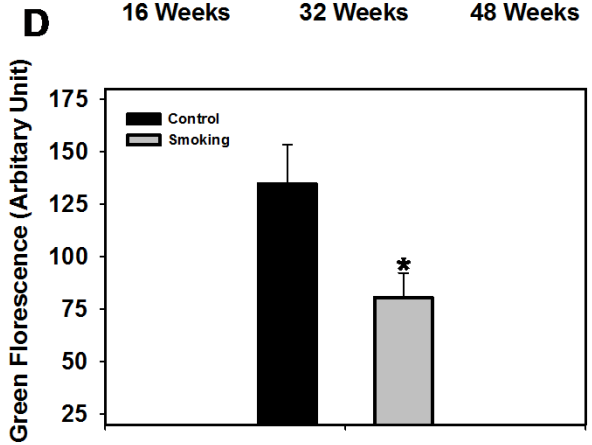


Smoking Downregulates eNOS

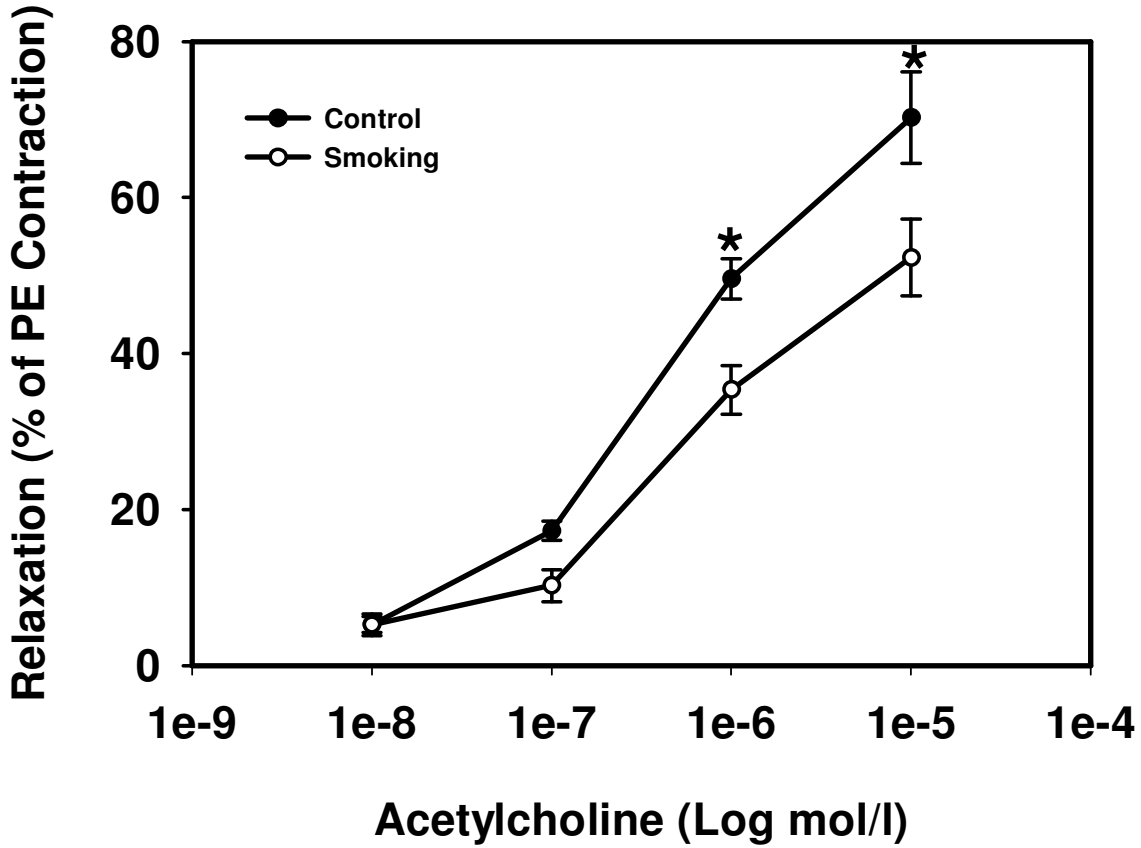




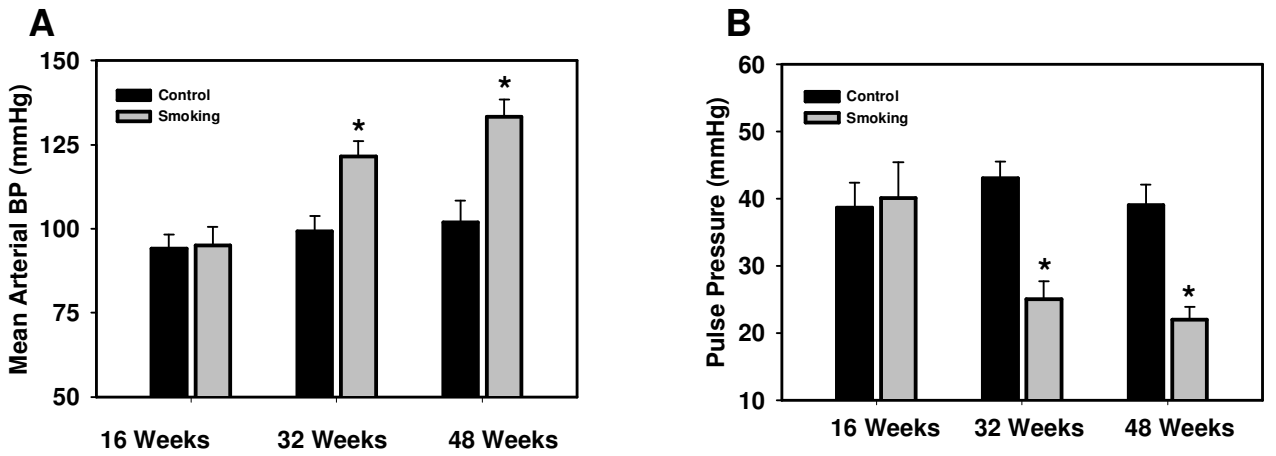




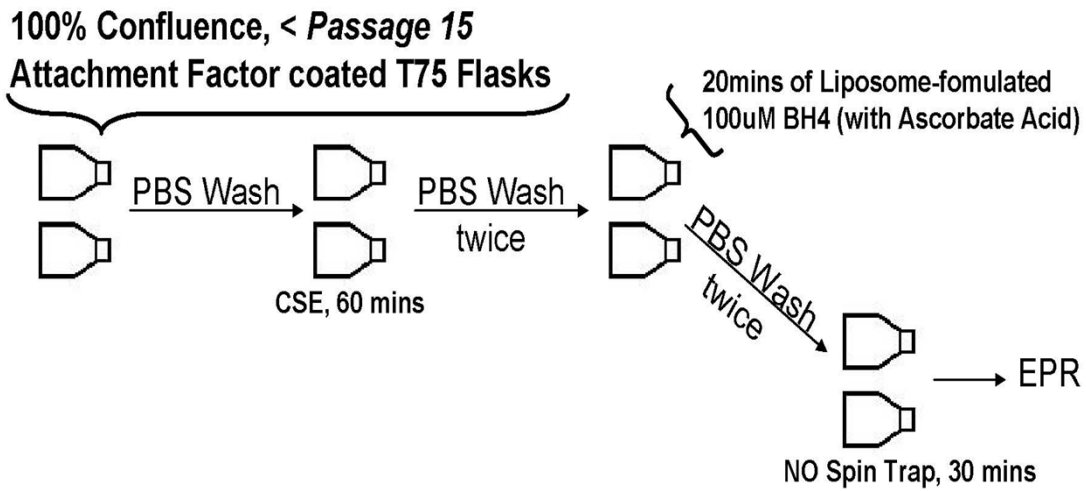
Smoking Impairs ED



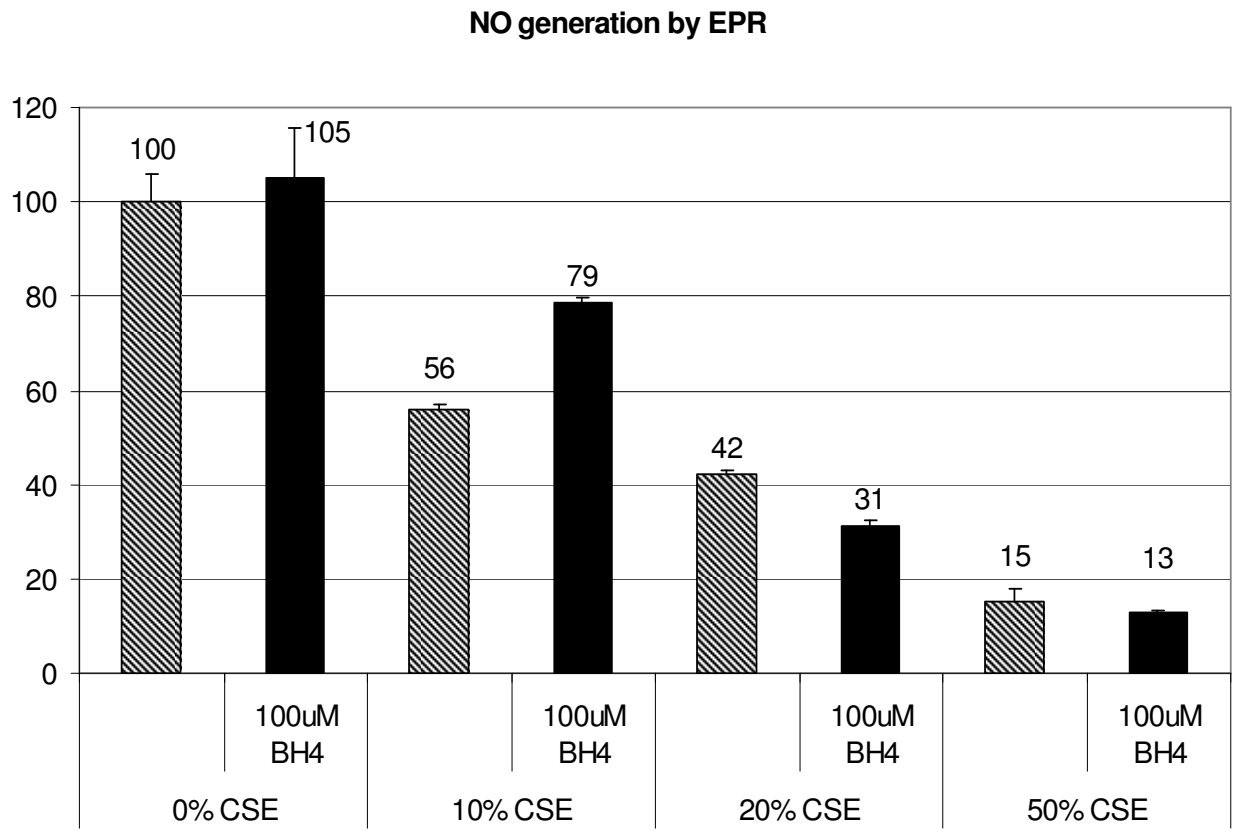
Smoking Elevates BP



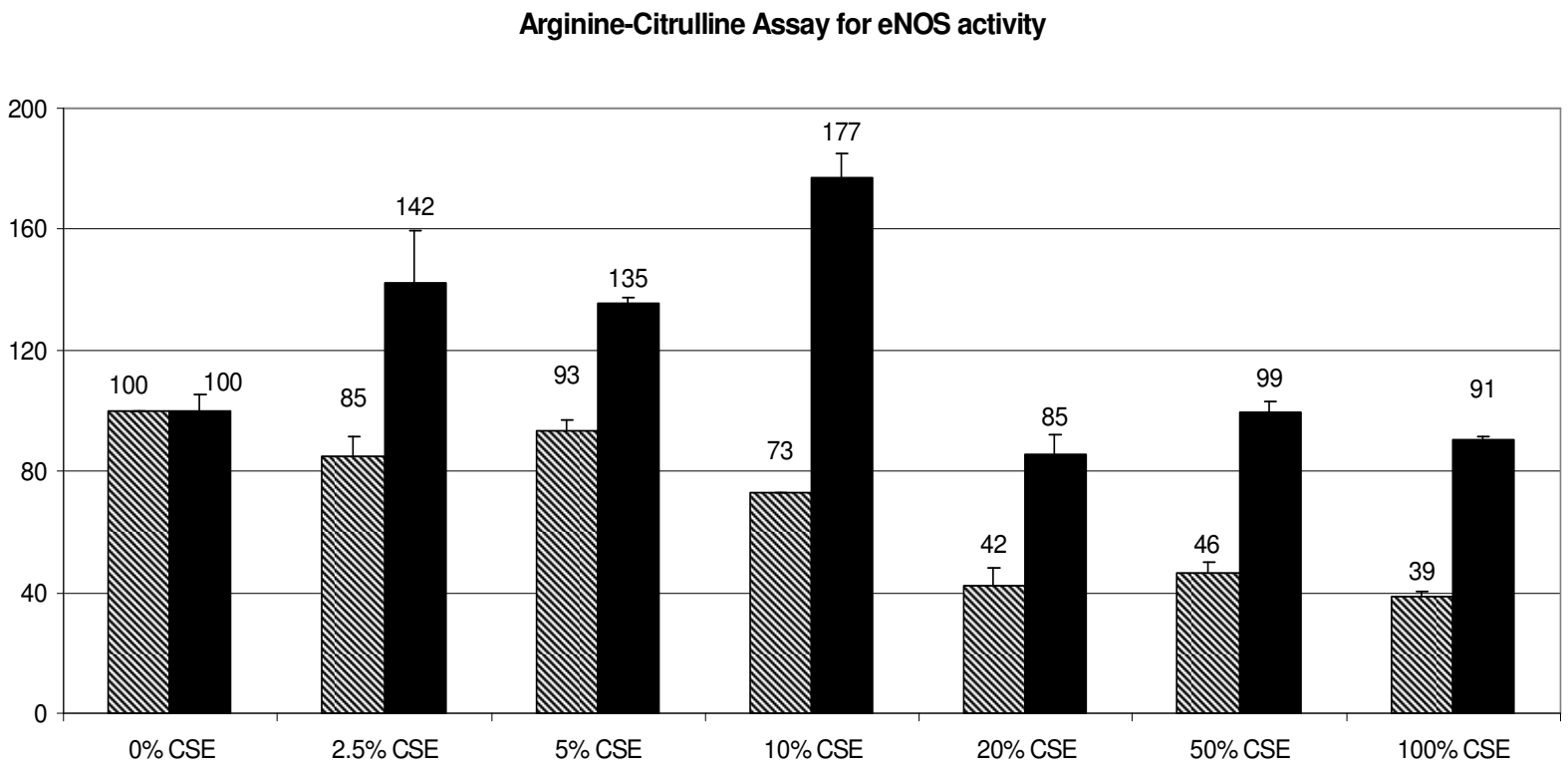
BH4 Treatment



BH4 Restores NO Generation



BH4 Restores eNOS Activity



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NO Bioavailability

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In vivo NO bioactivity is determined by:

1-NO biosynthesis

2-NO degradation

-Reaction with superoxide anion

-Reaction with globins:

Globins and NO Bioavailability

Hemecontaining proteins involved in dioxygen binding and/or transport

Bleived to be the major route of NO disposition in the vasculature

-**Hemoglobin: Oxygen transporter**

-Myoglobin: Oxygen buffer; facilitates O_2 diffusion and storage

-Neuroglobin: Oxygen supply to nerve tissues

-Cytoglobin---------

Cytoglobin

A recently discovered globin expressed in many different mammalian tissues with structural similarity to Hb and Mb

-Oxygen storage
-Oxygen diffusion
-Oxygen sensor

Recently, Cygb was found to be expressed in vascular wall

Cytoglobin and NO Bioavailability

The reaction of NO with intraerythrocytic oxyhemoglobin is the major route of NO disposition in the vasculature

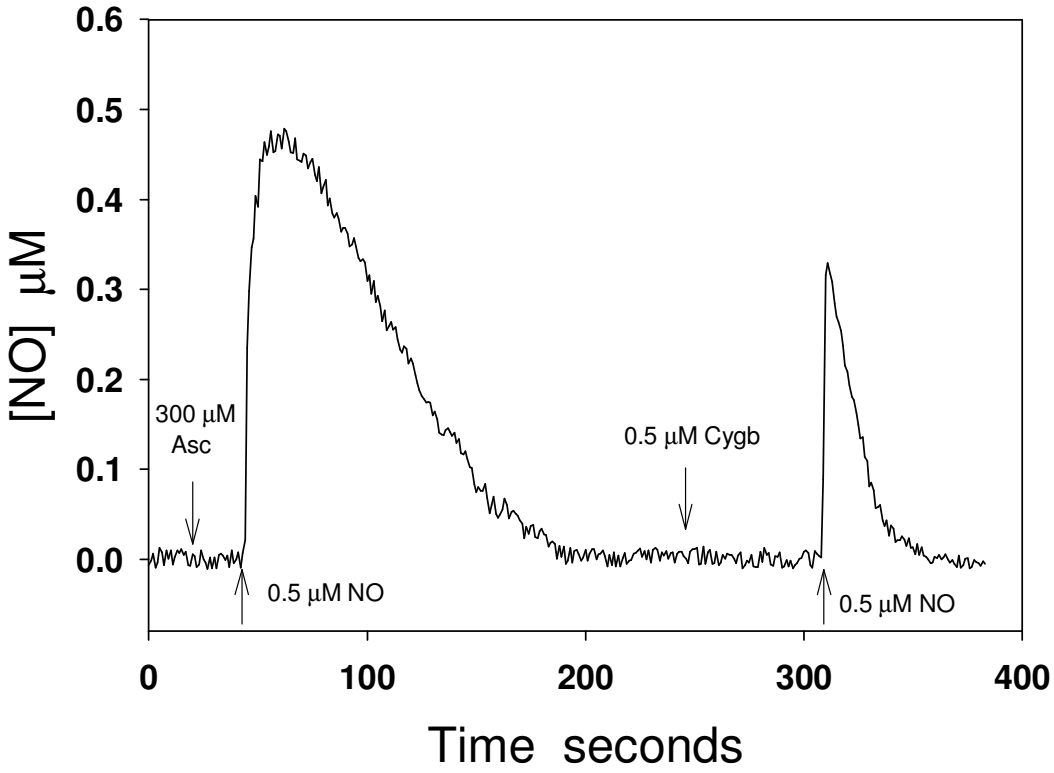
However, the discovery that diffusional barriers may limit scavenging of NO in the vascular wall opens the possibility that other mechanisms may control NO levels

The observation that aortic adventitial fibroblasts and medial smooth muscle cells express cytoglobin has recently been reported, indicating an alternative mechanism for NO decomposition in the vascular wall

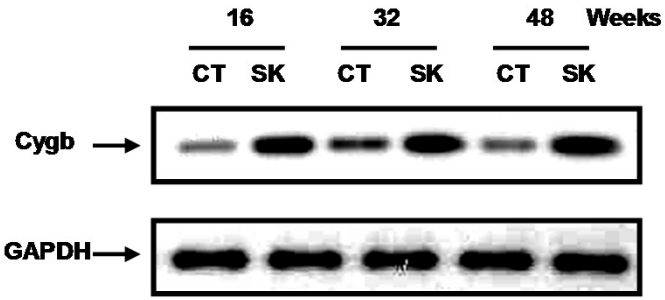
Cytoglobin and Smoking Induced ED

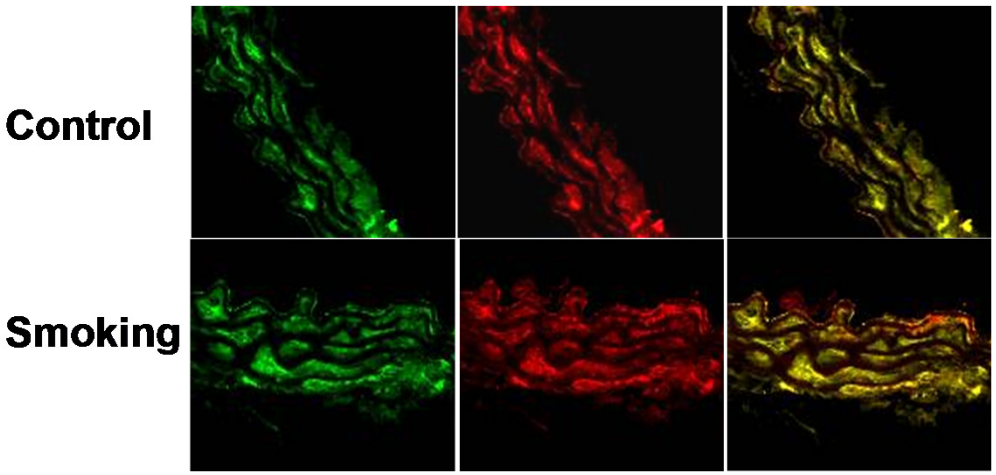
Could cytoglobine be a novel protein involved in cigarette smoking-induced endothelial dysfunction?

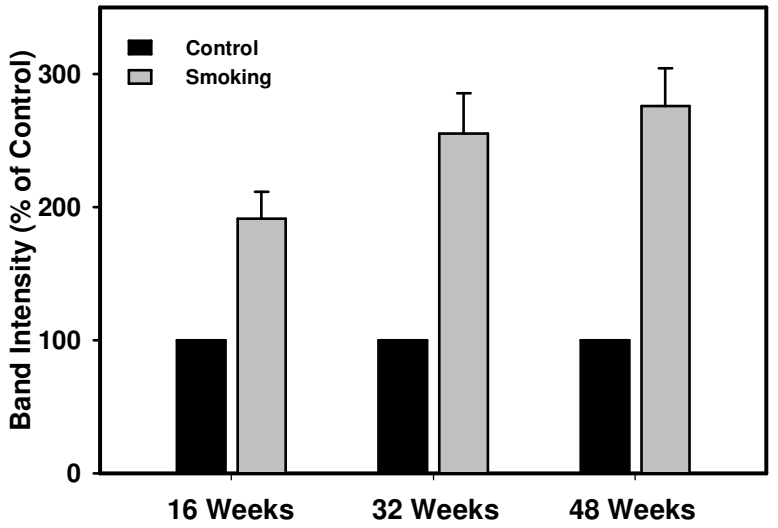
Cytoglobin Increases NO Decay



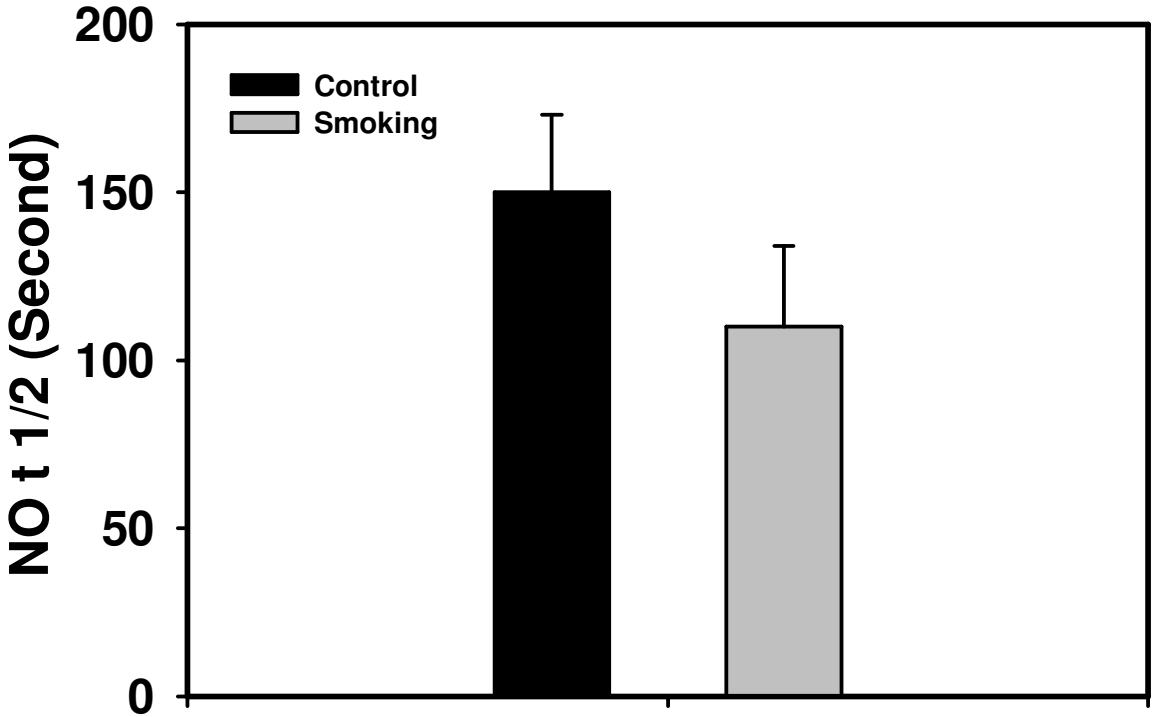
Smoking Upregulates Cytoglobin







Smoking Increases NO Decay



Overall Summary

1. CSE inhibited NO generation and eNOS activity
2. Smoking decreased BH4 with coordinate overexpression of NADPH oxidase and ROS production
3. Smoking downregulated the expression of eNOS, p-eNOS Ser^{1177}, and p-AKt Ser^{473}
2. Smoking upregulated cytoglobin expression and decreased NO half life
3. Smoking impaired vascular endothelial function and elevated blood pressure
4. BH4 restored the reduction of NO generation and eNOS activity

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