Jane Mitchell
'Inflammation pathways and the vasculature'

Thursday 9th Dec 2010

Professor Jane A. Mitchell
Head of Cardiothoracic Pharmacology,
NHLI, Dovheouse Street,
Imperial College,
London

j.a.mitchell@ic.ac.uk

Learning objectives:

To understand that vascular function is central to inflammation.

To know that mediators released by vascular cells mediate the inflammatory response.

To know that mediators can be released by vascular cells acutely and/or chronically after prolonged periods ad following gene induction and new protein synthesis.

To understand that in healthy vessels the endothelium is the site of mediator release whereas in inflamed vessels the underlying smooth muscle acquires the ability to synthesis mediators

Know that nitric oxide is an important acute and chronic mediator released by vascular cells mediated by different forms of the enzyme nitric oxide synthase (NOS)

To appreciate that inappropriate activation of the vascular smooth muscle Leads to vascular dysfunction.

Vessels - mediators and inflammation:

The spread of the acute inflammatory response following injury to a small area of tissue suggests that chemical substances are released from injured tissues, spreading outwards into uninjured areas. These chemicals, called endogenous chemical mediators, ***cause vasodilatation****, emigration of neutrophils, chemotaxis and increased vascular permeability .*

The boundaries of what constitutes an acute or a chronic mediator blur in health and disease. – we will discuss this

Examples of chronic mediators include:

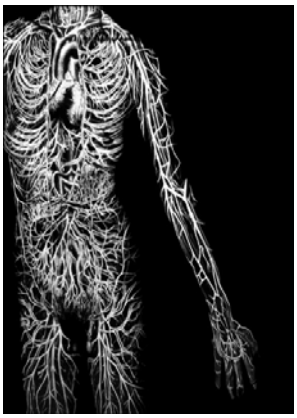
cytokines and chemokines

Examples of acute mediators include:

- Nitric oxide
- Prostaglandins (prostacyclin)
- Leukotrienes
- Histamine
- 5HT
- Endothelin-1

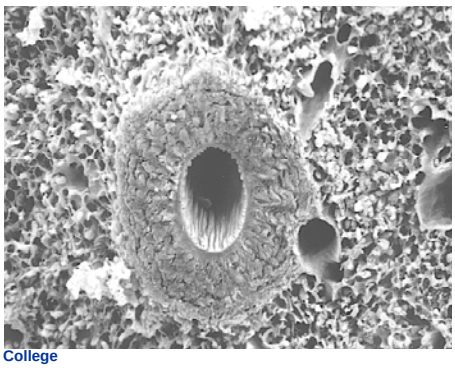
For some of the above mentioned 'acute mediators' a definition of 'chronic mediator' can also be applied under some conditions.

Blood vessels infiltrate every area of the body



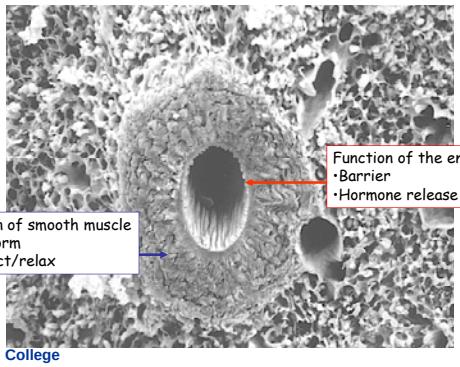
Imperial College
London

Muscular arteriole



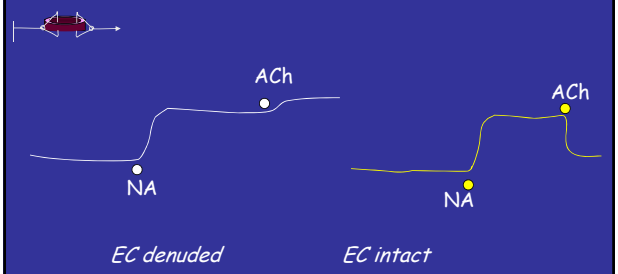
Imperial College
London

vessel



Imperial College London

The obligatory role of the endothelium in vasodilator Responses to acetylcholine

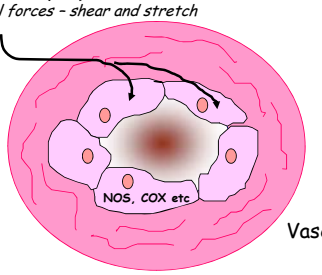


EC denuded *EC intact*

Furchgott & Zawadzki, Z Nature 1980

Endothelium in health

·*Acetylcholine (Ach)*
·*Physical forces – shear and stretch*



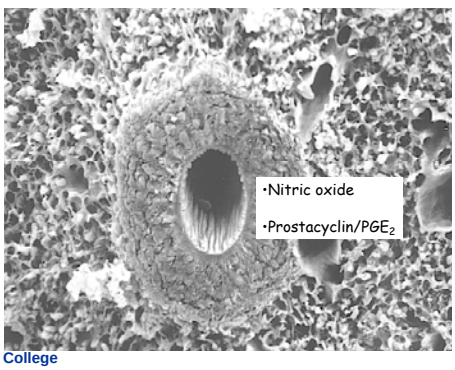
Endothelium
·**NO**
·**Prostacyclin**
·**Endothelin**
·**CO**
·**EDHF**
·**H_2S**

Vascular smooth muscle

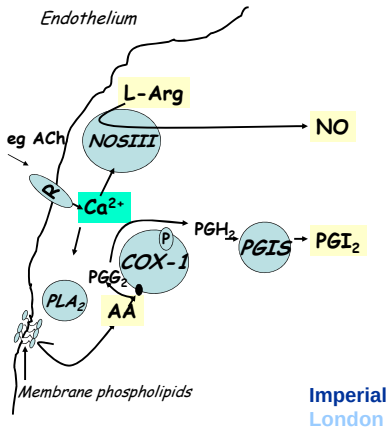
Smooth muscle signalling pathways

Vasodilatation/constriction

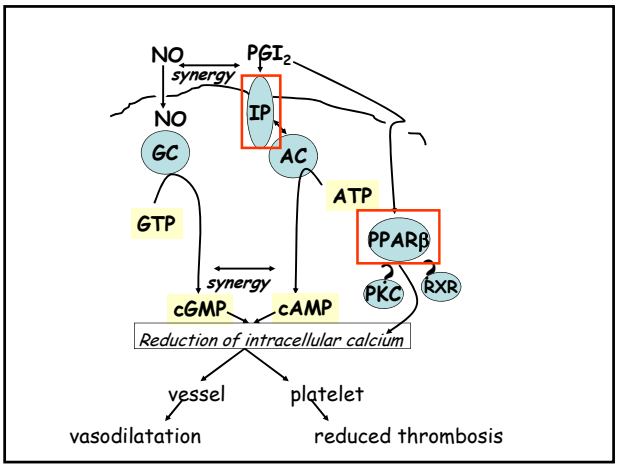
Muscular arteriole

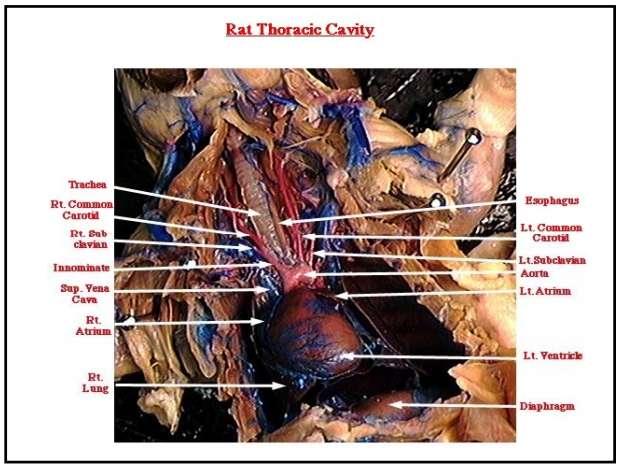


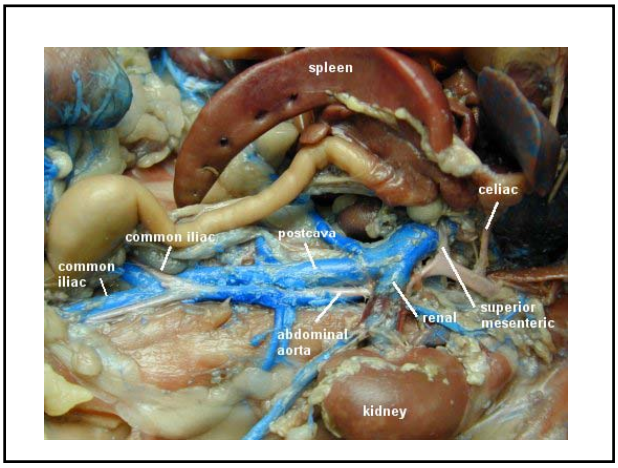
Imperial College London

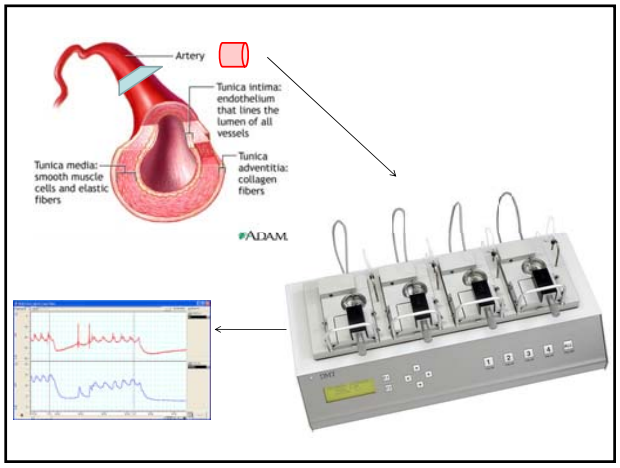


Imperial College London

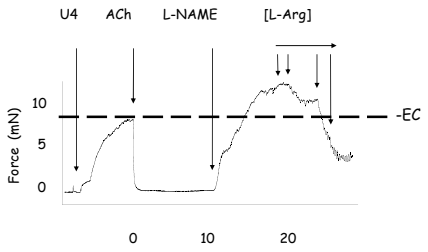








Acetylcholine causes endothelium dependent dilation of blood vessels

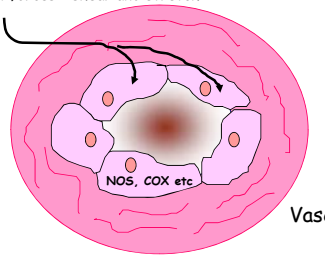


Harrington et al., 2007 Am. J. Physiol.

Imperial College London

Endothelium in health

- *Acetylcholine (Ach)*
- *Physical forces – shear and stretch*



Endothelium
- NO
- Prostacyclin
- Endothelin
- CO
- EDHF
- H_2S

Vascular smooth muscle

Vasodilatation/constriction

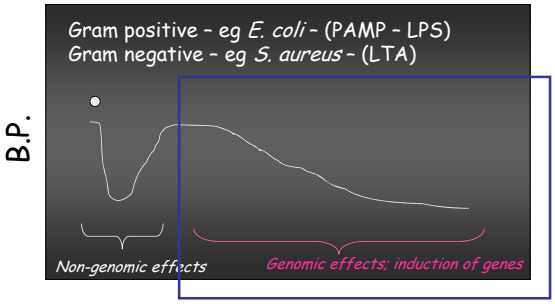
Smooth muscle signalling pathways

Endothelium – dilator hormones and inflammation

Oedema:
Two component model of leak and oedema – vasodilator plus another

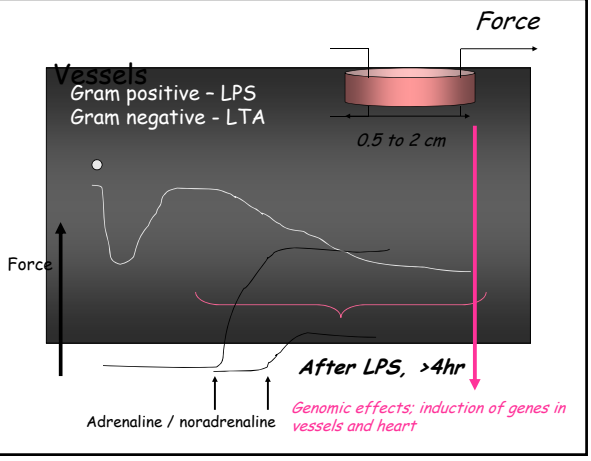
Cell recruitment:
Endothelium releases cytokines and chemokines – calling leuokcytes to the site of inflammation.

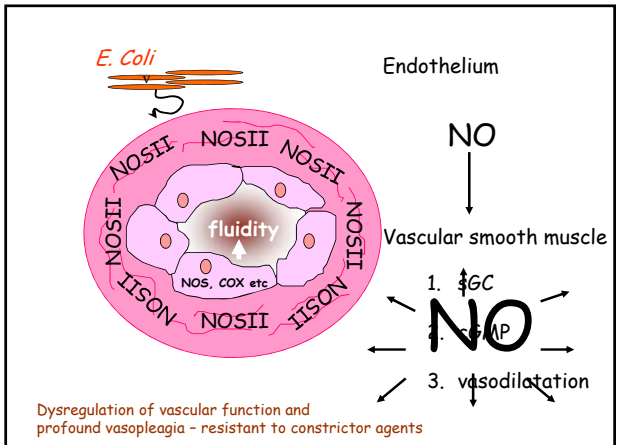
'Sepsis' induces a biphasic hypotension

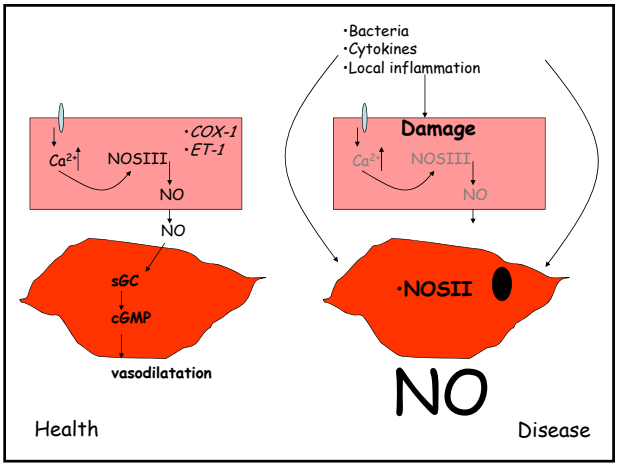


Immediate activation of endothelium by LPS

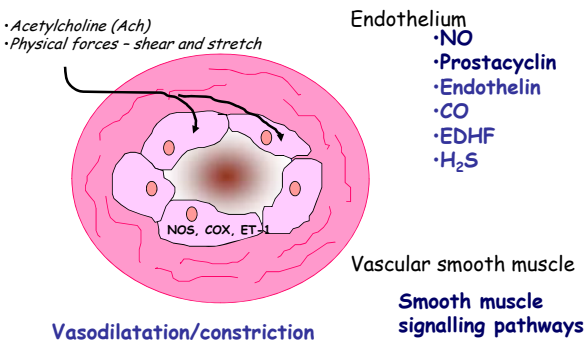
unlikely to involve endothelial derived mediators



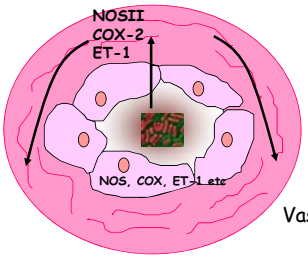




Endothelium in health



Endothelium - disease



Endothelium
- ·NO
- ·Prostacyclin
- ·Endothelin

Vascular smooth muscle
- **·NO**
- **·Prostacyclin**
- **·Endothelin**

Vasodilatation/constriction

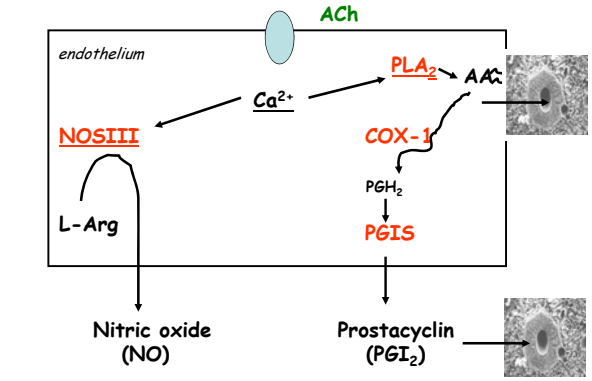
In a healthy vessel the endothelium is the site of vasoactive hormone release:

NO
Prostacyclin
ET-1

These mediators work together to regulate blood flow – to supply organ need. Under conditions of acute, resolving inflammation, mediators released by the endothelium incrase blood flow to allow the normal processes of healing and resolution to occur.

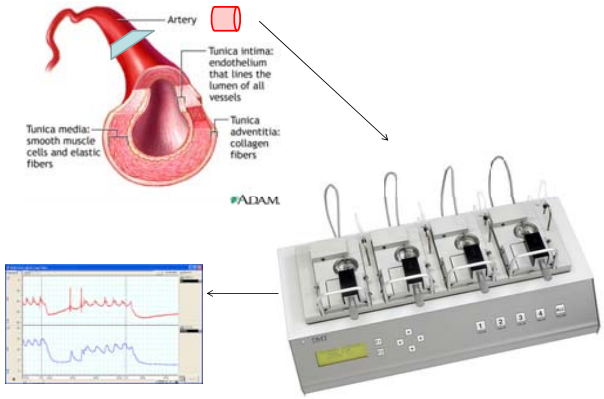
In disease pathogens, cytokines or other antigens cause dysfunction and damage to the endothelium and, at the same time induce a switch in the vascular smooth muscle cells causing profound genomic changes which mean they take on the ability to produce hormones normally only produced by the endothelium.

Where hormones (NO, prostaglandins, ET-1) are produced as a result of induction of inflammatory forms of NOS, COX etc in the smooth muscle, the levels are very high and not regulated – in the case of NOS, that is because the inducible form (NOSII) is calcium independent.



·*Smooth muscle*
·*Platelet*

Imperial College London



In vivo methods of measuring vascular responses:

- Canulate artery and record pressure from a transducer
- Implant tomography device and monitor pressures online in conscious animals
- Coloured or radioactive microspheres