

Jane Mitchell
'Inflammation pathways and the vasculature'

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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 and 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 synthesize 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

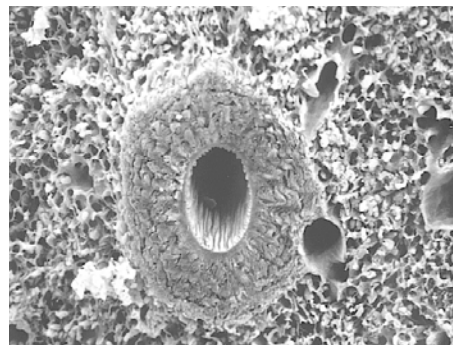
For some of the above mentioned 'acute mediators' a definition of 'chronic mediator' can also be applied under some conditions.

Blood vessels infiltrate every area of the body

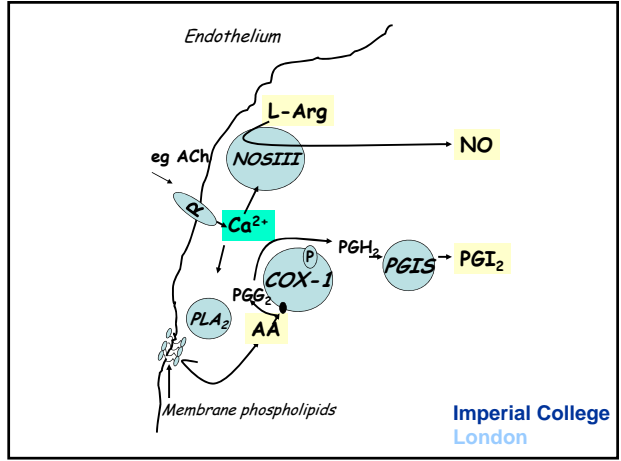
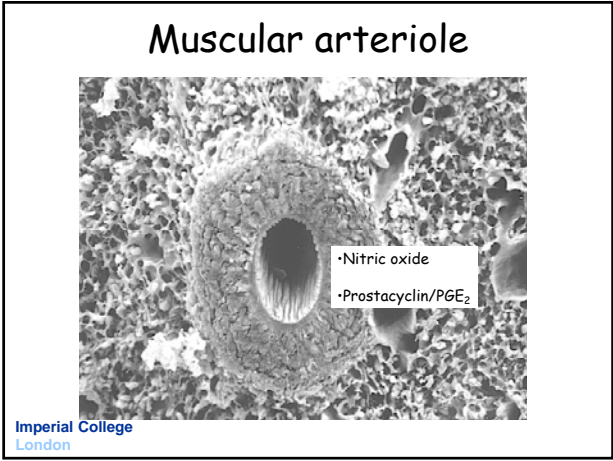
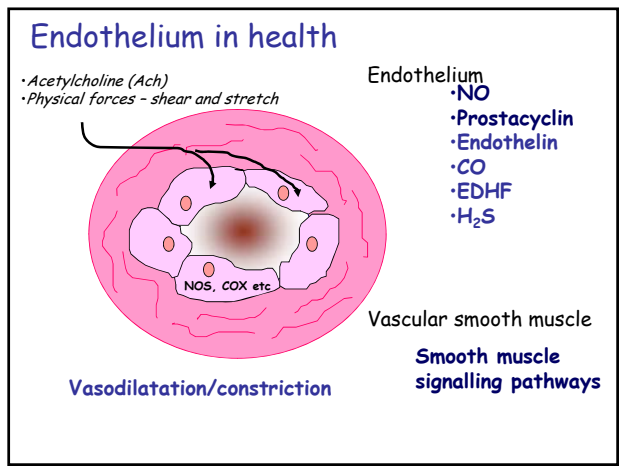
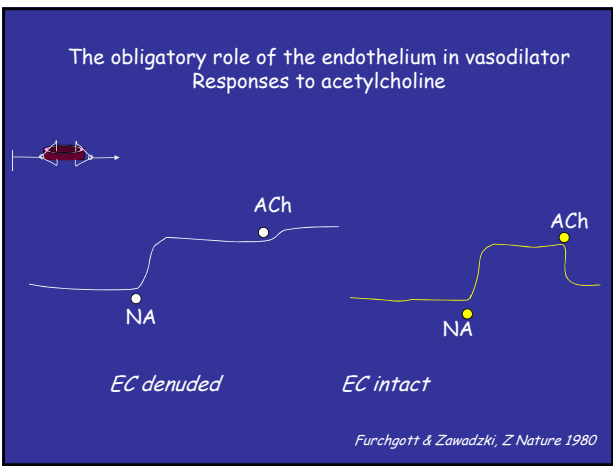
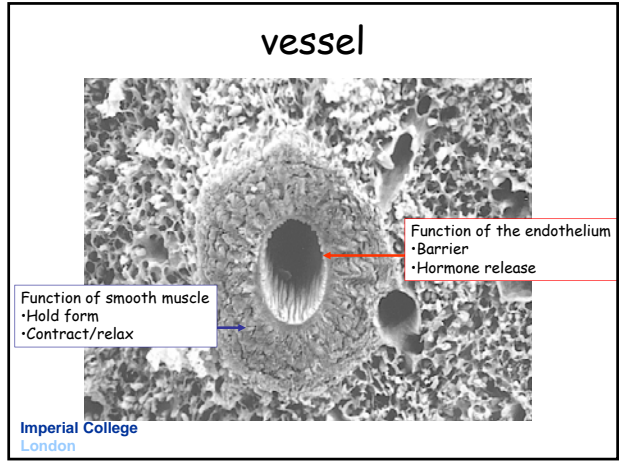


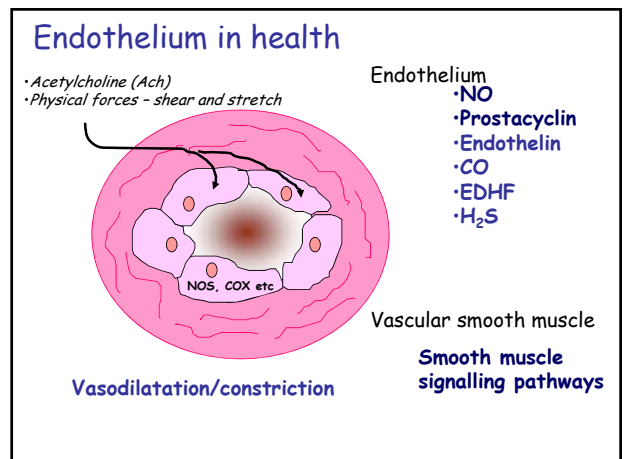
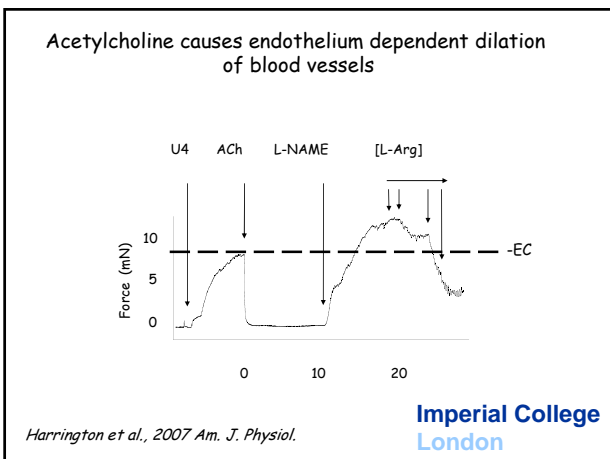
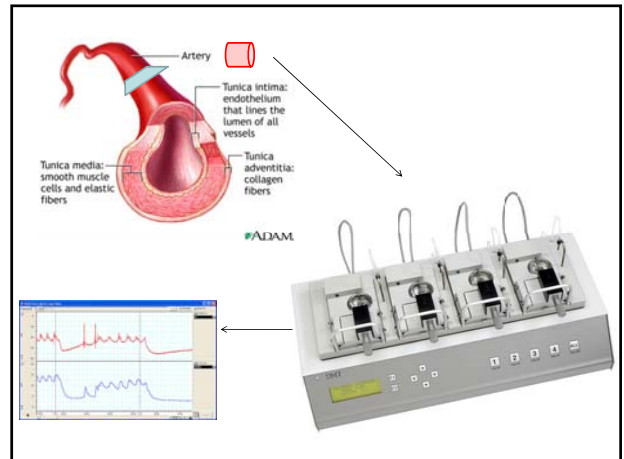
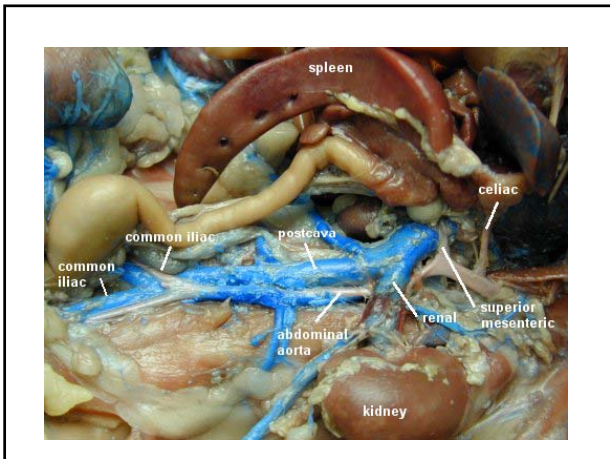
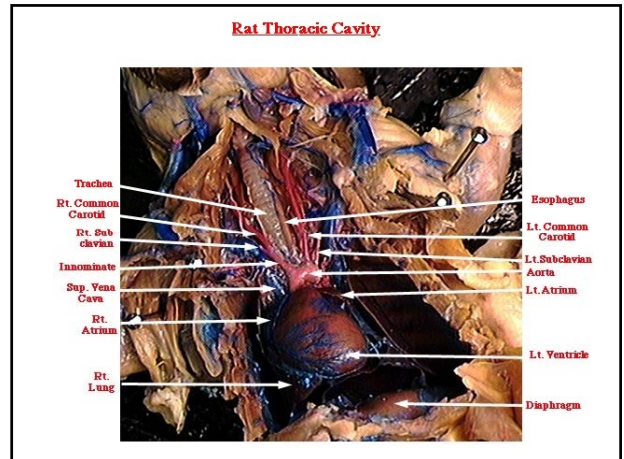
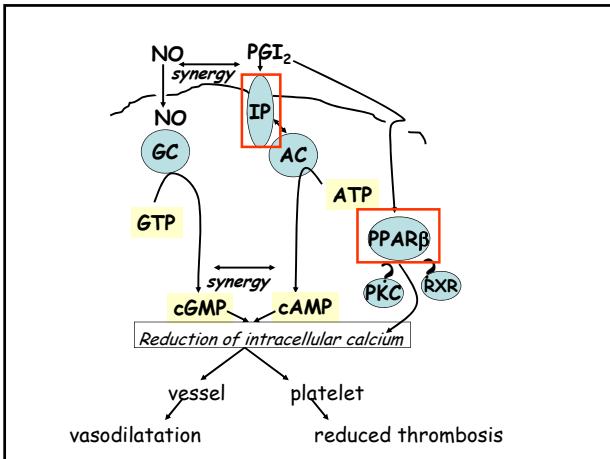
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Muscular arteriole



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Endothelium - dilator hormones and inflammation

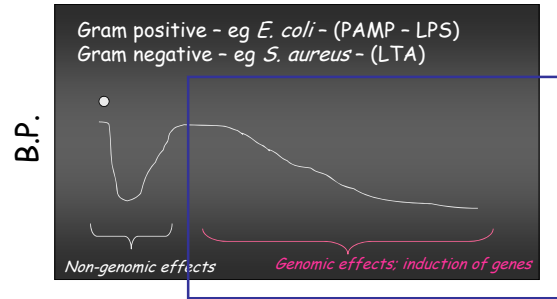
Oedema:

Two component model of leak and oedema - vasodilator plus another

Cell recruitment:

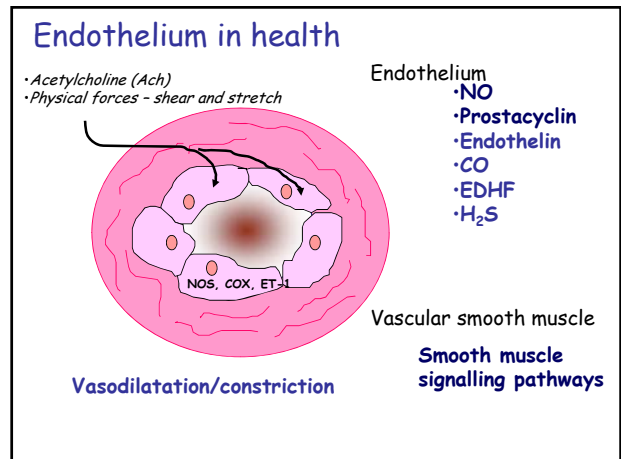
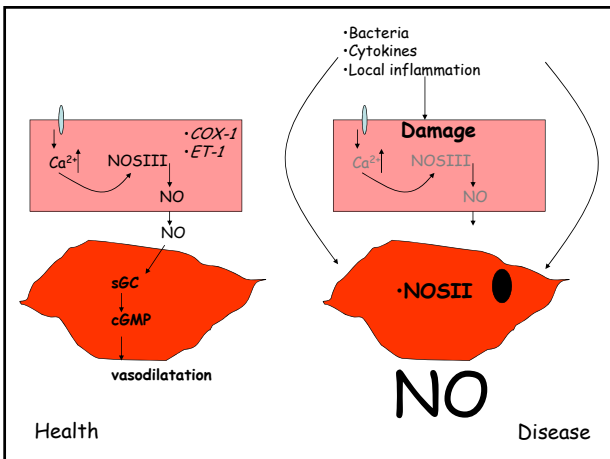
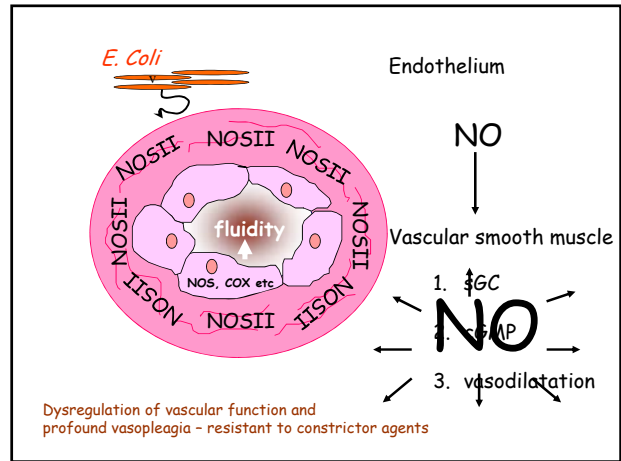
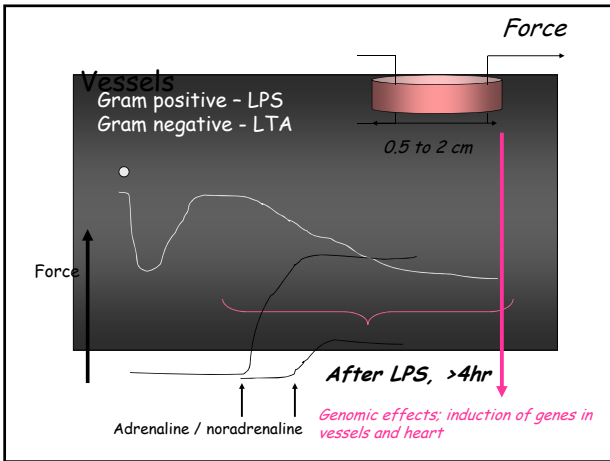
Endothelium releases cytokines and chemokines - calling leukocytes to the site of inflammation.

'Sepsis' induces a biphasic hypotension

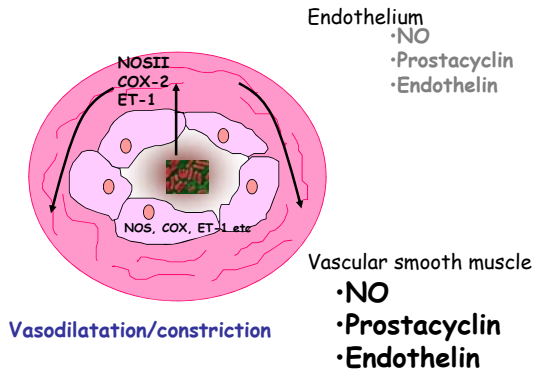


Immediate activation of endothelium by LPS

unlikely to involve endothelial derived mediators



Endothelium - disease



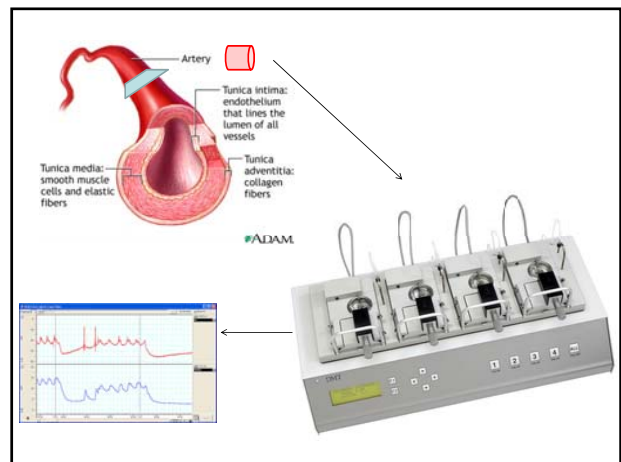
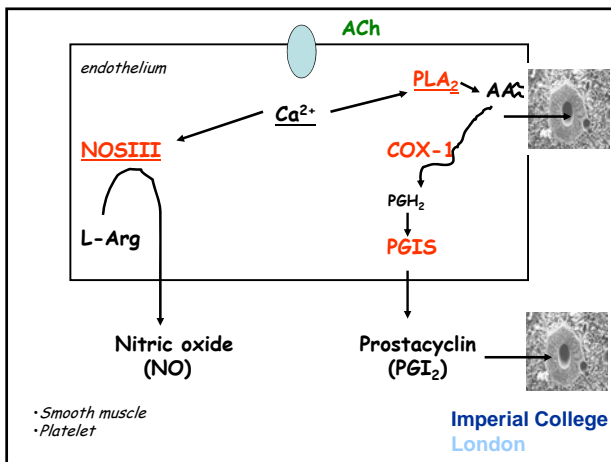
In a healthy vessel the endothelium is the site of vasoactive hormone release:

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 increase 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.



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