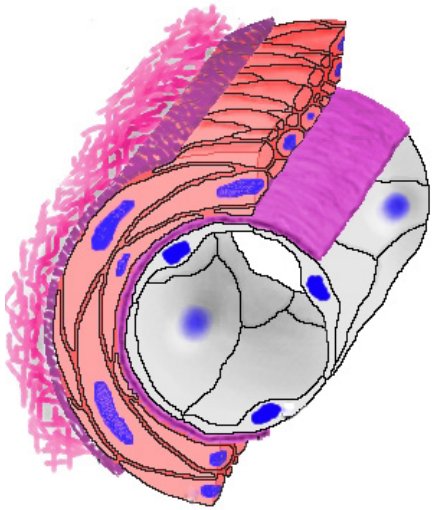
THE UNIVERSITY OF MELBOURNE

FACULTY OF VETERINARY & AGRICULTURAL SCIENCES



Vascular smooth muscle function

Dr Laura Dooley
laura.dooley@unimelb.edu.au

Intended learning outcomes

- Describe the basic mechanism of contraction of vascular smooth muscle cells
- Define autoregulation of blood flow and briefly describe the **myogenic response, metabolic hyperaemia and reactive hyperaemia**
- Describe the intrinsic (local) and extrinsic (neuronal and hormonal) influences on arteriolar tone
- Explain the importance of the vascular endothelium in regulating vascular tone and how nitric oxide functions as a vasodilator.

Vascular smooth muscle cells: overview

- Three types of muscle in the body: skeletal, cardiac and smooth

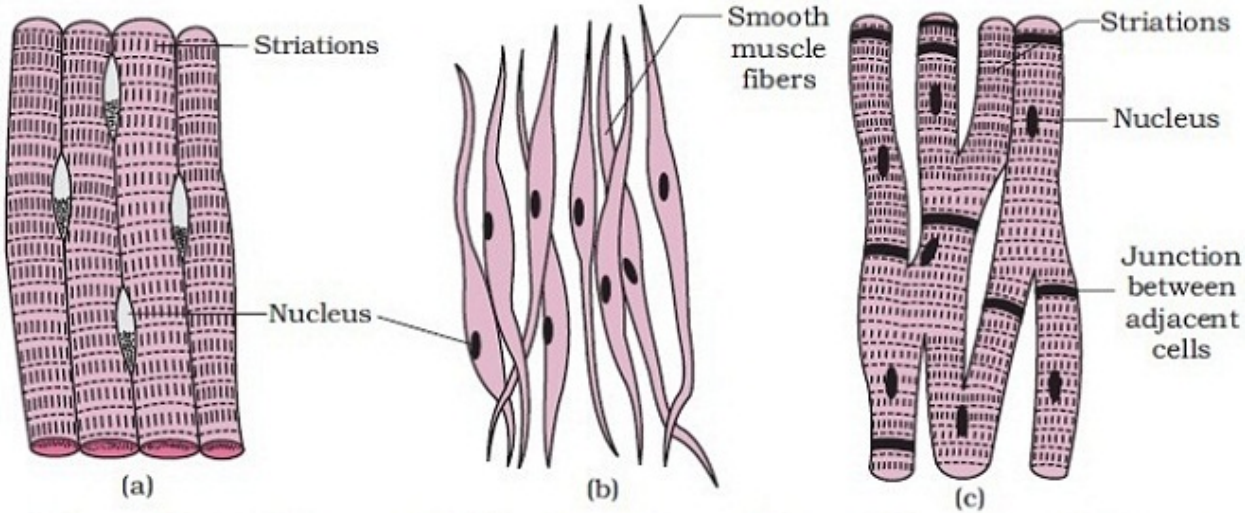
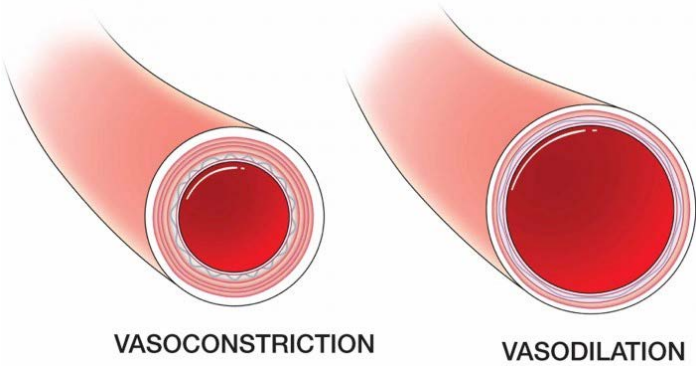


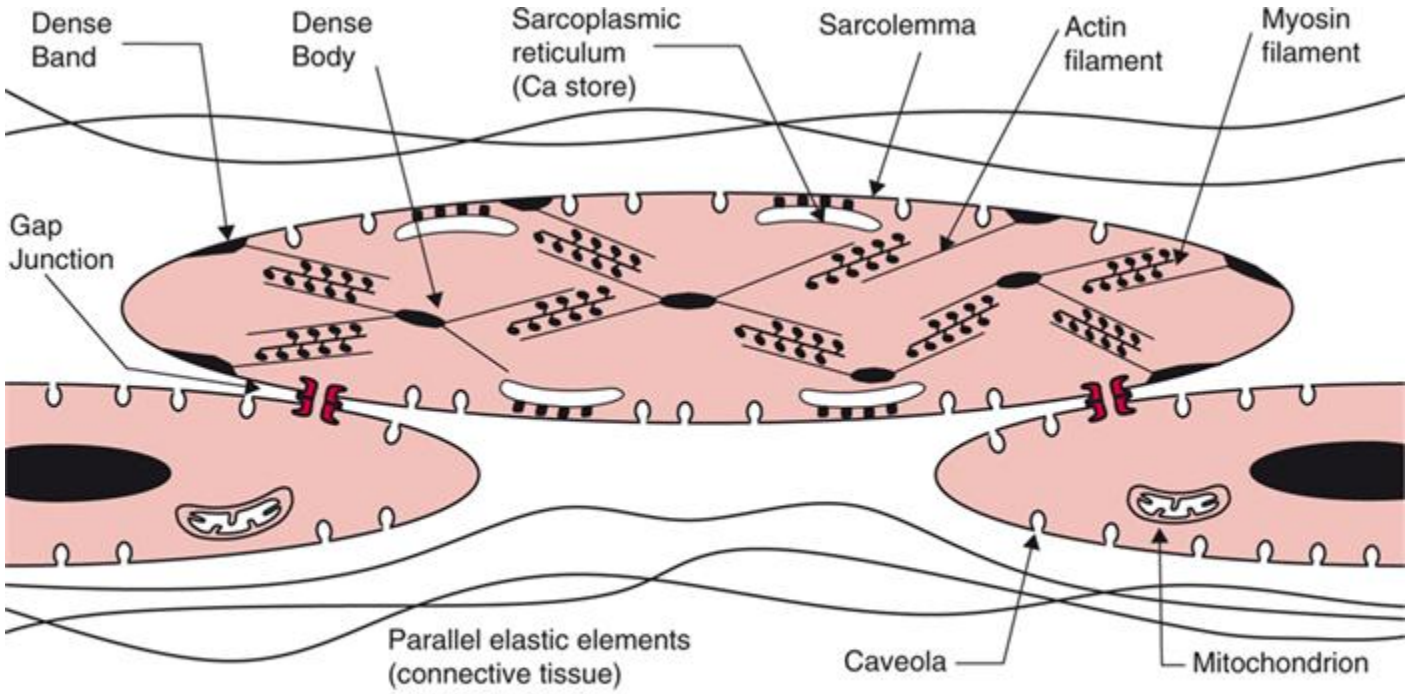
Figure 7. Muscle tissue : (a) Skeletal (striated) muscle tissue (b) Smooth muscle tissue (c) Cardiac muscle tissue

- Vascular smooth muscle cells present in the tunica media of (some) blood vessels
- Changes in their contractile tension (tone) constrict and dilate vessels



Vascular smooth muscle cells: overview

- Spindle shaped cells wrapped around vessels

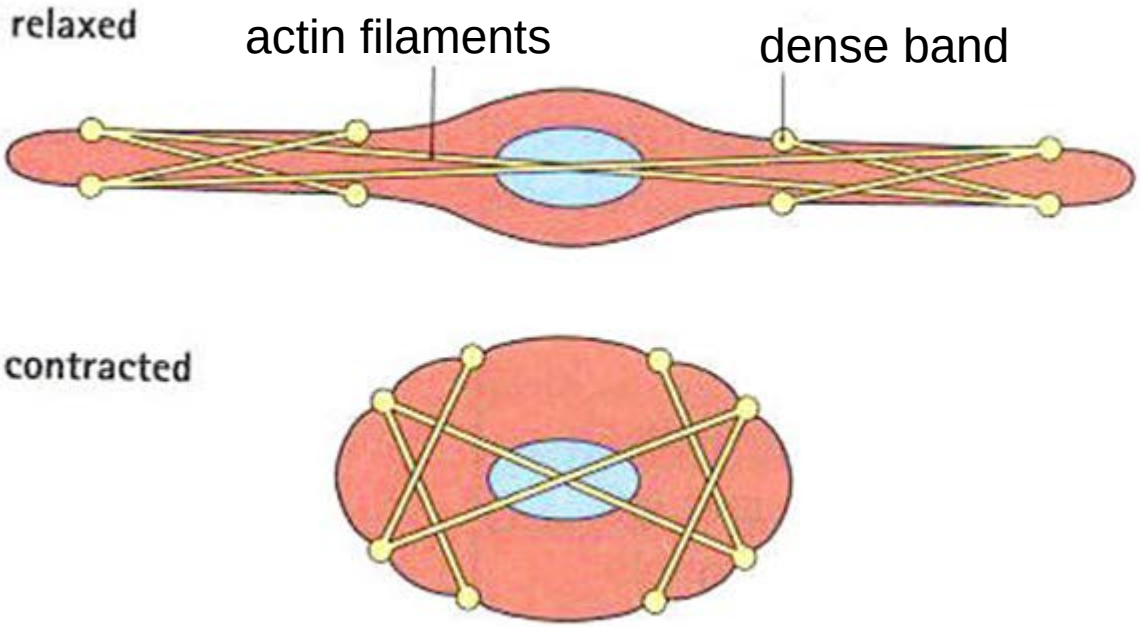


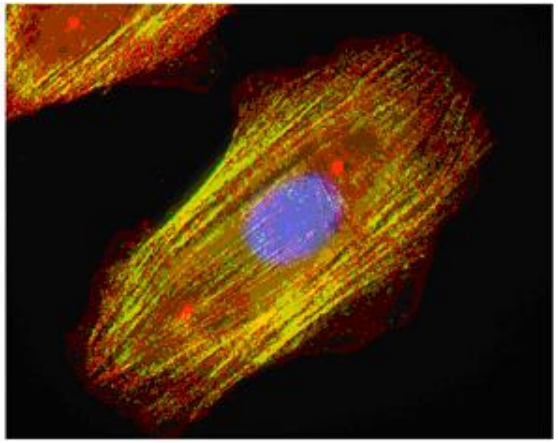
An Introduction to Cardiovascular Physiology/Hodder Arnold © 2010 JR Levick

- Overlapping actin-myosin filaments are the contractile units
- Thin filament (actin) is longer → enables greater shortening (cf. cardiac)
- Poorly developed sarcoplasmic reticulum → rely primarily on diffusion of Ca^{2+} ions from ECF to initiate contraction

Vascular smooth muscle cells: overview

- Actin filaments anchored to **dense bodies** (instead of Z disks) in cytoplasm and **dense bands** in cell membrane
- Not aligned across the cell→ no striations
- Appear to ‘wrinkle’ on contraction





Vascular smooth muscle contraction

- Contraction triggered by a rise in intracellular [Ca^{2+}]
- Most of the increase in [Ca^{2+}] arises from influx of extracellular calcium; relatively small contribution from intracellular stores

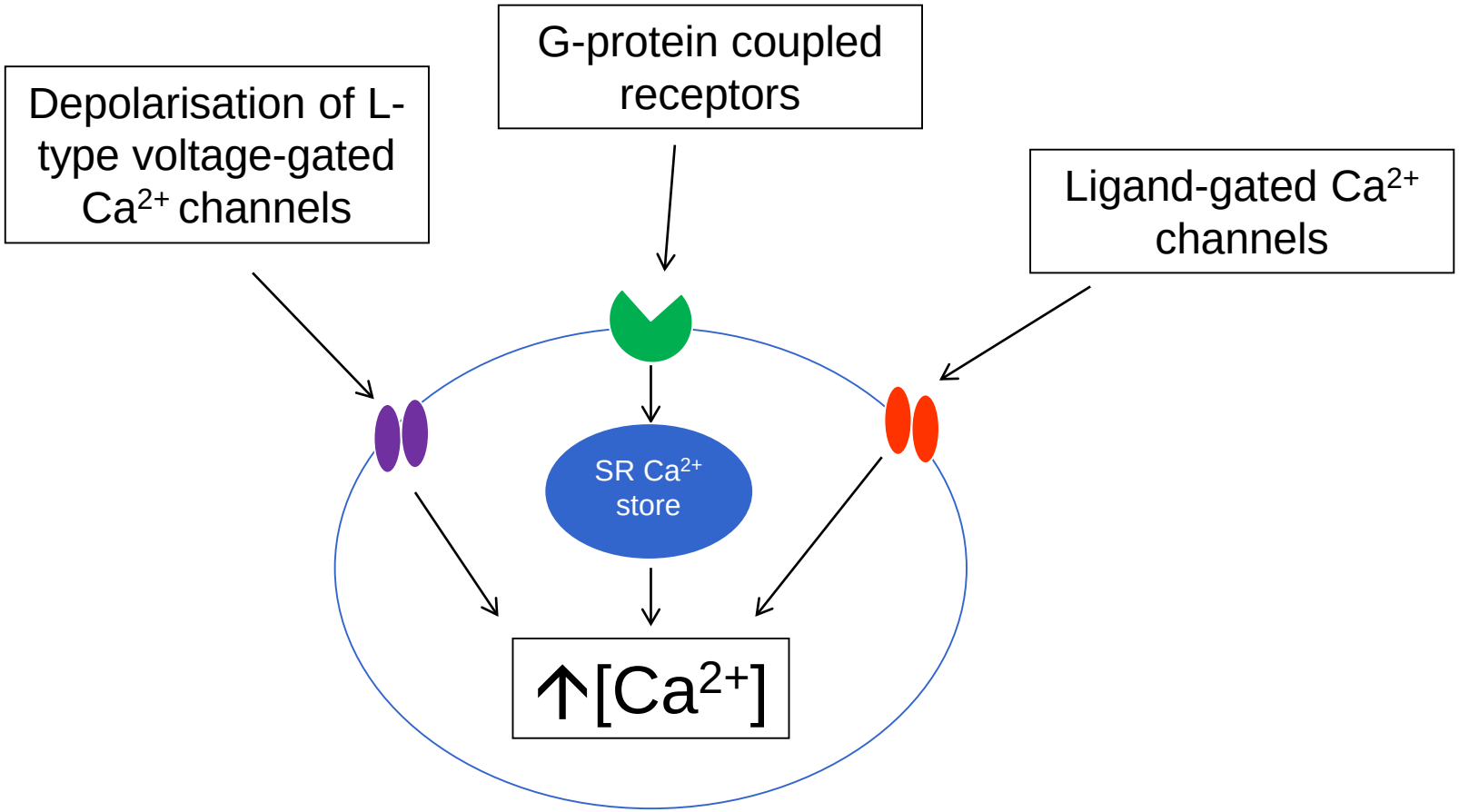
Two broad groups of excitation-contraction coupling:

1. **Electromechanical coupling:** depolarisation of the VSM cell → opening of L-type voltage gated calcium channels
2. **Pharmacomechanical coupling**: Binding of signalling molecule to a receptor leads to increase in intracellular [Ca^{2+}]; either via G-protein coupled release of intracellular stores or opening of receptor-operated calcium channels

   (no change in membrane potential)

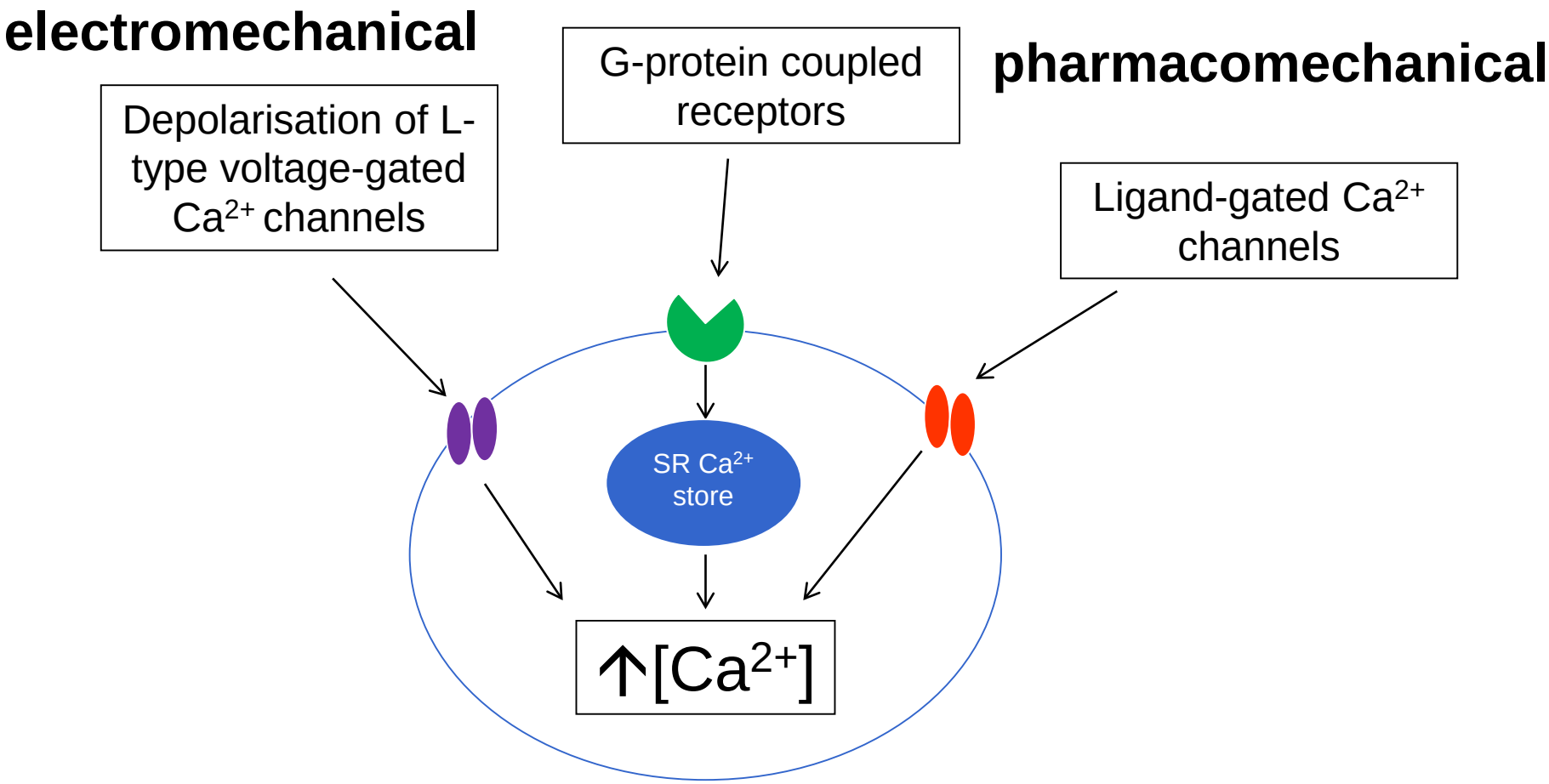
Vascular smooth muscle contraction

- Contraction triggered by a rise in intracellular [Ca^{2+}]



Vascular smooth muscle contraction

- Contraction triggered by a rise in intracellular [Ca^{2+}]



Vascular smooth muscle contraction

Increase in $[Ca^{2+}]_i$

↓

Ca^{2+} + calmodulin complex

↓

[Ca - calmodulin] - Myosin Light Chain Kinase

↓

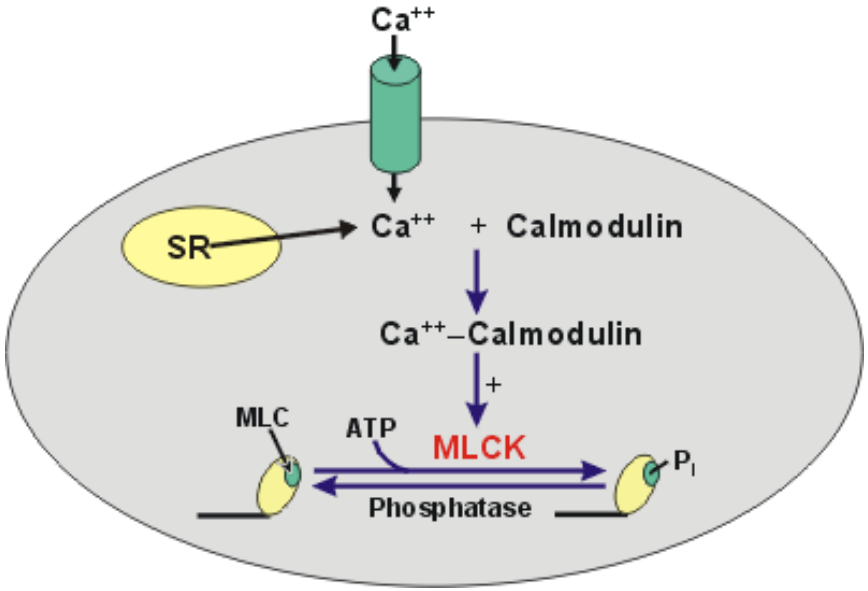
Phosphorylation of Myosin Light Chains

↓

Mysoin forms a crossbridge with actin

↓

Contraction of Smooth Muscle Cells

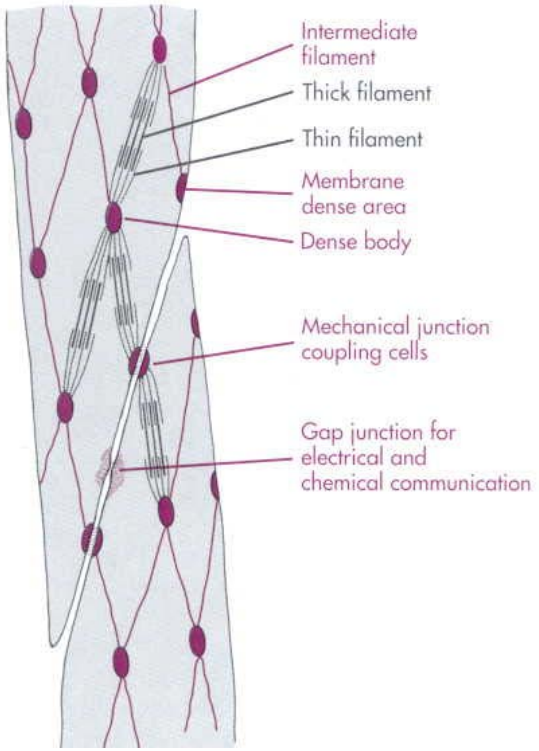


Example: Amlodipine

Ca^{2+} channel blocker → causes VSM relaxation

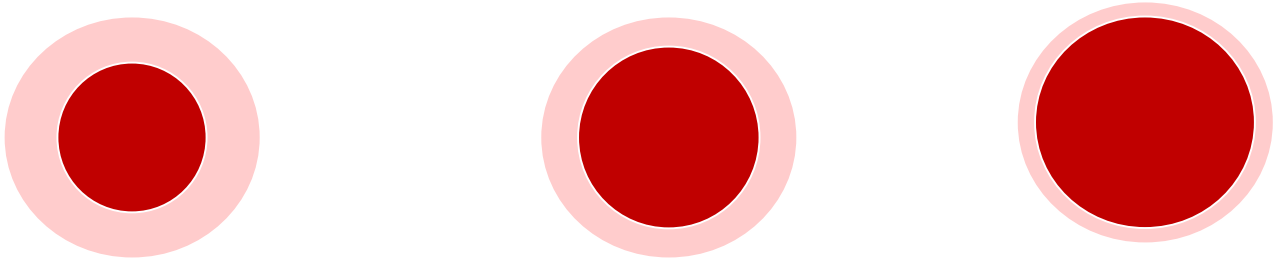
What is different about vascular smooth muscle?

- Contracts slowly, maintains tone for long periods of time
- Low energy requirements (low ATP utilisation)
- Poorly developed sarcoplasmic reticulum
- Cell to cell conduction via gap junctions (as for cardiac muscle)
- No troponin, no voltage operated Na channels



Vascular tone

- Vascular tone is *the state of contractile tension in vessel walls*
- Basal vascular tone produced by vascular smooth muscle contraction sustained continually → this maintains arterial blood pressure
- ↑ tone (relative to basal) = vasoconstriction, ↓ tone = vasodilation



VASOCONSTRICTION **BASAL** **VASODILATION**

- Can be maintained by spontaneous depolarisation
- Changes in tone modify resistance and therefore flow
- A number of factors modify this tone → fine control of tone

Factors controlling vascular tone

1. Intrinsic mechanisms
   - Regulation by factors entirely within the vasculature
   - Myogenic response
   - Vasoactive metabolites
   - Endothelial secretions

   Intrinsic mechanisms are responsible for **autoregulation**, **active** and **reactive hyperaemia**

2. Extrinsic mechanisms
   - Regulation by factors outside the vasculature
   - Neural control (vasomotor nerves)
   - Hormonal control (vasoactive hormones)

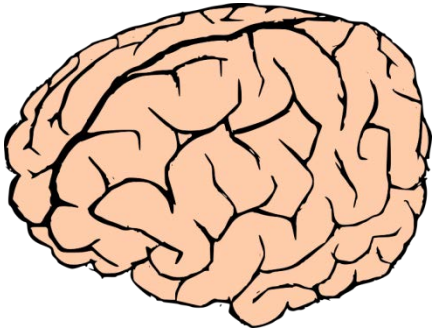
   Extrinsic mechanisms can override intrinsic mechanisms to meet the needs of the whole animal

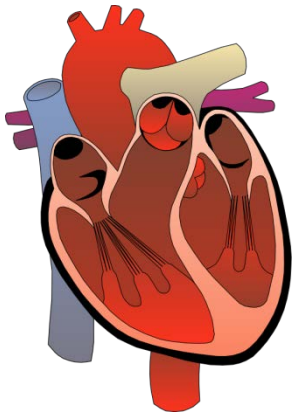
Myogenic response

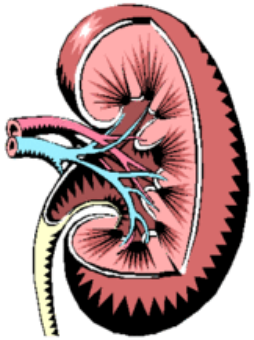
- Vascular smooth muscle contracts in response to stretch and relaxes with a reduction in tension

- Important because:
  - Contributes to basal tone
  - Stabilises tissue blood flow if arterial pressure changes

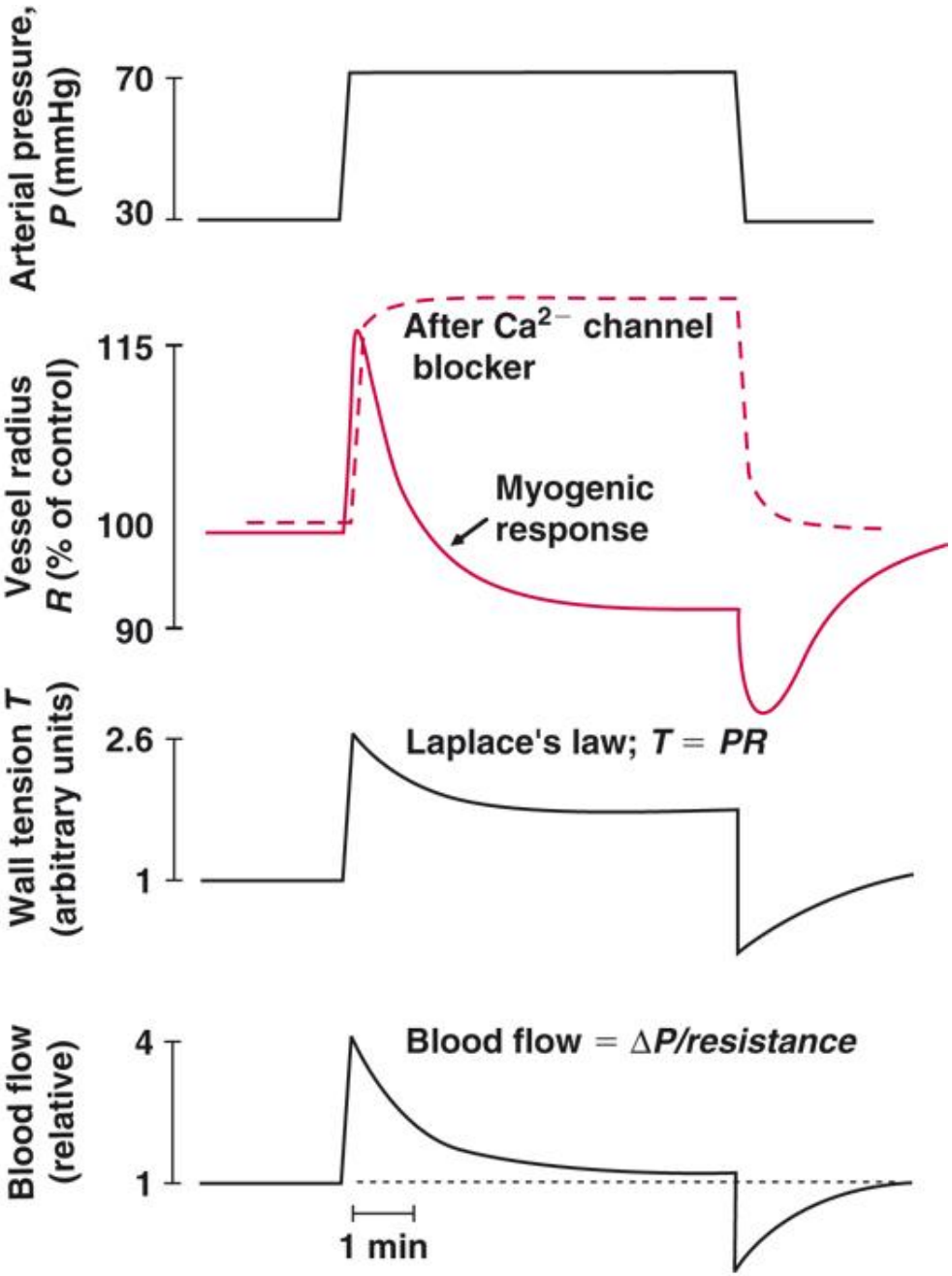
- Particularly prominent mechanism in cerebral, coronary and renal arterioles.



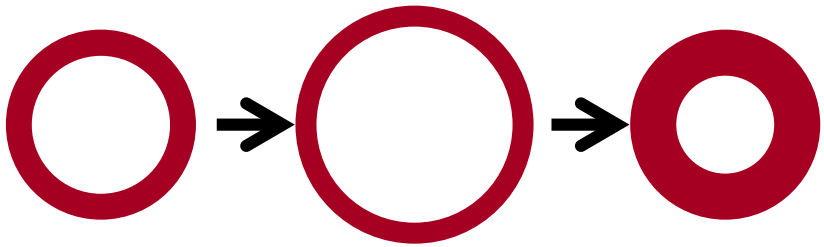




Myogenic response



Change in diameter of rat cerebral artery upon raising intraluminal pressure (P)



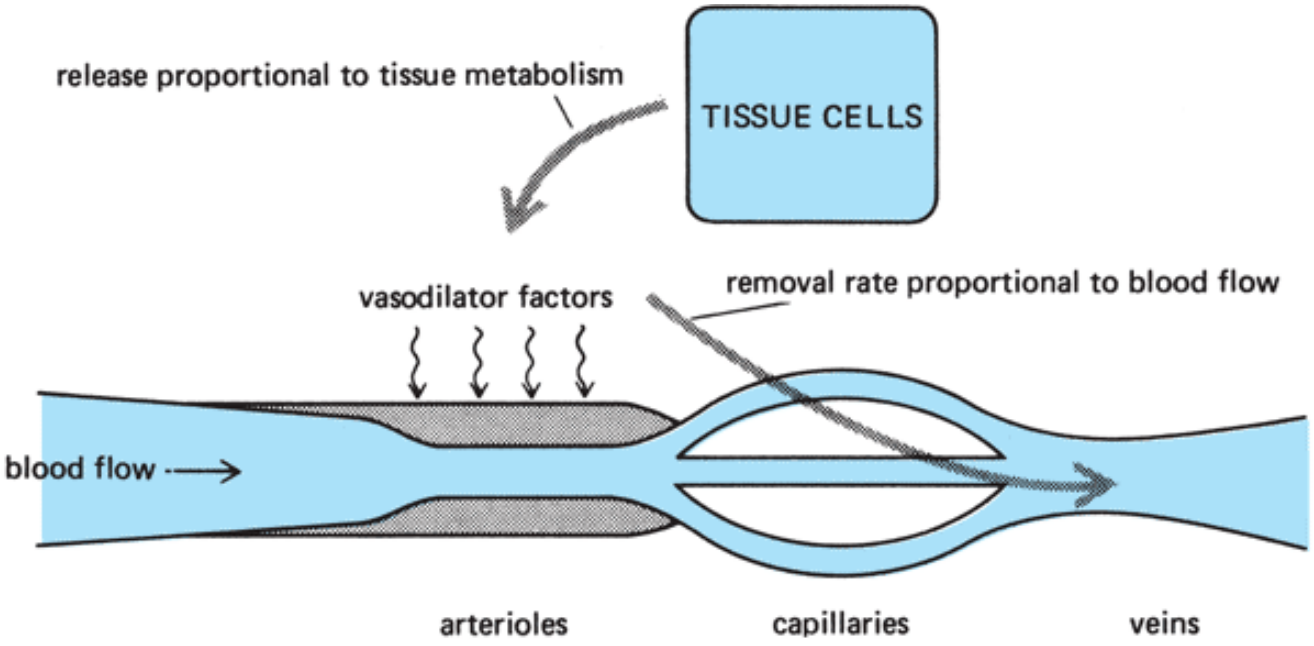
Initial passive stretch followed by active contraction

Mediated by depolarisation and Ca^{2+}

Depolarisation **initiated** by **stretch-activated channels**; Response **sustained** by **tension sensitive** channels

Vasoactive metabolites

- Metabolic products released into interstitial fluid cause alterations in local blood flow
- Function to match blood flow to metabolic demands of tissue

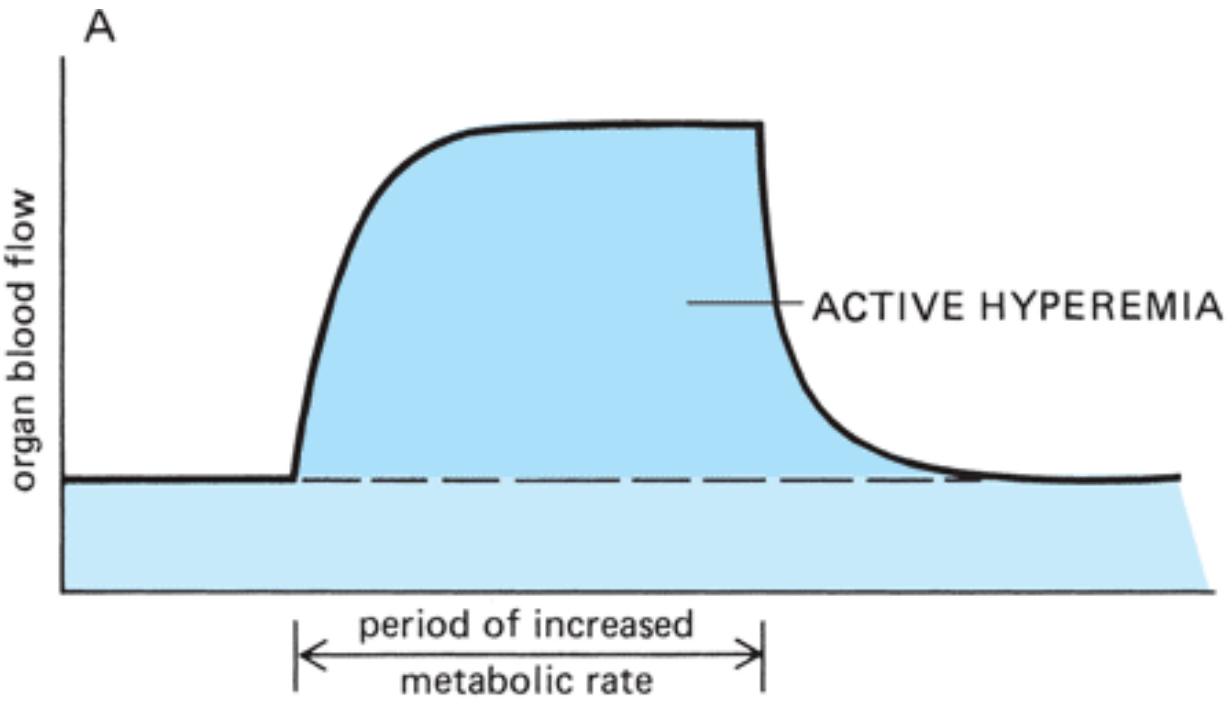


- Vasoactive metabolites contribute to **metabolic** (active) hyperaemia and **reactive** hyperaemia

Metabolic (active) hyperaemia

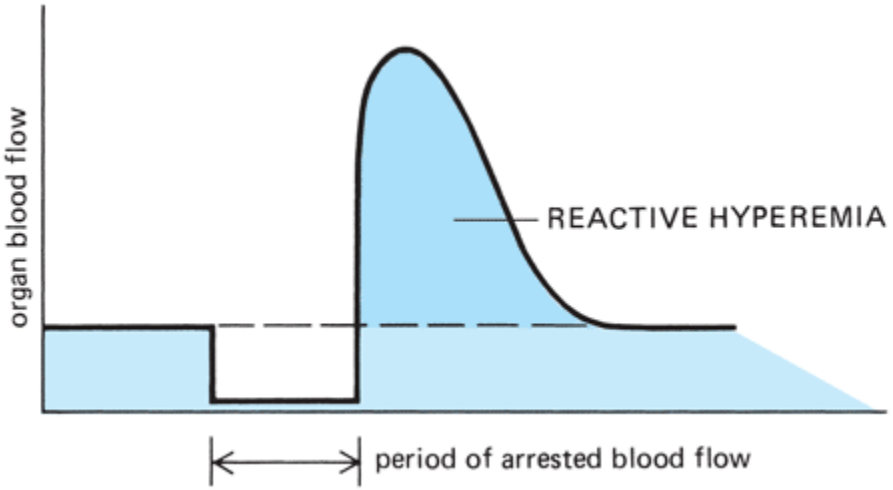
- Increased blood flow in response to ↑ metabolic rate

Examples:
- CO_2,
- Lactate,
- Adenosine
- K+

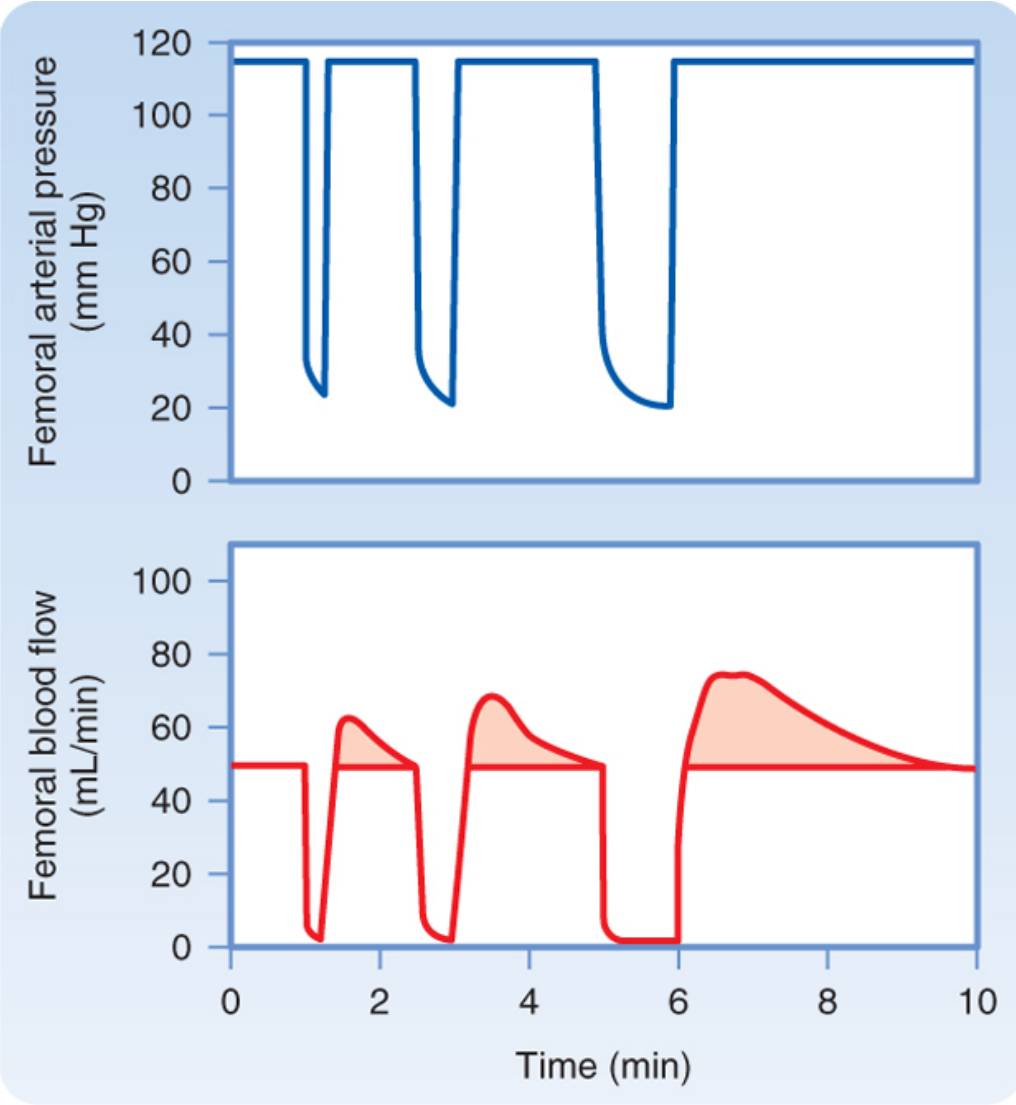


Reactive hyperaemia

- Temporary ↑ blood flow following a period of reduced blood flow
- Leads to rapid restoration of O_2 supply and ‘wash out’ of accumulated waste products



Reactive hyperaemia



- Blood flow stopped by clamping the femoral artery (dog) for 15, 30, 60 seconds
- Release after 60s resulted in peak blood flow 70% greater than control flow, return to normal after around 2 mins
- Peak flow and duration of hyperaemia proportional to duration of occlusion

Factors controlling vascular tone

1. Intrinsic mechanisms
   - Regulation by factors entirely within the vasculature
   - ➢ Myogenic response ✓
   - ➢ Vasoactive metabolites ✓
   - ➢ Endothelial secretions

   Intrinsic mechanisms are responsible for **autoregulation**, **active** and **reactive hyperaemia**

2. Extrinsic mechanisms
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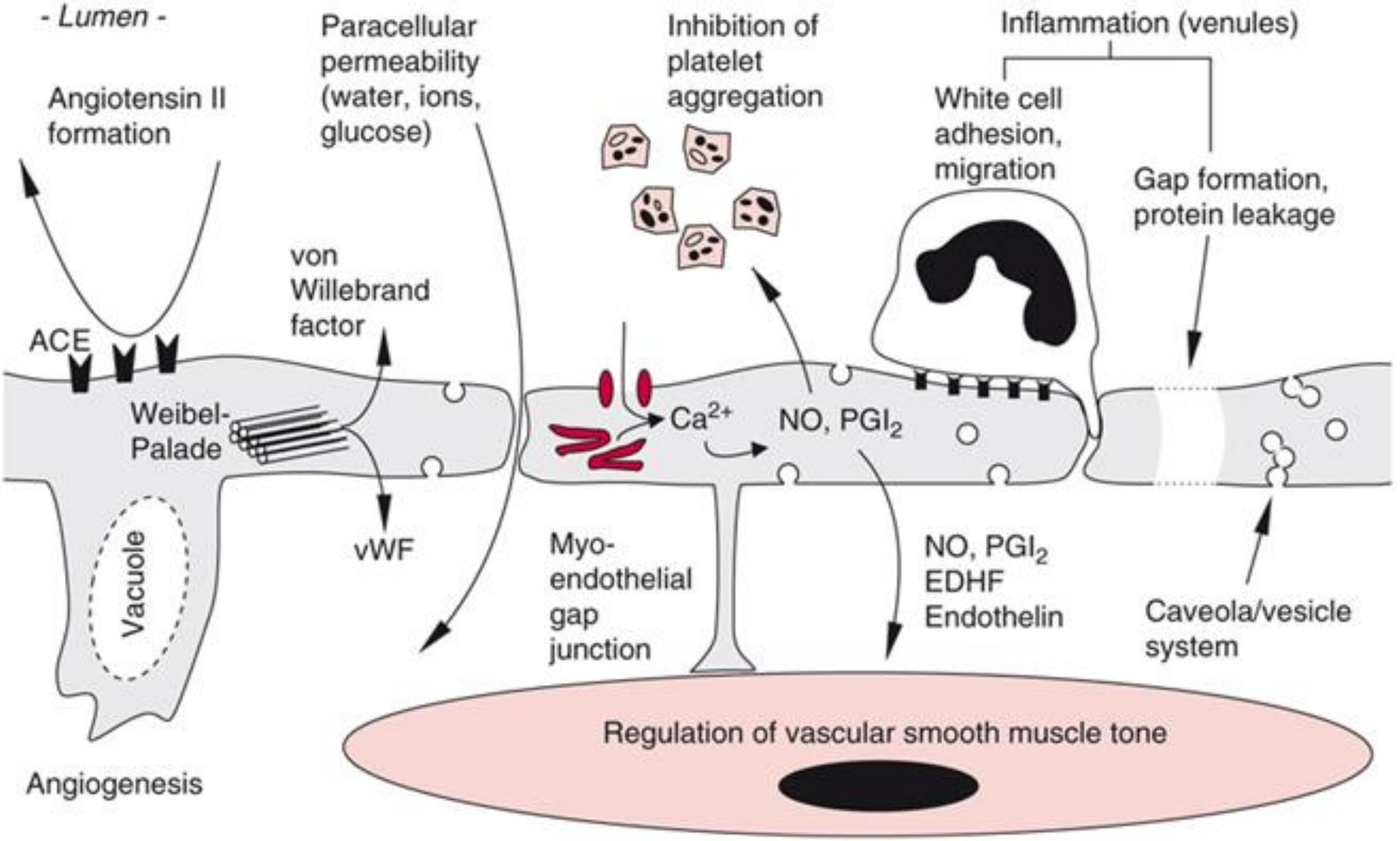
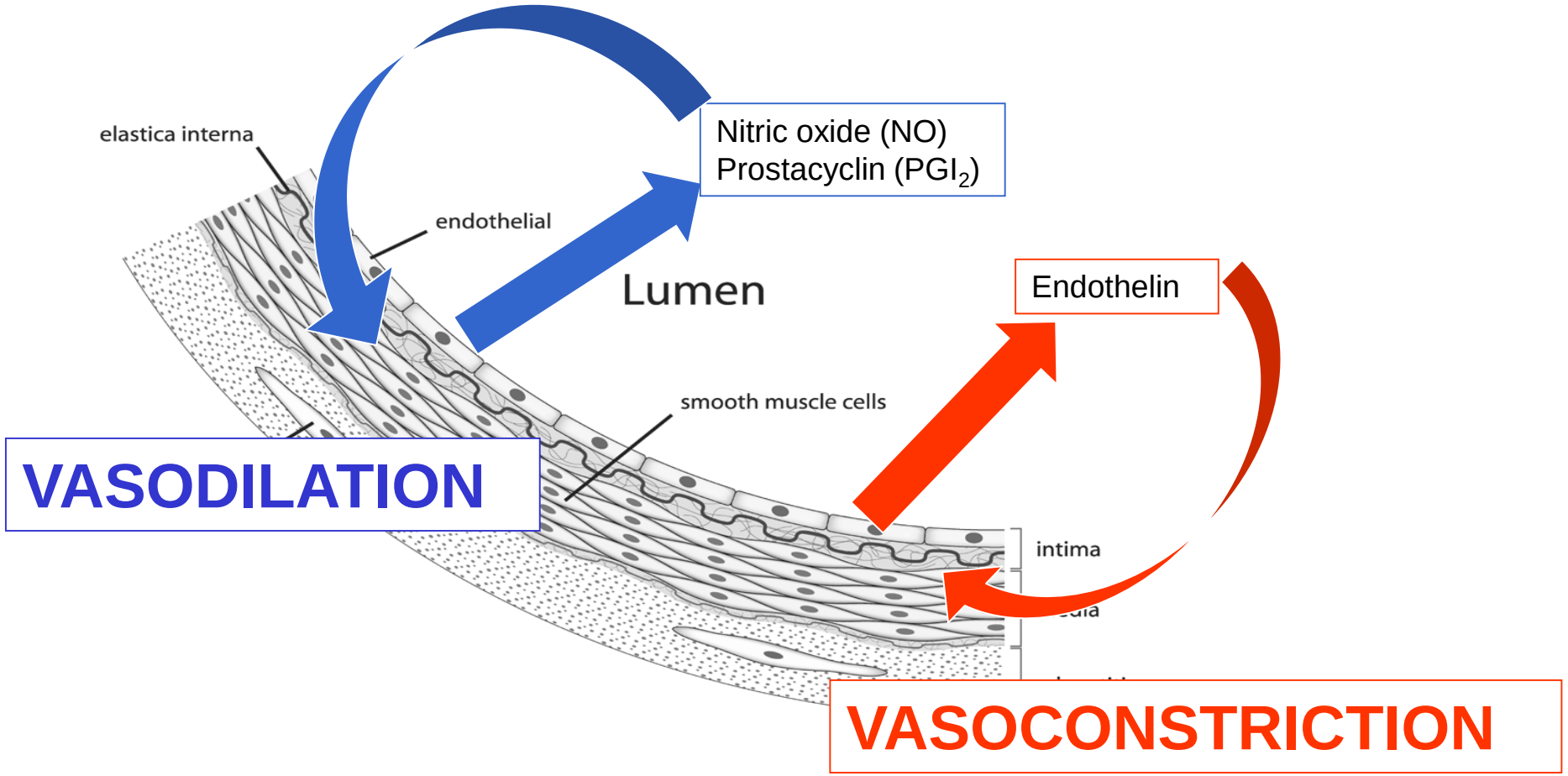
   Extrinsic mechanisms can override intrinsic mechanisms to meet the needs of the whole animal

Endothelial cells have multiple functions



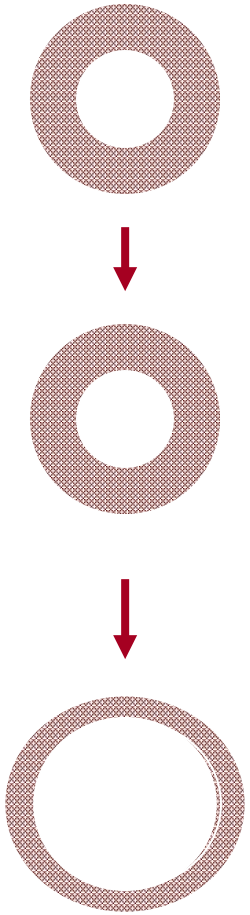
Endothelial secretions

- Endothelial cells produce a range of vasoactive molecules – both constrictors and dilators



Endothelial secretions

- Endothelium-induced flow dependent relaxation



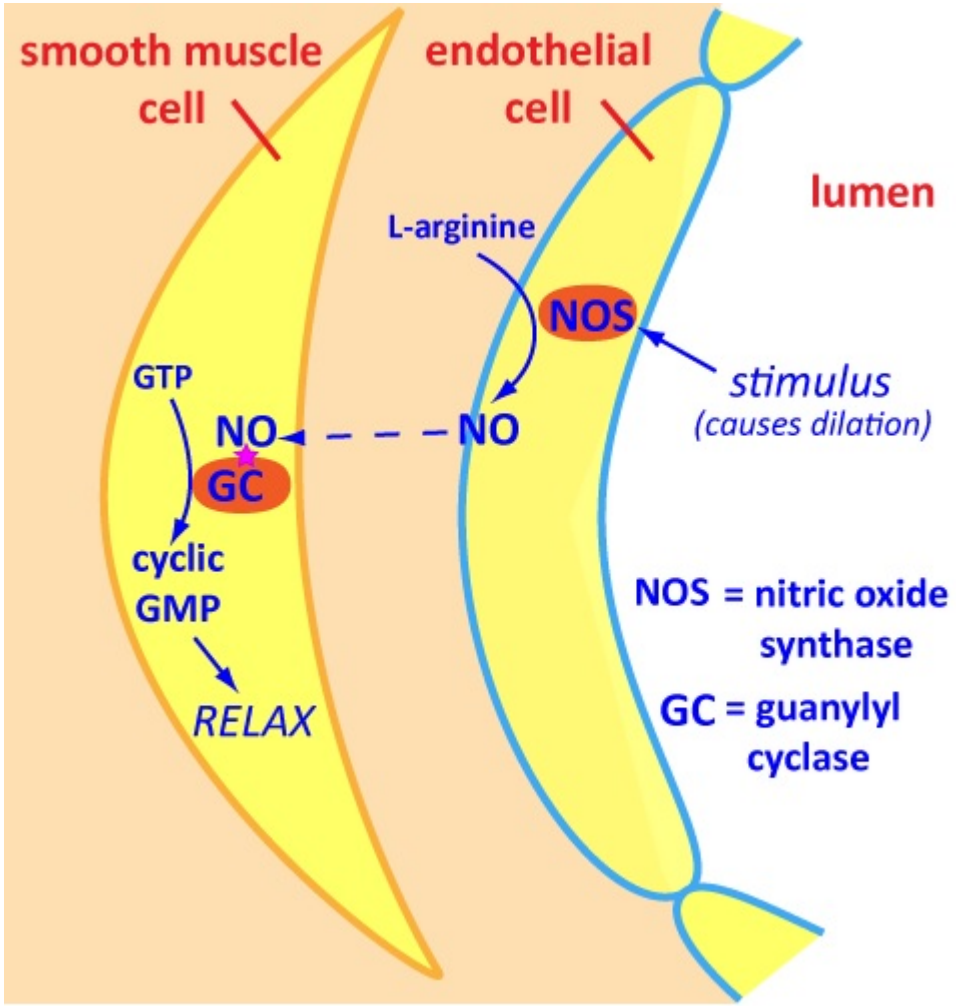
Normal pressure

Increased flow → ↑ 'shear stress' → ECs produce NO

Endothelium dependent muscle relaxation

NO–induced vasodilation

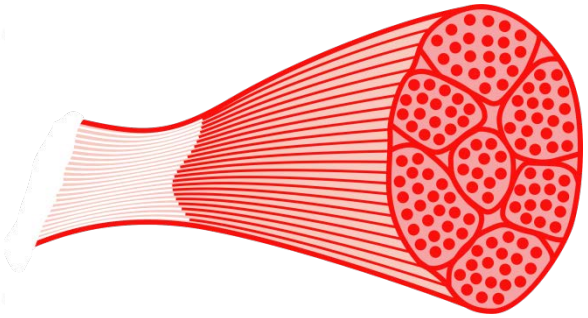
- Nitric oxide is a labile gas molecule produced by ECs



NO Signalling:

- activates **guanylyl cyclase** (GC)
- GC converts GTP to **cyclic GMP** (**cGMP**)
- cGMP activates kinases that promote relaxation

Example: exercise

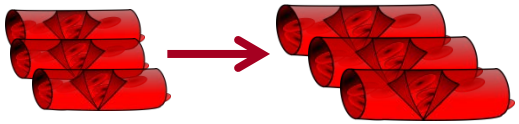


Triceps muscle contraction

Contraction → generation of metabolites → local arterioles dilate

↓ Resistance in the 'resistance vessels'

Metabolic hyperaemia



↑ Flow in 'distributing arteries' (e.g. *brachial artery*) = ↑ shear stress on ECs

Flow = <u>pressure difference</u> resistance

Endothelium-induced flow dependent relaxation

ECs produce NO → dilation of distributing artery

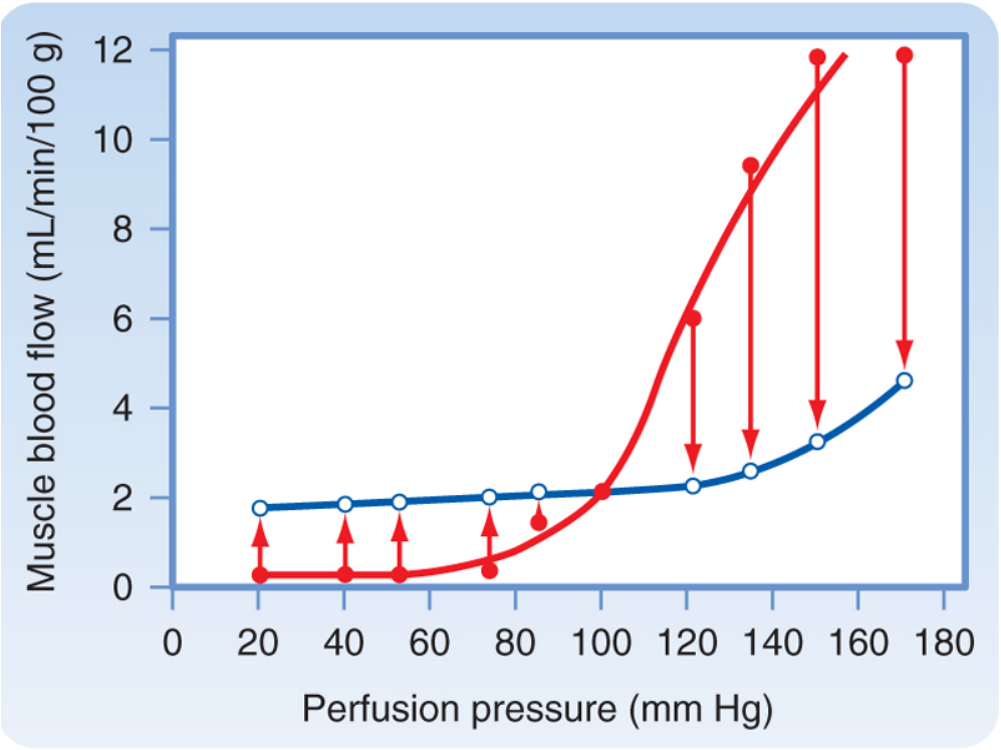
Example: nitroprusside

Nitric oxide donor

Autoregulation

- Autoregulation: *vascular resistance changes that tend to maintain a constant blood flow*

→ Constant flow despite range of perfusion pressures



Pressure-flow relationship: skeletal muscle (dog)

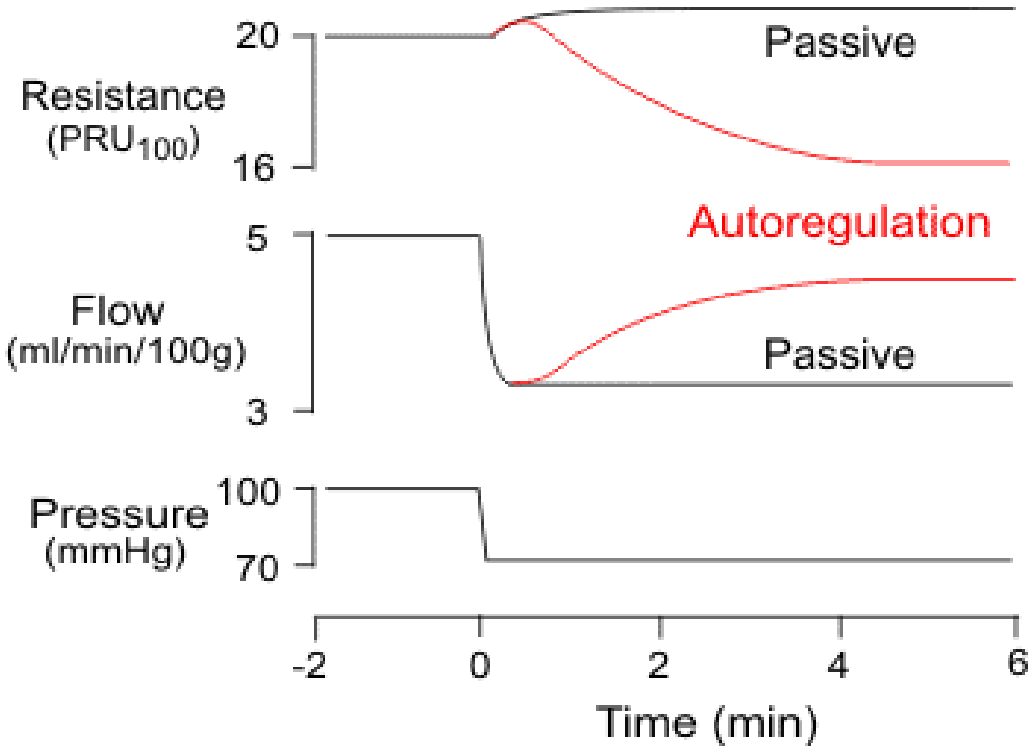
- Closed circles = flows immediately after abrupt changes in perfusion pressure (experimental)
- Open circles = steady state blood flow (30-60s later)

Autoregulation

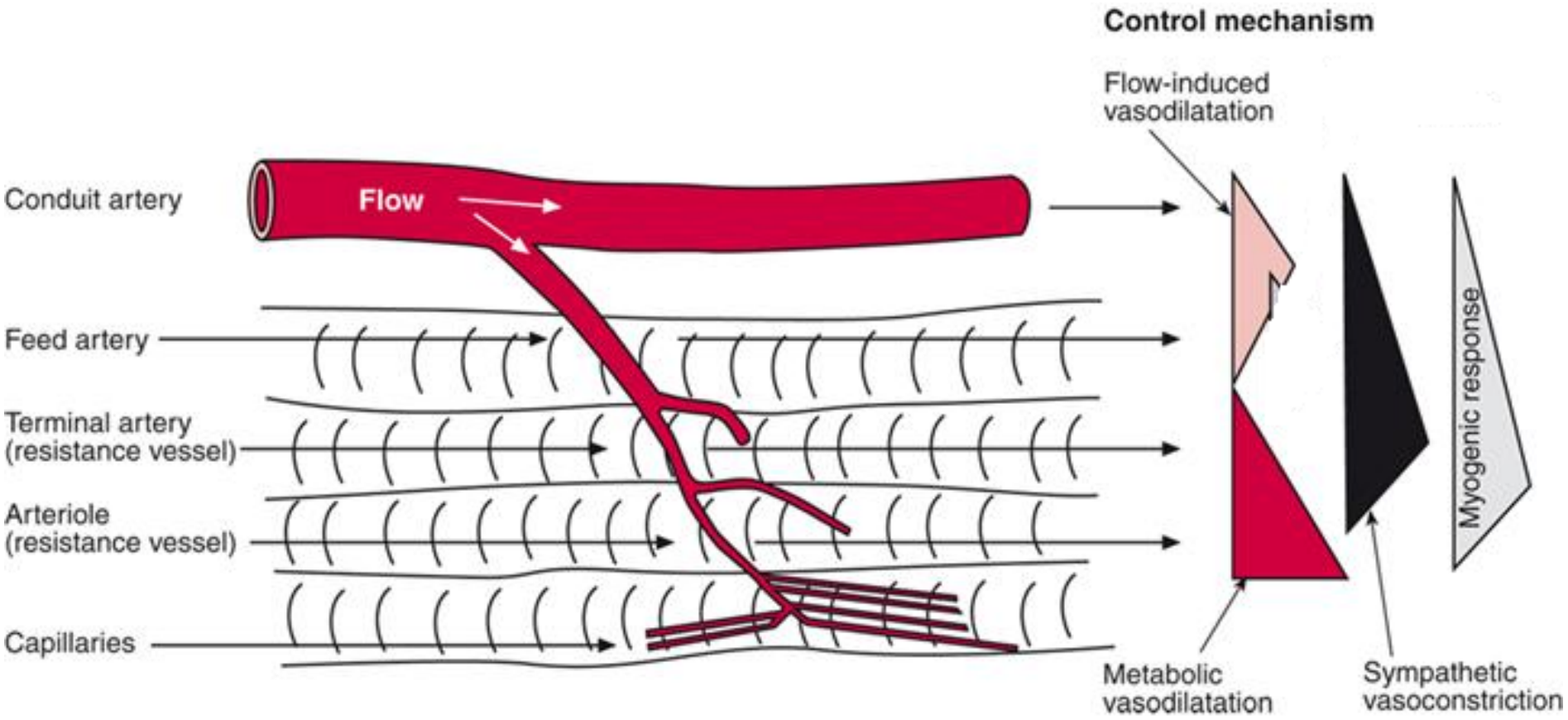
Achieved by:

- Myogenic response
- Flow induced endothelial relaxation

→ Preserves tissue flow in the face of changing arterial pressure
→ Protects capillaries from excessive hydrostatic pressure



Differential control of arterial tree



Factors controlling vascular tone

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   - ➢ Vasoactive metabolites
   - ➢ Endothelial secretions

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2. Extrinsic mechanisms
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   - ➢ Hormonal control (vasoactive hormones)

   Extrinsic mechanisms can override intrinsic mechanisms to meet the needs of the whole animal

Neural control

Neural control of vascular tone involves two types of autonomic nerves:

1. Sympathetic nerves – predominantly vasoconstrictor
2. Parasympathetic nerves – vasodilator

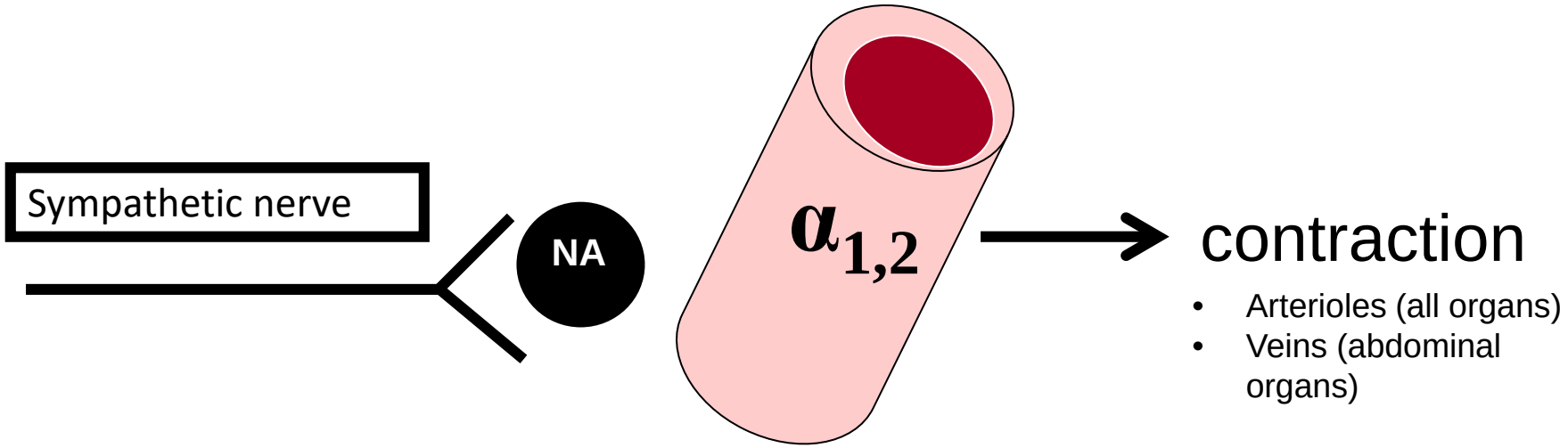
- ‘vasoconstrictor’ and ‘vasodilator’ refer to the effect of an increase in nerve activity

Remember that:

- *a reduction in vasoconstrictor activity can cause vasodilation*

Sympathetic vasoconstrictor nerves

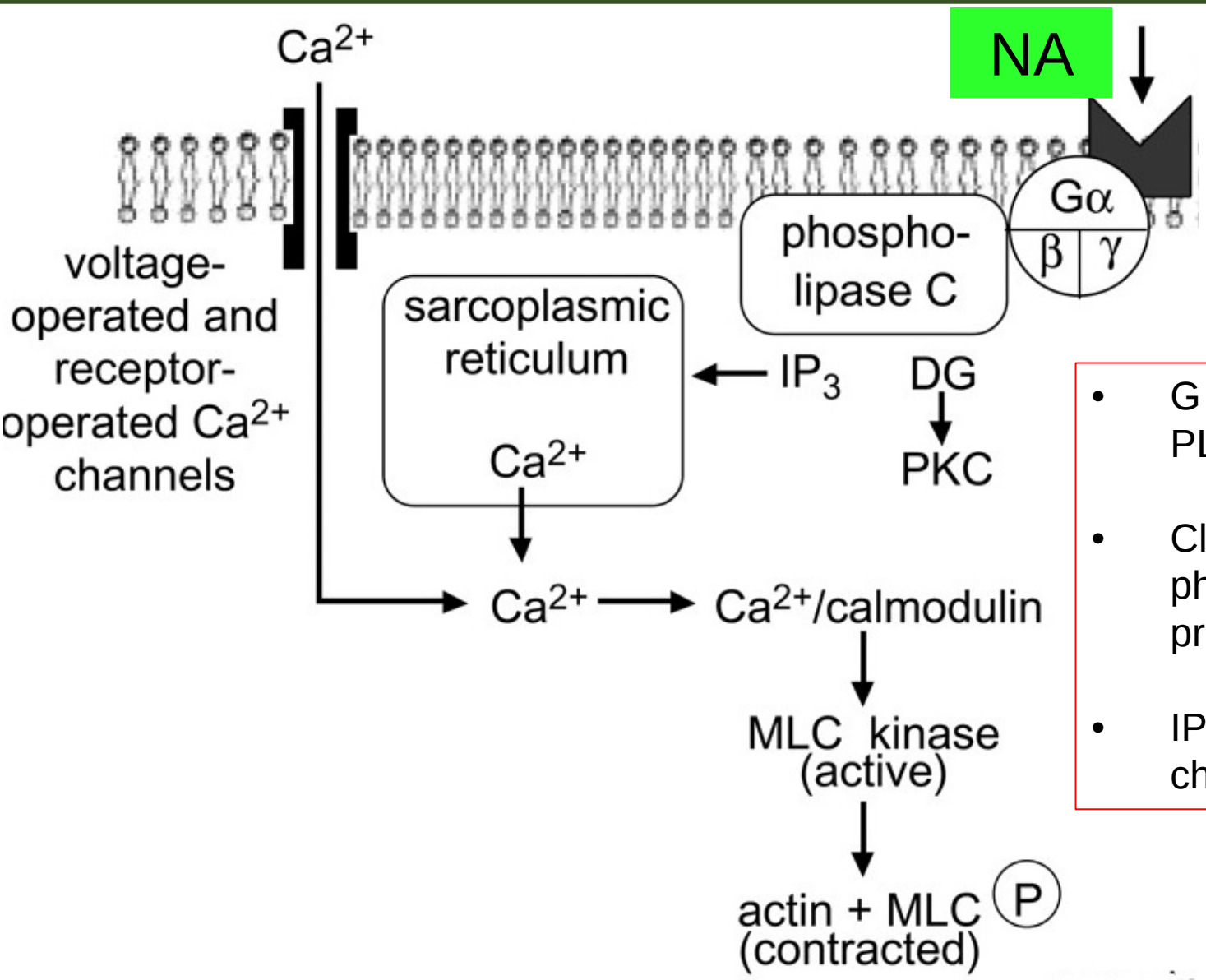
- Post ganglionic sympathetic fibres terminate in the outer border of the *tunica media*
- Fibres release vesicles containing noradrenaline (NA)
- NA activates α- adrenoreceptors causing vasoconstriction



Increased sympathetic activity:

- Increases peripheral resistance (↑TPR)
- Reduces local blood flow
- Displacement of blood from peripheral to central veins

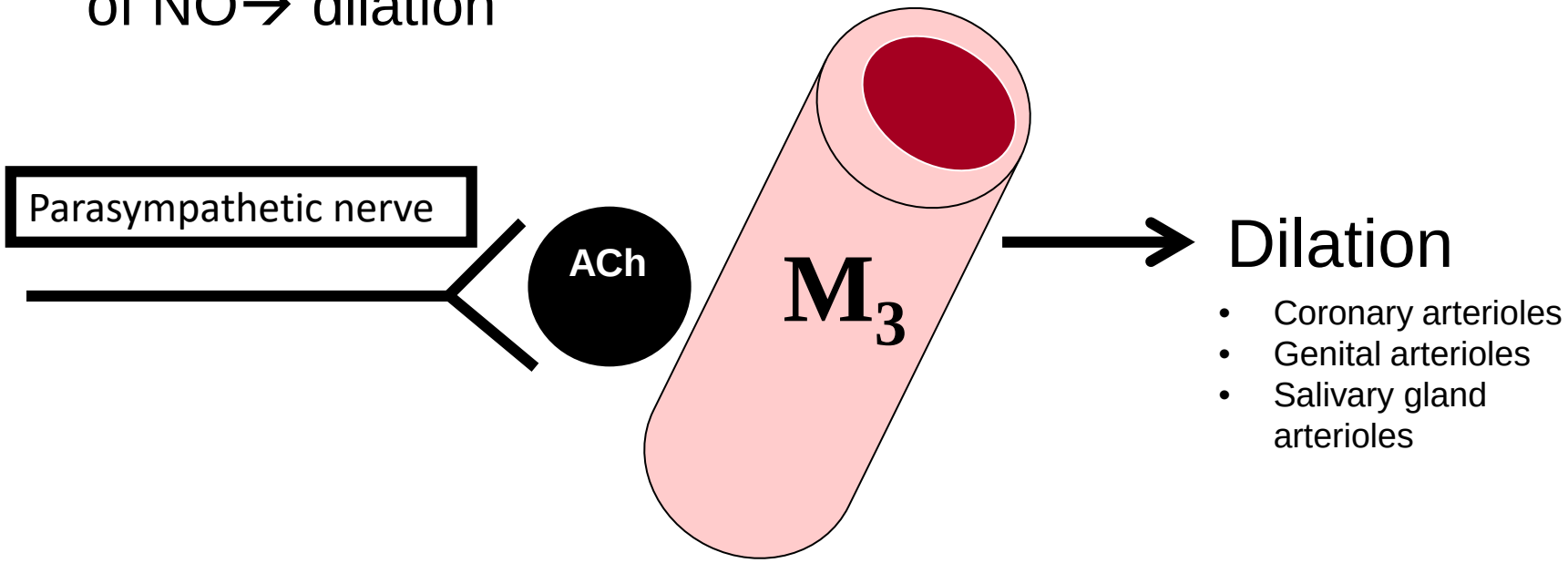
α-adrenoceptor-mediated constriction of smooth muscle



- G protein activates PLC
- Cleaves membrane phospholipid to produce IP3
- IP3 opens Ca^{2+} channels on the SR

Parasympathetic vasodilator nerves

- Parasympathetic fibres release vesicles containing acetylcholine (ACh)
- ACh activates M_3 muscarinic receptors on ECs → synthesis of NO→ dilation



Hormonal control

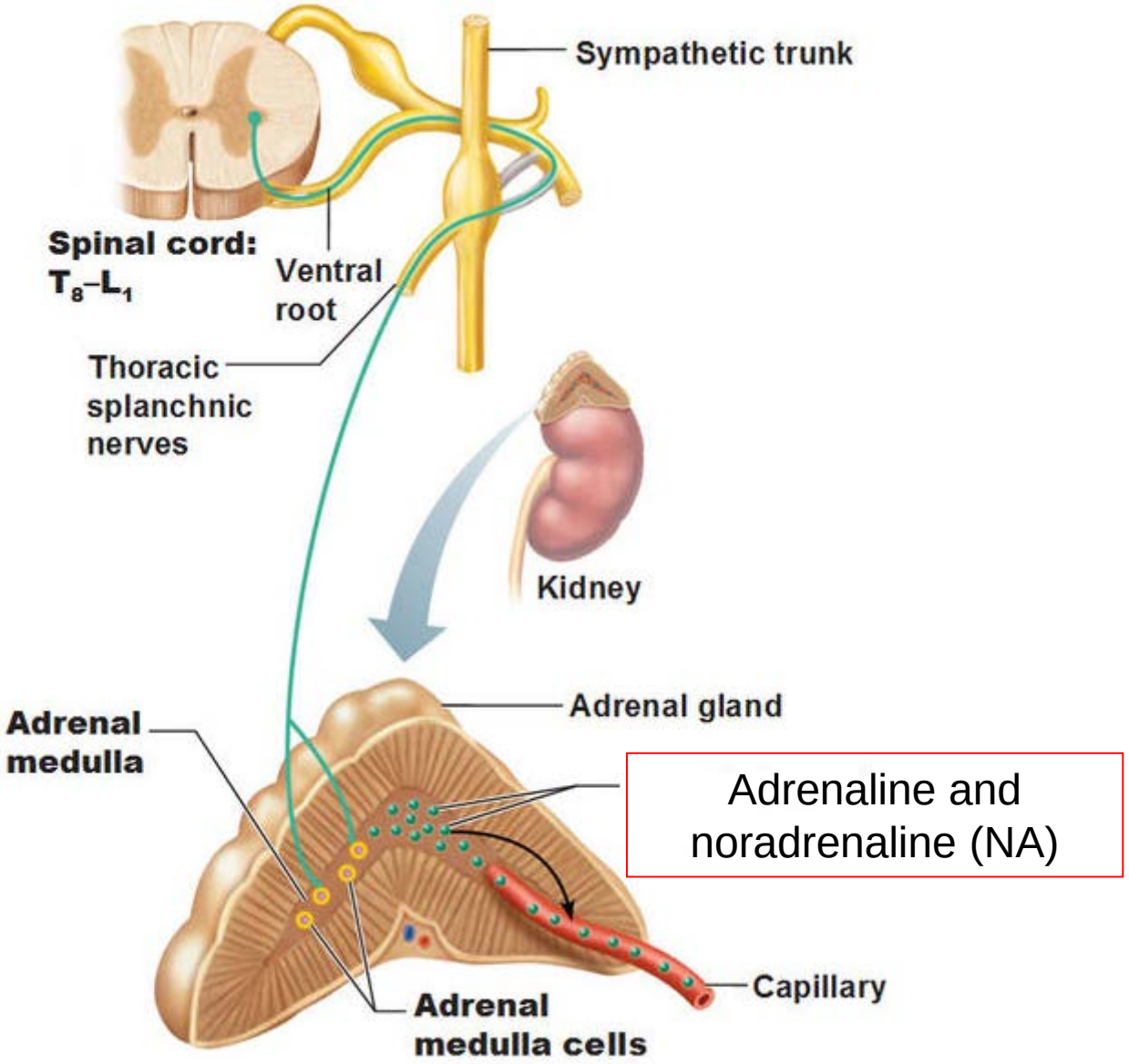
A number of hormones contribute to regulation of vascular tone:

- Adrenaline
- Antidiuretic hormone (ADH)
- Angiotensin
- Insulin
- Thyroxine
- Oestrogen

Also other signalling molecules (paracrine and autocrine) such as:

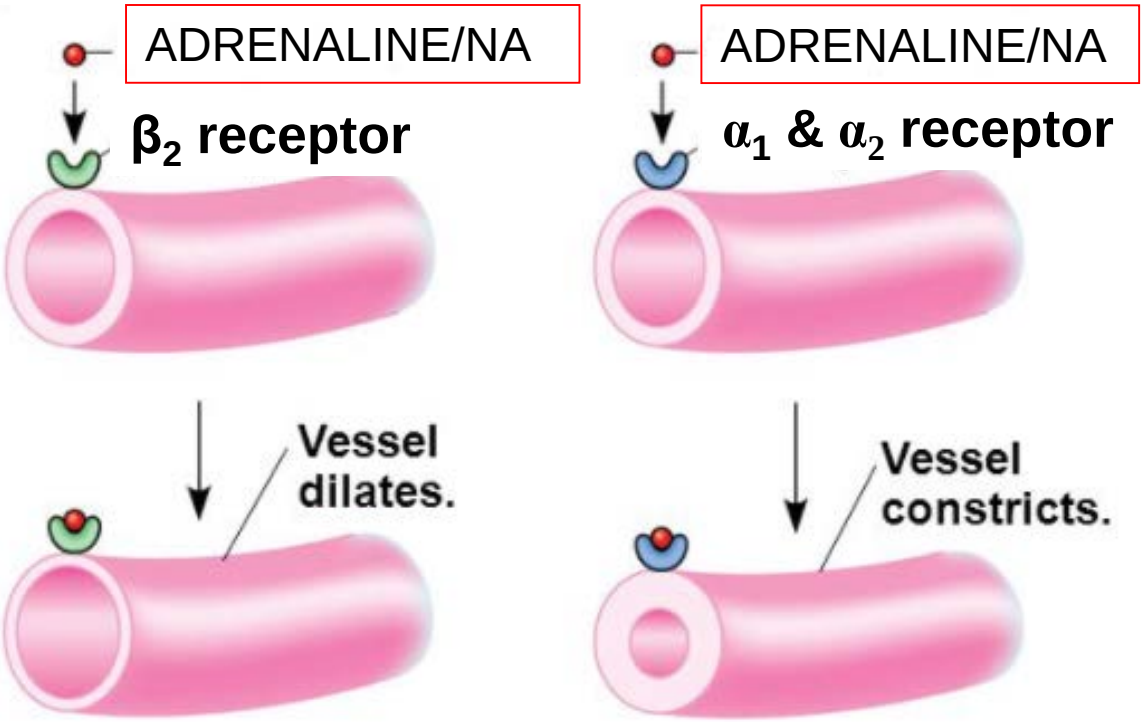
- Serotonin
- Histamine
- Bradykinin
- Thromboxane

Adrenaline



Adrenaline and noradrenaline (NA)

Adrenaline



β2 receptors predominate in the coronary circulation and skeletal muscle

α receptors predominate in **most tissues**

Unlinke α adrenoreceptors, β_2 receptors are not innervated by sympathetic nerves → they respond to circulating adrenaline and NA

Extrinsic control can override intrinsic control: haemorrhage

Extrinsic control can override intrinsic control: haemorrhage

Atrial baroreceptor & volume receptor

↓

Sympathetic activation

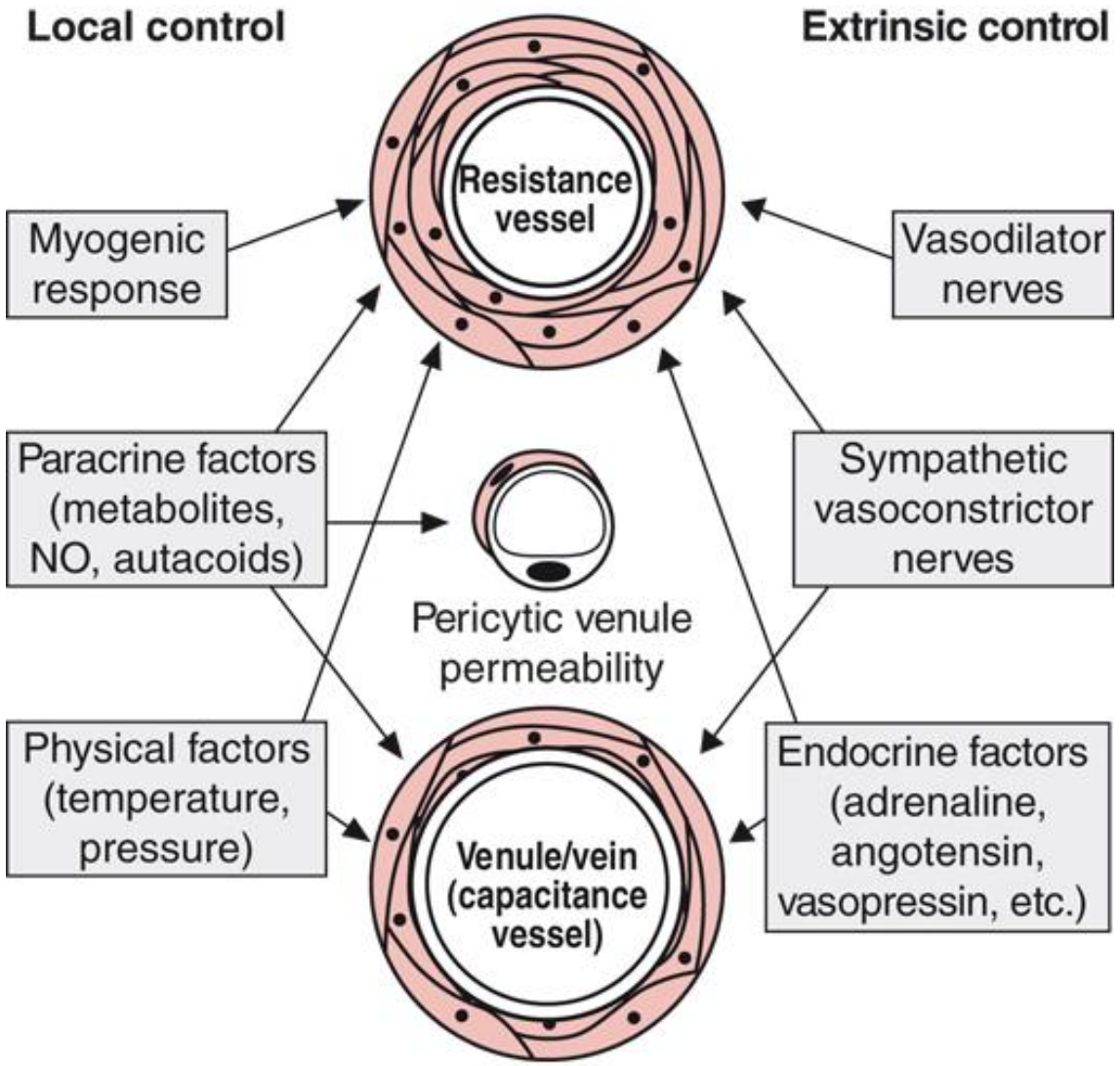
↓

Increased TPR
Reduced local blood flow
AND
Contraction of veins → displacement of blood to central veins

↓

Partial restoration of cardiac filling pressure

Overview of vascular control



Summary

- Vascular smooth muscle cells
  - » Structure
  - » Excitation –contraction coupling
- Factors controlling vascular tone
  - o Intrinsic
    - ➢ myogenic response
    - ➢ vasoactive metabolites
    - ➢ endothelial secretions
  - o Extrinsic
    - ➢ neural control (vasomotor nerves)
    - ➢ hormonal control (vasoactive hormones)