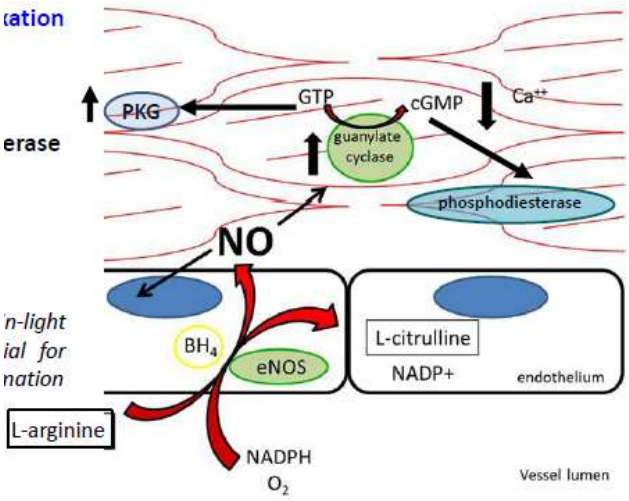
- Freely diffusible gas that acts as a signalling molecule
- Very short half-life 6-30s = local activity
- Activity in blood limited by circulating haemoglobin α
- Prevents thrombosis – inhibits platelets adhesion to vessels and activation
- Anti-inflammatory – inhibits leukocyte adhesion and migration
- Antioxidant
- Inhibits smoot muscle cell proliferation and migration
- Atheroprotective

Relaxation of vascular smooth muscle (vSMC)

- Mechanism of vSMC relaxation
  - cGMP reduces [Ca^{2+}]
  - regulates phosphodiesterase
  - Activates PKG → limit activation of myosin-light chain kinase (MLCK) essential for myosin-actin cross bridge formation → smoot muscle relaxation



Prostacyclin synthesis

- Phospholipase A2 activity leads to prostacyclin – rate limiting step – activated by Ca^{2+} & PKC
- Cyclooxygenases
  - COX-2 – inducible
  - COX-1 – constitutive (predominant isoform in endothelium)
- Endothelial cells express prostacyclin synthase (PGCIS)
- Platelets use thromboxane synthase to produce thromboxane

Prostacycline (PGI_2) and vSMC relaxation

- Prostacyclin binds IP receptors (GPCRs)
  - Activates adenylate cyclase
  - Increasing (cAMP) activates PKA
  - Decreases [Ca^{2+}] limiting vSMC contraction

Endtothelium-derived hyperpolarising factors (EDHF)

- The phenomenon of endothelium-dependent hyperpolarisation and relaxation
- Ach stimulation of artery preparation in the presence of NO scavengers (e.g. haemoglobin) & COX inhibitors (indomethacin) indication an additional endothelial-dependent vasodilatory activity
- Small molecule with a short half-life
- EDHF effects are blocked with endothelial K^+ (e.g. $IKca^{2+}$) channel inhibitors
- EC become hyperpolarised and signal to vSMCs resulting in hyperpolarisation to produce vasodilation
- EC hyperpolarisation transmitted to myocytes via myo-endothelial gap junctions

OR

- EDHF is K^+ exciting EC through K^+ channels to activate myocyte K^+ channels & Na^+/K^+ ATPases

Endtothelium dysfunction/activation

- Shift in EC function to reduced vaasodilation & more pro-inflammatory & pro-thrombotic state
- Classically associated with reduced bioavailability of NO & reduced vasodilation
- Blood vessels may become damage and leaky with loss of EC