

Abstract  Cyclic guanosine 3′,5′-monophosphate (cGMP) plays an integral role in the control of vascular function. Generated from guanylate cyclases in response to the endogenous ligands, nitric oxide (NO) and natriuretic peptides (NPs), cGMP influences a number of vascular cell types and regulates vasomotor tone, endothelial permeability, cell growth and differentiation, as well as platelet and blood cell interactions. Reciprocal regulation of the NO-cGMP and NP-cGMP pathways is evident in the vasculature such that one cGMP generating system may compensate for the dysfunction of the other. Indeed, aberrant cGMP production and/or signalling accompanies many vascular disorders such as hypertension, atherosclerosis, coronary artery disease and diabetic complications. This chapter highlights the main vascular functions of cGMP, its role in disease and the resulting current and potential

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therapeutic applications. With respect to pulmonary hypertension, heart failure and erectile dysfunction, as well as cGMP signal transduction, the reader is specifically referred to other dedicated chapters.

1 Vascular Physiology of cGMP

1.1 cGMP Signalling and Compartmentalisation

cGMP is generated in the vasculature via two main guanylate cyclases, the cytosolic soluble guanylate cyclase (sGC) and the membrane-bound particulate guanylate cyclase (pGC) (Münzel et al. 2003). sGC serves as a receptor for the biologically active gas nitric oxide (NO) (Fribe and Koesling 2003; Moncada and Higgs 2006). NO is produced endogenously in the vascular system via a family of NO synthases, namely the constitutive forms of endothelial NOS (eNOS) and neuronal NOS (nNOS) and the inducible form, iNOS (Moncada and Higgs 2006). Once generated, NO binds to the prosthetic heme group of sGC to induce a conformational change, breakage of the histidine-to-iron bond and activation of the enzyme (Fribe and Koesling 2003). In addition to NO, carbon monoxide (CO), generated via heme oxygenase (HO)-mediated degradation of cellular heme, also stimulates sGC, albeit to a lesser extent than NO (Brune and Ullrich 1987; Fribe et al. 1996; Sharma and Magde 1999) and modulates vascular function (Wang 1998; Kaczorowski and Zuckerbraun 2007; Li and Moore 2007). Moreover, sGC may also be activated by the reactive oxygen species, hydrogen peroxide (H$_2$O$_2$), which is generated predominantly via the dismutation of superoxide (O$_2^−$) (Ardanaz and Pagano 2006). Thus H$_2$O$_2$ has been reported to stimulate sGC and increase cGMP in the vasculature (Burke-Wolin et al. 1991; Fujimoto et al. 2001; Sato et al. 2003); other studies have refuted this concept (Thengchaisri and Kuo 2003; Gao et al. 2003; Iida and Katusic 2000).

pGC is the target of the natriuretic peptides (NPs), atrial (ANP), B-type (BNP) and C-type (CNP) natriuretic peptide and urodilatin (Ahluwalia et al. 2004b). ANP and BNP, released from the heart in response to hypervolaemia, circulate in the blood to regulate vascular function via the activation of the NP receptor termed GC-A (Ahluwalia et al. 2004b). Conversely, CNP is generated in the endothelium (Stingo et al. 1992) and acts in a local, paracrine fashion, targeting GC-B (Scotland et al. 2005). Similarly, urodilatin, which is secreted by the kidney, acts in the renal vasculature via activation of GC-A (Forssmann et al. 2001). The effects of NPs are limited by neutral endopeptidases (Soleilhac et al. 1992) which are found in high concentrations on the luminal surface of endothelial cells and via binding to the clearance receptor, GC-C, resulting in their subsequent internalisation.

Following production from either sGC or pGC, the effects of cGMP in vascular tissues are mediated via a number of effectors including cGMP-dependent protein kinases (cGKs, Hofmann et al. 2006), cGMP regulated phosphodiesterases (PDEs,