Regulation of Gene Expression by Cyclic GMP
Renate B. Pilz, Darren E. Casteel

Abstract—Cyclic GMP, produced in response to nitric oxide and natriuretic peptides, is a key regulator of vascular smooth muscle cell contractility, growth, and differentiation, and is implicated in opposing the pathophysiology of hypertension, cardiac hypertrophy, atherosclerosis, and vascular injury/restenosis. cGMP regulates gene expression both positively and negatively at transcriptional as well as at posttranscriptional levels. cGMP-regulated transcription factors include the cAMP-response element binding protein CREB, the serum response factor SRF, and the nuclear factor of activated T cells NF/AT. cGMP can regulate CREB directly, through phosphorylation by cGMP-dependent protein kinase, or indirectly, through activation of mitogen-activated protein kinase pathways; regulation of SRF and NF/AT by cGMP is indirect, through modulation of RhoA and calcineurin signaling, respectively. Downregulation of the RNA-binding protein HuR by cGMP leads to destabilization of guanylate cyclase mRNA, but this posttranscriptional mechanism may affect many more cGMP-regulated genes. In this review, we discuss the role of cGMP-regulated gene expression in (patho)physiological processes most relevant to the cardiovascular system, such as regulation of vascular tone, cardiac hypertrophy, phenotypic modulation of vascular smooth muscle cells, and regulation of cell proliferation and apoptosis. (Circ Res. 2003;93:1034-1046.)

Key Words: cyclic GMP ■ transcription ■ mRNA stability ■ translation ■ gene expression

Cyclic GMP is generated by cytoplasmic soluble guanylate cyclases (sGCs), which are activated by nitric oxide (NO), and by receptor guanylate cyclases (rGCs), which are activated by natriuretic peptides [atrial natriuretic peptide (ANP) or B- and C-type natriuretic peptides (BNP and CNP): Figure 1].1–3 cGMP effector proteins include cGMP-dependent protein kinase (PKG) I and II, cyclic nucleotide-regulated ion channels, and phosphodiesterases (PDEs), which hydrolyze cGMP and/or cAMP.1 PKG is the major intracellular cGMP target in many cell types, but high cGMP concentrations can cross-activate cAMP-dependent protein kinases (PKA).3,4 PKG I is highly expressed in platelets, smooth muscle, glomerular mesangial cells, cardiomyocytes, and many endothelial and neuronal cells.3,5–9 PKG II is encoded by a different gene with more limited expression3; throughout this article PKG will refer to PKG I. The importance of cGMP signaling for the cardiovascular system has been demonstrated in knockout mice lacking either PKG, neuronal, or endothelial NO synthase isoforms (nNOS and eNOS), ANP, or its rGC-A receptor.2,10,11

NO can regulate gene expression by multiple, including cGMP-independent mechanisms, as recently reviewed.12,13 We will concentrate on cGMP-mediated regulation of gene expression defined by the following criteria: the effects...
Although microarray analyses are providing large amounts of information regarding changes in gene expression in response to specific signals or gene alterations, only detailed analysis of single genes is able to distinguish direct versus indirect effects and determine the physiological significance of these changes. Table 1 summarizes cGMP regulation of specific genes that are discussed in the following sections.

Regulation of Vascular Tone
NO regulates vascular tone through stimulation of sGC, and ANP/BNP through stimulation of rGC-A, with cGMP activation of PKG causing smooth muscle relaxation via multiple mechanisms, including lowering of intracellular Ca2+ and inhibition of RhoA-dependent Ca2+ sensitization of contraction.1,9 However, cGMP also positively regulates RhoA expression in vascular smooth muscle cells (VSMCs).10 Prolonged exposure to nitrates leads to downregulation of sGC and PKG expression associated with nitrate tolerance,11,12 and prolonged elevation of circulating ANP leads to downregulation of rGC.13 These negative feedback loops involve cGMP inhibition of sGC, PKG, and rGC expression.

Soluble Guanylate Cyclase (sGC)
Low concentrations of NO donors, ANP, or cGMP analogues decrease mRNA and protein levels of both sGC-α1 and -β1 subunits in VSMCs by >90% within 24 hours.14 cGMP accelerates the decay of sGC-α1 and β1 mRNA; the effect is mediated by cGMP-induced downregulation of the RNA-stabilizing protein HuR (described later).15,16

PKG
Continuous exposure to NO-releasing agents, cGMP, or cAMP analogues suppresses PKG mRNA and protein levels in VSMCs by decreasing transcription without affecting mRNA stability.17 Similarly, reduced PKG levels are found in cGMP-treated cardiomyocytes, and in the aortas of transgenic mice overexpressing eNOS in the endothelium.18,19 Two SP-1 binding sites appear to be required for basal PKG promoter activity, and SP-1 and SP-3 DNA binding activities are reduced in cyclic nucleotide-treated cells.20

Receptor Guanylate Cyclase A (rGC-A)
Ligand-dependent downregulation of rGC-A is associated with cGMP-mediated reduction in rGC-A mRNA levels and promoter activity in VSMCs.21 Correspondingly, rGC-A expression is upregulated in ANP-deficient mice.22 The effect of cGMP on the rGC-A promoter is not mimicked by cAMP; it is mediated by a negative cis-acting element localized approximately 1400 nucleotides upstream of the transcription start site, but the trans-acting factors remain to be identified.23

RhoA
Long-term exposure of primary VSMCs to NO donors or cGMP analogues increases RhoA expression through increased rhoA transcription as well increased RhoA protein stability due to PKG phosphorylation.10 The PKG-mediated transcriptional effect requires an intact CRE in the RhoA promoter and is associated with increased phosphorylation of CREB and ATF-1.10 Inhibition of NO synthesis in rats decreases RhoA mRNA and protein expression in aorta and pulmonary artery, suggesting that basal release of NO is...
<table>
<thead>
<tr>
<th>Gene</th>
<th>Cell Type</th>
<th>Culture Conditions</th>
<th>Regulation by cGMP</th>
<th>PKG-Mediated*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>sGC (α1, β1)</td>
<td>VSMCs</td>
<td></td>
<td>↓ mRNA stability (HuR)</td>
<td>ND</td>
<td>21, 24</td>
</tr>
<tr>
<td>PKG</td>
<td>VSMCs</td>
<td></td>
<td>↓ mRNA, ↓ transcription</td>
<td>ND</td>
<td>6, 22, 25, 26</td>
</tr>
<tr>
<td>rGC-A</td>
<td>VSMCs, RTCs</td>
<td></td>
<td>↓ mRNA, ↓ transcription</td>
<td>ND</td>
<td>23, 27</td>
</tr>
<tr>
<td>RhoA</td>
<td>VSMCs</td>
<td></td>
<td>↑ mRNA, ↑ transcription</td>
<td>Yes</td>
<td>20</td>
</tr>
<tr>
<td><strong>Genes associated with vascular tone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANP</td>
<td>CMs</td>
<td>PE-stimulated</td>
<td>↓ mRNA</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>BNP</td>
<td>CMs</td>
<td>PE-stimulated</td>
<td>↓ mRNA, ↓ transcription</td>
<td>Yes</td>
<td>30</td>
</tr>
<tr>
<td>Skeletal α-actin</td>
<td>CMs</td>
<td>PE-stimulated</td>
<td>↓ mRNA</td>
<td>No</td>
<td>29</td>
</tr>
<tr>
<td>β-MHC</td>
<td>CMs</td>
<td>PE-stimulated</td>
<td>↓ mRNA</td>
<td>No</td>
<td>29</td>
</tr>
<tr>
<td>MLP</td>
<td>CMs</td>
<td>ET-1–stimulated</td>
<td>↓ mRNA</td>
<td>Yes</td>
<td>16</td>
</tr>
<tr>
<td><strong>Genes associated with cardiac hypertrophy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANP</td>
<td>CMs</td>
<td>PE-stimulated</td>
<td>↓ mRNA</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>BNP</td>
<td>CMs</td>
<td>PE-stimulated</td>
<td>↓ mRNA, ↓ transcription</td>
<td>Yes</td>
<td>30</td>
</tr>
<tr>
<td>Skeletal α-actin</td>
<td>CMs</td>
<td>PE-stimulated</td>
<td>↓ mRNA</td>
<td>No</td>
<td>29</td>
</tr>
<tr>
<td>β-MHC</td>
<td>CMs</td>
<td>PE-stimulated</td>
<td>↓ mRNA</td>
<td>No</td>
<td>29</td>
</tr>
<tr>
<td>MLP</td>
<td>CMs</td>
<td>ET-1–stimulated</td>
<td>↓ mRNA</td>
<td>Yes</td>
<td>16</td>
</tr>
<tr>
<td><strong>Genes associated with VSMC differentiation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANP</td>
<td>CMs</td>
<td>Dedifferentiated</td>
<td>↑ protein, ↑ transcription?</td>
<td>Yes</td>
<td>32, 35–37</td>
</tr>
<tr>
<td>BNP</td>
<td>CMs</td>
<td>Dedifferentiated</td>
<td>↑ protein, ↑ transcription?</td>
<td>Yes</td>
<td>32</td>
</tr>
<tr>
<td>Skeletal α-actin</td>
<td>CMs</td>
<td>Dedifferentiated</td>
<td>↑ protein, ↑ transcription?</td>
<td>Yes</td>
<td>32</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>CMs</td>
<td>Dedifferentiated</td>
<td>↓ protein, ↓ translation?</td>
<td>Yes</td>
<td>33</td>
</tr>
<tr>
<td>Thrombospondin</td>
<td>CMs</td>
<td>Dedifferentiated</td>
<td>↓ protein, ↓ translation?</td>
<td>Yes</td>
<td>33</td>
</tr>
<tr>
<td>FMRF-1/2</td>
<td>VSMCs</td>
<td></td>
<td>↓ mRNA</td>
<td>Yes</td>
<td>34</td>
</tr>
<tr>
<td><strong>Genes associated with proliferation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MKP-1</td>
<td>VSMCs, ECs, MCs, BHK</td>
<td></td>
<td>↑ mRNA</td>
<td>Yes</td>
<td>53, 59–61</td>
</tr>
<tr>
<td>Cyclins A, D1, E</td>
<td>VSMCs, MCs</td>
<td></td>
<td>↓ mRNA</td>
<td>ND</td>
<td>48, 50, 62</td>
</tr>
<tr>
<td>p21Rfl/Cip1</td>
<td>Fibroblasts</td>
<td></td>
<td>↑ mRNA</td>
<td>ND</td>
<td>36, 49</td>
</tr>
<tr>
<td>p16INK4a</td>
<td>VSMCs</td>
<td></td>
<td>↑ mRNA</td>
<td>ND</td>
<td>36</td>
</tr>
<tr>
<td>ET-1</td>
<td>ECs, Cardiac fibroblasts</td>
<td></td>
<td>↑ mRNA</td>
<td>ND</td>
<td>52, 55</td>
</tr>
<tr>
<td>VEGF</td>
<td>VSMCs, other</td>
<td>Normoxic</td>
<td>↑ mRNA</td>
<td>ND</td>
<td>63, 64</td>
</tr>
<tr>
<td>VSMCs, ECs</td>
<td>Normoxic</td>
<td></td>
<td>↓ mRNA, ↓ transcription</td>
<td>ND</td>
<td>65</td>
</tr>
<tr>
<td><strong>Genes associated with apoptosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mcl-1</td>
<td>CMs</td>
<td></td>
<td>↓ mRNA</td>
<td>ND</td>
<td>67</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>Neuronal cells</td>
<td></td>
<td>↑ mRNA</td>
<td>Yes</td>
<td>73</td>
</tr>
<tr>
<td>B lymphocytes</td>
<td></td>
<td></td>
<td>↑ mRNA</td>
<td>ND</td>
<td>75</td>
</tr>
<tr>
<td>Tpx-1</td>
<td>Neuronal cells</td>
<td></td>
<td>↑ mRNA</td>
<td>Yes</td>
<td>9</td>
</tr>
<tr>
<td>BNIP3</td>
<td>Hepatocytes</td>
<td></td>
<td>↓ mRNA</td>
<td>ND</td>
<td>74</td>
</tr>
<tr>
<td><strong>Other genes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGC-1</td>
<td>3T3-L1, U937, HeLa</td>
<td></td>
<td>↑ mRNA</td>
<td>ND</td>
<td>76</td>
</tr>
<tr>
<td>TNF-α</td>
<td>CMs, VSMCs</td>
<td>Unstimulated</td>
<td>↑ mRNA</td>
<td>Yes</td>
<td>77, 84</td>
</tr>
<tr>
<td>Macrophages, glia</td>
<td>Unstimulated</td>
<td></td>
<td>↑ mRNA</td>
<td>ND</td>
<td>85</td>
</tr>
<tr>
<td>Macrophages</td>
<td>LPS-stimulated</td>
<td></td>
<td>↓ mRNA stability</td>
<td>ND</td>
<td>86</td>
</tr>
<tr>
<td>NOS-2</td>
<td>CMs, VSMCs</td>
<td>Cytokine-stimulated</td>
<td>↑ mRNA</td>
<td>Yes</td>
<td>79, 84</td>
</tr>
<tr>
<td>Macrophages</td>
<td>LPS-stimulated</td>
<td></td>
<td>↓ mRNA stability</td>
<td>ND</td>
<td>86</td>
</tr>
<tr>
<td>CDX-2</td>
<td>RTCs</td>
<td>Salt-depleted</td>
<td>↑ mRNA</td>
<td>ND</td>
<td>89</td>
</tr>
<tr>
<td>Macrophages</td>
<td>LPS-stimulated</td>
<td></td>
<td>↑ mRNA stability</td>
<td>ND</td>
<td>87</td>
</tr>
<tr>
<td>PAI-1</td>
<td>VSMCs, ECs</td>
<td>Ang II–stimulated</td>
<td>↓ mRNA</td>
<td>ND</td>
<td>90, 91</td>
</tr>
<tr>
<td>MMP-13</td>
<td>ECs</td>
<td>Serum-starved</td>
<td>↑ mRNA, ↑ transcription</td>
<td>No</td>
<td>132</td>
</tr>
<tr>
<td>H-1</td>
<td>ECs</td>
<td>Serum-starved</td>
<td>↑ mRNA, ↑ transcription</td>
<td>No</td>
<td>132</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>Cardiac fibroblasts</td>
<td></td>
<td>↓ mRNA stability</td>
<td>ND</td>
<td>140</td>
</tr>
<tr>
<td>KCI cotransporter-3</td>
<td>VSMCs</td>
<td></td>
<td>↑ mRNA stability</td>
<td>ND</td>
<td>142</td>
</tr>
</tbody>
</table>

Ang II indicates angiotensin II; CMs, cardiomyocytes; ECs, endothelial cells; ET-1, endothelin-1; FGFR, fibroblast growth factor receptor; HO-1, heme oxygenase-1; HuR, Hu family RNA-binding protein; KCI cotransporter-3, potassium chloride cotransporter-3; LPS, lipopolysaccharide; MCs, mesangial cells; MHC, myosin heavy chain; MKP-1, MAP kinase phosphatase-1; MLP, muscle LIM protein; MMP-13, matrix metalloproteinase-13; PAI-1, plasminogen activator inhibitor-1; PE, phenylephrine; PGC-1, peroxisome proliferator-activated receptor-γ coactivator-1α; RTCs, renal tubule cells; TGF-β3, transforming growth factor-β3; TNF-α, tumor necrosis factor-α; and VEGF, vascular endothelial growth factor. *ND indicates not determined; yes, effect observed in PKG-expressing cells and inhibited by specific cell-permeable PKG inhibitor and/or enhanced by PKG overexpression.
Cardiac Hypertrophy

Cardiac hypertrophy involves induction of embryonic genes, including ANP, BNP, and skeletal α-actin, by hypertrophic stimuli such as ET-1, angiotensin II (Ang II), phenylephrine, and fibroblast growth factor (FGF). Hypertrophy-promoting signaling pathways include the small GTPases Ras, RhoA, and Rac, mitogen-activated protein kinases (MAP kinases), and Ca²⁺/calcineurin. Mice deficient in ANP or rGC-A develop increased ventricular mass out of proportion to the mild changes in blood pressure, and mice deficient in nNOS develop cardiac hypertrophy with normal systemic blood pressure, suggesting that NO/cGMP negatively regulate antihypertrophic effects, because MLP expression is necessary and decreased expression of osteopontin, thrombospondin, and FGF receptors-1/2. Whether the PKG-mediated induction of contractile protein expression occurs at the transcriptional level is unclear, although one preliminary report suggests that PKG activation may activate the SM-MHC promoter. In addition, SM-MHC-2 mRNA and protein expression is increased in CNP peptide-overexpressing VSMCs in vitro and in vivo after angioplasty, and down-regulation of the SM-MHC promoter by platelet-derived growth factor is prevented by NO. These data suggest that PKG plays an important role during VSMC phenotypic modulation, positively and negatively regulating gene expression. A preliminary report of cDNA microarray analyses comparing PKG-transfected and control-transfected, late passage VSMCs suggests that >100 transcripts may be up- or downregulated more than 3-fold by cGMP/PKG.

The mechanism(s) responsible for PKG downregulation in dedifferentiating VSMCs remains unknown, but PKG mRNA is downregulated when differentiated VSMCs are chronically exposed to NO, cyclic nucleotides, or various growth factors in vitro. PKG levels may transiently decrease after vascular injury, and appear to decrease in proliferating neointimal VSMCs coincidentally with transcriptional down-regulation of contractile marker expression and increased synthesis of osteopontin. Increased growth factor and cytokine production at the site of vascular injury could increase local cGMP through iNOS induction and may explain PKG downregulation. Reexpression of constitutively active PKG (or wild type PKG with cGMP stimulation) inhibits VSMC migration, enhances apoptosis, reduces proliferation, and decreases neointima formation after vascular injury. These results suggest that PKG modulates the VSMC phenotype in vivo and are consistent with the finding that adenoviral overexpression of CNP or soluble guanylate cyclase reduces neointima formation, whereas eNOS-deficient mice demonstrate a hyperplastic response after vascular injury.

Regulation of Cell Proliferation

Depending on the cell type, cGMP can have pro- or antiproliferative effects. In VSMCs, mesangial cells, and various fibroblasts, cGMP inhibits proliferation, and the effect is mostly mediated by PKG, although it may involve PKA cross-activation under some conditions. Antiproliferative effect correlates with cGMP inhibition of growth factor-induced extracellular signal-regulated kinase (Erk-1/2) activity (online Table, available in the online data supplement at http://www.circresaha.org; also discussed later), increased expression of MAP kinase phosphatase-1 (MKP-1), modulation of cell cycle-associated genes, and reduction of ET-1 synthesis. In contrast to the antiproliferative effects in VSMCs and fibroblasts, cGMP increases proliferation of endothelial cells. The proliferative effect of cGMP in endothelial-
Table). Inhibition of Raf-1 by cGMP/PKG and PKG-dependent way, depending on the cell type and growth conditions (online activation of MEK-1/2,106,133 MEK-3,139 or MEKK-171 have been antiproliferative effect of cGMP-elevating agents.53,60

Erk-1/2 activity, and MKP-1 induction contributes to the MKP-1 mRNA sufficiently to inhibit growth factor-induced MAP kinases comprise the extracellular signal-regulated kinases Erk-1/2, p38 and c-Jun amino terminal kinases JNK-1/2/3. All three pathways are activated by multiple extracellular stimuli, including growth factors, cytokines, and stress (such as oxidative stress and heat shock), and all three types of MAP kinases are inactivated by MAP kinase phosphatase-1 (MKP-1). Some transcription factors targeted by MAP kinases are shown; a more complete list has been reviewed.92 cGMP can either activate or inhibit each pathway, depending on the cell type and growth conditions (online Table). Inhibition of Raf-1 by cGMP/PKG and PKG-dependent activation of MEK-1/2,106,133 MEK-2,138 or MEKK-1,71 have been reported; however, it is not clear whether PKG directly activates these enzymes (indicated by “?”). GEFs, guanine nucleotide exchange factors.

Vascular Endothelial Growth Factor (VEGF)
VEGF mediates angiogenesis and vascular permeability; in normoxic VSMCs, hepatoma, and glioma cells, NO donors increase basal VEGF mRNA levels in a cGMP-dependent fashion.63,64 An in vivo model of embolic stroke suggests a positive role for cGMP in angiogenesis, which is dependent on VEGF.56 However, VEGF expression is induced by hypoxia, and treating hypoxic VSMCs or endothelial cells with NO or cGMP decreases VEGF mRNA,65 and NOS inhibition increases VEGF mRNA in balloon-injured arterial walls, suggesting that endogenous NO may suppress VEGF expression under these conditions.66

Apoptosis
Pro- and antiapoptotic effects of cGMP have been described in different cell types. In VSMCs, cardiomyocytes, and endothelial cells, NO, natriuretic peptides, and cGMP analogues increase apoptosis, and the effect appears to be PKG mediated.45,67–69 In cardiomyocytes, cGMP sharply decreases mRNA expression of the antiapoptotic Bcl-2 homologue Mcl-1.70 In VSMCs and endothelial cells, the effect of cGMP occurs in low serum–containing medium and is counteracted by Ang II and ET-1, respectively.68,69 The mechanism(s) of the proapoptotic effects of cGMP in vascular cells remains to be determined, but cGMP may increase apoptosis through PKG-dependent activation of JNK and/or phosphorylation and inactivation of β-catenin.70–72

In neuronal cells, hepatocytes, and lymphocytes, cGMP has antiapoptotic effects that appear to be mediated by Bcl-2 or Bcl-2–associated proteins.73–75 In neuronal cells, prolonged inhibition of NOS or sGC induces apoptosis that is prevented by cGMP analogues; the protective effect of cGMP is associated with increased CREB phosphorylation and increased mRNA and protein expression of the apoptosis inhibitor Bcl-2.76 During growth factor deprivation, cGMP/PKG protect neuronal cells from apoptosis by increasing expression of the oxidative stress–related proteins thioredoxin and thioredoxin peroxidase (Tpx-1), which leads to increased Bcl-2 expression.9

Mitochondrial Biogenesis
NO, in a cGMP-dependent fashion, triggers mitochondrial biogenesis in many different cell types, and mitochondrial biogenesis induced by cold exposure is reduced in eNOS–deficient mice.76 The cGMP effect is mediated by induction of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1), a master regulatory factor of mitochondrial biogenesis in brown adipose tissue and in cardiac and skeletal muscle; this coactivator increases expression of other transcription factors that regulate nuclear and mitochondrial genes encoding mitochondrial proteins.76

Cyclins and Cyclin Inhibitors
cGMP decreases expression of cell cycle-promoting genes, such as cyclin A, D1, and E.48,50,62 In addition, cGMP may increase expression of cell cycle inhibitors, such as p21Waf1/Cip1 and p16INK4a.36,49 Under some conditions, cGMP-induced changes in expression of cell cycle–associated genes appear to be dependent on inhibition of Erk-1/2, but this is not always the case.47,49,50

Endothelin-1 (ET-1)
ET-1 is a potent vasoconstrictor and mitogenic peptide produced by proteolytic cleavage from an inactive precursor and secreted by endothelial cells.55 Basal prepro-ET-1 mRNA levels and peptide synthesis appear to be decreased by cGMP, because incubation of endothelial cells with NO inhibitors, NO scavenger molecules, or sGC inhibitors increase prepro-ET-1 synthesis and ET-1 peptide secretion, and this effect is reversed by cGMP analogues.55 Thrombin– or Ang II–mediated increases in prepro-ET-1 mRNA levels are also inhibited by natriuretic peptides and cGMP analogues.52

MAP Kinase Phosphatase-1 (MKP-1)
MKP-1 dephosphorylates and inactivates the MAP kinases Erk-1/2, p38, and c-Jun N-terminal kinase (JNK) (Figure 2).59 MKP-1 mRNA expression is increased by NO-releasing agents, ANP, and cGMP analogues in endothelial and smooth muscle cells;60 induction by cGMP can occur in the absence of Erk-1/2 stimulation.53 cGMP, via PKG, induces MKP-1 mRNA sufficiently to inhibit growth factor–induced Erk-1/2 activity, and MKP-1 induction contributes to the antiproliferative effect of cGMP–elevating agents.53,60

Mitochondrial Biogenesis
NO, in a cGMP-dependent fashion, triggers mitochondrial biogenesis in many different cell types, and mitochondrial biogenesis induced by cold exposure is reduced in eNOS-deficient mice.76 The cGMP effect is mediated by induction of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1), a master regulatory factor of mitochondrial biogenesis in brown adipose tissue and in cardiac and skeletal muscle; this coactivator increases expression of other transcription factors that regulate nuclear and mitochondrial genes encoding mitochondrial proteins.76
Other cGMP-Regulated Genes

cGMP regulates expression of the inflammatory cytokine TNF-α, and the cytokine-inducible genes iNOS and COX-2 involved in inflammatory processes. Both positive and negative effects of cGMP have been described for each of these genes, in some cases leading to biphasic regulation, e.g., early transcriptional upregulation followed by downregulation due to mRNA destabilization; the latter could be related to HuR downregulation by cGMP (discussed later). Tumor Necrosis Factor-α (TNF-α)

In cardiomyocytes, NO increases TNF-α mRNA in a cGMP- and PKG-dependent fashion, and this effect correlates with increased nuclear factor-κB (NF-κB) activity and is mimicked by cGMP, but not cAMP analogues. In VSMCs and resting macrophages, cGMP analogues induce basal TNF-α mRNA and enhance IL-1-induced TNF-α mRNA. However, in LPS-stimulated macrophages, induction of TNF-α mRNA and protein is attenuated by cGMP due to mRNA destabilization.

Inducible NO Synthase (iNOS)

In cardiomyocytes, VSMCs, and mesangial cells, cytokine-induced transcription of iNOS is enhanced by NO donors, ANP/BNP, or cGMP analogues, and reduced by NOS inhibitors, whereas in the absence of cytokines, cGMP-elevating agents have very little or no effect on basal iNOS expression. In addition, in some cell types, cGMP destabilizes iNOS mRNA leading to downregulation of cytokine-induced iNOS mRNA at later time points.

Inducible Cyclooxygenase-2 (COX-2)

Like iNOS, COX-2 is transcriptionally induced in response to inflammatory stimuli, and the effects of NO on cytokine-induced COX-2 and iNOS expression are similar. NO is necessary for cytokine induction of COX-2 mRNA in mesangial cells, and NO donors, ANP, and cGMP analogues synergistically enhance the effect of IL-1β on COX-2 mRNA at early time points. However, at later time points, NO donors decrease cytokine-induced COX-2 mRNA levels, reminiscent of the biphasic effects of NO on iNOS expression in these cells. Destabilization of COX-2 mRNA by ANP and cGMP analogues has been described in LPS-stimulated macrophages.

In whole animal models, NO positively affects COX-2 expression, and its importance for prostaglandin synthesis has been confirmed in iNOS-deficient mice. Induction of COX-2 mRNA by salt depletion and/or angiotensin-converting enzyme inhibition in renal cortex is blocked by NOS inhibitors, and this effect is relieved by cGMP analogues; correspondingly, NO donors and cGMP analogues increase basal COX-2 mRNA levels in renal tubule cells.

Plasminogen Activator Inhibitor-I (PAI-1)

PAI-1 is produced by VSMCs and endothelial cells, and elevated levels are found in atherosclerotic and balloon-injured vessels. NO donors, natriuretic peptides, and cGMP analogues reduce Ang II–induced PAI-1 mRNA levels without affecting mRNA stability.

Mechanisms of Transcriptional Regulation by cGMP

Overview

cGMP can regulate transcription factors directly by inducing phosphorylation or by increasing expression of short-lived proteins. Transcription factors controlled by cGMP-dependent phosphorylation include the cAMP response-element (CRE)-binding protein CREB, activating transcription factor-1 (ATF-1), and the multifunctional transcription factor TFIIB (summarized in Table 2). Transcription factors whose expression is regulated by cGMP include the AP-1 family proteins c-Fos and JunB, the early growth response gene Egr-1, and the growth arrest–specific homeobox gene GAX (Table 2). In addition, cGMP can regulate transcription factors indirectly, through modulation of upstream signal transduction pathways. Examples include cGMP regulation of an inhibitor of NF-κB, and inhibition of calcineurin signaling to NF-AT and of RhoA signaling to SRF (Table 2). Through activation or inhibition of MAP kinase pathways, cGMP can regulate the activity of multiple transcription factors, including ternary complex factor (TCF), CREB, ATF-2, and c-Jun (online Table and Figure 2).

Transcription Factors Directly Controlled by cGMP-Dependent Phosphorylation

CREB and ATF-1

The transcription factor CREB is activated by a diverse array of stimuli through phosphorylation of Ser133 in its kinase-inducible domain; CREB is critical for proliferation, differentiation, and survival of many different cell types, and absence of CREB causes dwarfism and cardiac myopathy. Increased intracellular cGMP leads to increased CREB Ser133 phosphorylation in VSMCs, neuronal cells, and PKG-transfected Baby Hamster Kidney (BHK) cells, but not in PKG-deficient BHK cells. cGMP-induced CREB phosphorylation in BHK cells occurs at physiologically relevant PKG levels and is independent of changes in intracellular Ca2+, activation of MAP kinases (Erk-1/2 and p38), or cross-activation of PKA, thus ruling out the effect of other known CREB kinases. PKG can directly phosphorylate CREB on Ser133 in vitro; the kinetics are slower than those of PKA, but comparable to those of Ca2+/calmodulin-dependent protein kinase IV. Correspondingly, PKG is less effective than PKA, but similar to Ca2+/calmodulin-dependent protein kinase, in stimulating cAMP-response-element (CRE)–dependent transcription in intact cells. In BHK cells and in some neuronal cells, cGMP-mediated transactivation of the c-fos promoter is dependent on CREB phosphorylation and nuclear translocation of PKG, as demonstrated by the ineffectiveness of extranuclear PKG constructs. Nuclear translocation of PKG has been demonstrated in neuronal cells, neutrophils, macrophages, and some embryonal smooth muscle cells. However, other investigators found no evidence of PKG nuclear translocation in primary VSMCs, HEK293, and CV-1 cells, or observed nuclear PKG only in a minority of the cell population. Based on recent findings, we have speculated that PKG may be retained in extranuclear compartments by binding to cell
type-specific anchoring proteins. TFII-I is a transcriptional regulator for many genes, including c-fos and so-called endoplasmic reticulum stress-response genes; TFII-I interacts with multiple transcription factors including SRF, TCF, ATF-6, c-Myc, and NF-κB, and with histone deacetylases. We found that TFII-I physically interacts with PKG Iβ, with these two proteins coimmunoprecipitating in C2C12 myoblasts. PKG phosphorylates TFII-I in vitro and in vivo; PKG Iβ activation enhances the transactivation potential of wild type, but not phosphorylation-deficient mutant TFII-I on an SRF/TCF-dependent reporter gene, and PKG cooperates with TFII-I to transactivate the fos promoter.

**TABLE 2. Transcription Factors Regulated by cGMP**

<table>
<thead>
<tr>
<th>Transcription Factor</th>
<th>Cell Type</th>
<th>Mechanism of Regulation</th>
<th>Effect of cGMP</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREB</td>
<td>Neuronal cells</td>
<td>▲ phosphorylation of CREB Ser133 (directly or indirectly PKG-mediated)</td>
<td>↑ transcriptional activity</td>
<td>73, 94</td>
</tr>
<tr>
<td></td>
<td>VSMCs</td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>BHK*</td>
<td></td>
<td></td>
<td>95</td>
</tr>
<tr>
<td>ATF-1</td>
<td>VSMCs</td>
<td>▲ ATF-1 phosphorylation (PKG-dependent)</td>
<td>↑ transcriptional activity?</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>BHK*</td>
<td></td>
<td></td>
<td>95</td>
</tr>
<tr>
<td>TFII-I</td>
<td>COS-7,* BHK,* C2C12 myoblasts</td>
<td>Direct TFII-I phosphorylation by PKG/association with PKG Iβ</td>
<td>↑ transcriptional activity</td>
<td>105</td>
</tr>
<tr>
<td>AP-1 (c-Fos,Jun B)</td>
<td>Neuronal cells, REF52, thyroid cells, BHK,* other cells</td>
<td>↑ transcription (CREB-dependent)</td>
<td>↑ mRNA</td>
<td>110, 112</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ AP-1 DNA binding</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ transcriptional activity</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(in serum-starved cells)</td>
<td>96, 113</td>
</tr>
<tr>
<td></td>
<td>Cardiac fibroblasts</td>
<td></td>
<td>↑ TNF-α-stimulated c-fos mRNA</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Endothelial cells</td>
<td></td>
<td>↑ mRNA, ↑ DNA binding</td>
<td>8, 110, 119</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ transcriptional activity</td>
<td></td>
</tr>
<tr>
<td>Egr-1</td>
<td>Neuronal cells</td>
<td>↑ transcription</td>
<td>↑ mRNA, ↑ DNA binding</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ transcriptional activity</td>
<td></td>
</tr>
<tr>
<td>GAX</td>
<td>VSMCs</td>
<td></td>
<td>↑ mRNA</td>
<td>120</td>
</tr>
<tr>
<td>NF-κB</td>
<td>T lymphocytes, other cells</td>
<td>p50/p65 phosphorylation</td>
<td>↑ DNA binding/transcriptional activity</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td>Cardiomyocytes</td>
<td>IκB phosphorylation/destabilization</td>
<td>↑ DNA binding/transcriptional activity</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Endothelial cells, hepatocytes</td>
<td>IκB stabilization</td>
<td>↓ cytokine-induced DNA binding of NF-κB</td>
<td>123, 124, 125</td>
</tr>
<tr>
<td>SRF</td>
<td>Cardiomyocytes</td>
<td>↓ calcium influx/ ▼ calcineurin activity</td>
<td>↓ NF/AT nuclear translocation</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>VSMCs, cardiomyocytes</td>
<td>Rho-dependent activation#</td>
<td>▼ SRF-dependent transcription#</td>
<td>5</td>
</tr>
</tbody>
</table>

*Transfection of PKG required for the effect of cGMP in PKG-deficient cells; #SRF/TCF complexes on the fos and egr-1 promoters are insensitive to Rho signaling.

**Short-Lived Transcription Factors With Expression Regulated by cGMP**

**AP-1 (Fos/Jun)**

Fos and Jun proteins dimerize to form the AP-1 transcription factor complex and are important for cell cycle progression and apoptosis; resting cells typically express low levels of fos and jun mRNA, but transcription of AP-1-related genes is rapidly induced in response to many stimuli. NO-releasing agents, natriuretic peptides, and cGMP analogues increase c-fos and junB mRNA expression in cultured cells and primary tissues, and NOS inhibitors can reduce c-fos expression. Cardiac expression profiling from eNOS-deficient mice demonstrate decreased c-fos mRNA expression compared with wild-type mice. In cardiac fibroblasts, cGMP-elevating agents modestly enhance c-fos induction by Ang II. As a consequence of NO/cGMP-induced c-fos and junB mRNA expression, AP-1 DNA binding activity increases resulting in increased transcription of AP-1-dependent reporter genes and endogenous genes. In pulmonary endothelial cells, NO-releasing agents and cGMP analogues increase AP-1 DNA binding activity only if cells are costimulated with TNF-α.

Although high concentrations of NO can decrease DNA binding of recombinant Fos and Jun in vitro through S-nitrosylation and/or S-glutathionylation, the in vivo significance of this effect is unknown. We demonstrated that NO stimulation of the fos promoter in different cell types is strictly cGMP-dependent and requires PKG activity. PKG targets several transcriptional elements in the fos promoter: the CRE and the fos AP-1 site, which both bind CREB-related proteins, and the serum response element (SRE), which binds multiple transcription factors including SRF, TCF, C/EBP-β, and TFII-I. cGMP/PKG transactivation of the fos promoter requires CREB-related proteins, but is independent of AP-1 and C/EBP-related transcription factors and can occur independently of MAP kinase activation by cGMP.
**Egr-1**

Transcription of egr-1 is induced by many growth factors and stress stimuli with similar kinetics as c-fos.118 Egr-1 plays an important role in cell growth, differentiation, and apoptosis, and high, sustained expression of Egr-1 has been observed in atherosclerotic lesions.118 In phacoemulsification cells, NO-releasing agents and natriuretic peptides increase egr-1 promoter activity, mRNA, and protein expression, and increase transcription from an Egr-1-responsive reporter.110,119 Moreover, cGMP analogues increase serum-stimulated Egr-1 DNA binding activity; this effect is enhanced by overexpression of PKG and occurs in the absence of significant changes in MAP kinase activity.9 In contrast, NO and cGMP analogues appear to have no effect on Ang II–induced egr-1 mRNA expression in cardiac fibroblasts.51

**The Growth Arrest–Specific Homeobox Gene (GAX)**

GAX is found predominantly in cardiovascular tissues; it is expressed in quiescent VSMCs and rapidly downregulated after mitogen-stimulation or after vascular injury; overexpression of GAX induces growth arrest.118,120 CNP and cGMP analogues increase GAX mRNA expression in serum-starved primary VSMCs and largely prevent the decrease in GAX mRNA in Ang II–stimulated cells;120 this could be important for VSMC phenotypic modulation.118

**Transcription Factors Indirectly Regulated by cGMP**

**NF-κB**

NF-κB is a transcriptional activator of genes involved in inflammation, including cytokines and adhesion molecules.121 NF-κB subunits are inactive when bound to cytoplasmic IκB proteins, but multiple stimuli can induce phosphorylation and degradation of IκB, thereby allowing activation and nuclear translocation of NF-κB.121 NO can increase or decrease NF-κB activity depending on the NO concentration, redox milieu, cell type, and co-stimulus, and in most cases, the effects of high NO concentrations on NF-κB appear to be cGMP-independent.12,13,80 However, in cardiomyocytes, NO-donors increase NF-κB (p50/p65) DNA binding activity and induce expression of an NF-κB–responsive gene in a cGMP/PKG-dependent fashion.77 In these cells, cGMP induces phosphorylation and degradation of IκB-α, and direct phosphorylation of IκB-α by PKG occurs in vitro.77 NF-κB may also be activated by cGMP through direct PKG phosphorylation of p50 and p65 subunits.121 In contrast, cytokine-induced NF-κB activation in human endothelial cells is inhibited by NO/cGMP and IκB-α is stabilized.123,124 Natriuretic peptides and cGMP analogues also inhibit NF-κB activation during hepatic ischemia/reperfusion injury through stabilization of IκB; this correlates with cGMP induction of heat shock protein 70 and increased HSP70 association with IκB.125

**Calcineurin-Dependent Transcription Factors**

Calcineurin is a Ca2+-dependent phosphatase that dephosphorylates and thereby activates the transcription factors NF/AT, myocyte enhancer factor-2 (MEF-2), and Elk-1. In cardiomyocytes, PKG activation inhibits calcineurin-dependent NF/AT nuclear translocation, phenylephrine-induced BNP promoter activity, and cell enlargement by interfering with Ca2+ entry.30 MEF-2–dependent transcription is also inhibited by cGMP/PKG.30

**Serum-Response Factor (SRF)**

Transcriptional activation of muscle-specific genes requires cooperation between SRF and other coactivators, such as myocardin or the myocardin-related protein MAL, and is regulated by RhoA-induced actin polymerization.126,127 RhoA activation induces MAL translocation from the cytoplasm to the nucleus and stimulates SRF-dependent transcription.127 Growth factor–induced transcriptional activation of immediate-early genes such as c-fos and egr-1 also involves SRF, but on these promoters SRF cooperates with TCF; the SRF-TCF complex is regulated by MAP kinases, but is insensitive to RhoA signaling.92,128

During differentiation of SM cells, RhoA appears to play a dual role: (1) in undifferentiated cells, high RhoA activity delays differentiation by restricting SRF to the cytoplasm, whereas RhoA downregulation induces nuclear translocation of SRF and promotes myogenesis129; (2) in differentiated cells, SRF is associated with active, hyperacetylated chromatin, and RhoA activation by G protein–coupled receptors stimulates SRF-dependent transcription from many muscle-specific promoters.130 Thus, PKG inhibition of RhoA in undifferentiated cells could provide a differentiation-promoting signal, while PKG inhibition of RhoA in differentiated cells may serve to restrict SM-specific promoter activity under conditions where RhoA is activated.

**Regulation of Gene Transcription Through cGMP Modulation of MAP Kinase Pathways**

Pathways that activate the MAP kinases Erk-1/2, p38, or JNK regulate gene expression through direct or indirect phosphorylation of multiple transcription factors, including TCF, CREB, ATF-2, and c-Jun (Figure 2).92 Increased intracellular cGMP can lead to increased or decreased activity of all three MAP kinase pathways depending on cell type and growth conditions (online Table), and changes in MAP kinase activity may explain the effect of cGMP on many genes involved in cell proliferation, differentiation, or apoptosis. This has been documented in some cases, eg, the cGMP–mediated increase of metalloproteinase-13 and heme oxygenase-1 expression in endothelial cells is dependent on Erk-1/2 activation.131,132

In neonatal cardiomyocytes, ANF and cGMP analogues increase Erk-1/2 activity but have little effect on p38 MAP kinase or JNK activity.133 In adult cardiomyocytes, NO increases both Erk-1/2 and p38 activity, but Erk-1/2 activa-
tion is cGMP-independent, whereas p38 activation is mediated by cGMP and PKG, with cAMP analogues having an opposing effect.134

In serum-starved aortic VSMCs, Erk-1/2 and JNK activities are stimulated by cGMP analogues in a PKG-dependent fashion.106 However, platelet-derived growth factor–, epithelial growth factor–, and Ang II–stimulated Erk-1/2 activities in early passage VSMCs and in aortic strips are inhibited by NO, ANP/CNP, with several studies demonstrating that this effect is not due to cross-activation of PKA.46,47,135 In fact, endothelium-derived NO appears to tonically inhibit the effect of endogenous Ang II on Erk-1/2 activity in the aorta.135 Thus, cGMP-elevating agents may augment basal, but inhibit mitogen-stimulated Erk activity in primary VSMCs. Inhibition of mitogen-stimulated Erk activity has also been observed in mesangial cells and fibroblast-like cells.53,136,137

In endothelial cells, NO donors stimulate basal Erk-1/2 activity in a cGMP-dependent fashion; this effect is mimicked by cGMP analogues and in some cases by overexpression of constitutively active PKG.57,58,131,132 Moreover, the mitogenic effect of VEGF on endothelial cells appears to be mediated by NO and cGMP, as VEGF-induced Erk-1/2 activation and proliferation is blocked by NOS and sGC inhibitors.57,58

In the classic MAP kinase pathway, growth factor receptors activate Ras, Raf kinases, MEK-1/2, and Erk-1/2 (Figure 2).92 Although NO can directly activate Ras in vitro through S-nitrosylation of C118, the in vivo significance of this reaction remains to be confirmed.138 In growth factor–stimulated VSMCs and BHK cells, NO/cGMP have no effect on Ras activity.46,53 One group suggested that PKG can directly activate Raf-1 through phosphorylation of the kinase in a soluble Ras/Raf-1/PKG complex present in VEGF-stimulated human umbilical vein endothelial cells (HUVECs); however, specificity of the PKG antibody used was not demonstrated,57 and HUVECs express very little or no detectable PKG by Western blotting,7 making it doubtful that specific coimmunoprecipitation of PKG with Raf-1 and Ras would be detectable. Other investigators were unable to find Raf-1 activation by cGMP in cardiomyocytes where cGMP activated MEK-1/2 and Erk133; MEK-1/2 activation by cGMP/PKG has been confirmed in VSMCs.106 PKG directly phosphorolizes Ser43 of Raf-1 in vitro and in vivo; this phosphorylation uncouples the Ras-Raf interaction and thereby prevents mitogen-induced Raf-1 activation.46,53 A phosphorylation-deficient Raf-1(A43) mutant is insensitive to cGMP/PKG inhibition and protects cells from the inhibition of mitogen-induced Erk activity by cGMP.43 Thus, Erk activation by cGMP in resting cells may or may not include activation of Ras and Raf kinases, but occurs at the level of MEK-1/2. On the other hand, Erk inhibition by cGMP/PKG in mitogen-stimulated cells may be explained by PKG phosphorylation of Raf-1 and by cGMP/PKG induction of the MAP kinase inhibitor MPK-1 (Figure 2 and Table 1).53 In addition, cross-activation of PKA under conditions of high intracellular cGMP can lead to Erk pathway inhibition.46,54 Cell type-specific activation of p38 or JNK by cGMP appears to involve activation of the upstream kinases MEK-3 or MEKK-1 by PKG, respectively.71,139

**Posttranscriptional Regulation of Gene Expression by cGMP**

Regulation of gene expression at the posttranscriptional level includes regulation of pre-mRNA splicing, mRNA stability, and translation. PKG phosphorylates splicing factor 1 (SF1) in vitro and in vivo, and thereby inhibits prespliceosome assembly; however, whether this phosphorylation results in alternative splice site selection or otherwise regulates RNA processing of specific genes is presently unknown.100 Elevation of intracellular cGMP can decrease mRNA levels of sGC-α1 and -β1 subunits, iNOS, COX-2, TNF-α, and TGF-β, via message destabilization in VSMCs, mesangial cells, and cardiac fibroblasts.21,24,81,86,87,140 Stability of sGC-α1 mRNA is regulated by the ubiquitous mRNA binding protein HuR, which binds to AU-rich elements in the 3′-untranslated region (UTR) and increases mRNA half-life; cGMP-elevating agents decrease expression and RNA binding of HuR, thereby destabilizing sGC-α1 mRNA.24 The cGMP-induced mRNA destabilization requires transcription of an unknown factor(s)24,140; this could be an RNA-digesting protein or a factor involved in downregulation of HuR. HuR regulates mRNA stability of many different genes also regulated by cGMP, including iNOS, COX-2, TNF-α, VEGF, and cyclins A and D.53,141 Therefore, cGMP downregulation of HuR could potentially explain the cGMP downregulation of these mRNAs observed under some conditions. cGMP can also increase mRNA stability, as illustrated by the example of the potassium chloride cotransporter-3.142

Translational regulation by cGMP has been most thoroughly studied for the asialoglycoprotein receptor (ASGR), a hepatocellular surface lectin.143,144 Increased intracellular cGMP shifts ASGR mRNA into a translationally active polysomal pool, whereas decreased intracellular cGMP causes a negative trans-acting factor (called COPI) to associate with the 5′-UTR of the ASGR mRNA, thereby preventing ribosomal scanning to the site of translational initiation.143,144 COPI induced phosphorylation of COPI in intact cells is prevented by PKG inhibition and correlates with increased ASGR synthesis; PKG-dependent phosphorylation of COPI may regulate association of the COPI/RNA complex.143 Synthesis of insulin receptor subunits α and β appears to be regulated by cGMP via a similar mechanism.143

**Conclusions**

Although transcriptional regulation by cAMP has been intensely studied for decades, the regulation of gene expression by cGMP has only more recently been recognized. Many (patho)physiological processes in the cardiovascular system involve cGMP-induced changes in gene expression: (1) cGMP downregulates genes involved in the modulation of vascular tone, including sGC, PKG and rGC-A; (2) cGMP negatively regulates cardiac hypertrophy by inhibiting the expression of prohypertrophic genes such as muscle LIM protein; (3) cGMP/PKG modulate the VSMC phenotype and increase expression of differentiation-associated genes such
as SM-myosin heavy chain-2 and SM-α-actin; (4) cGMP regulation of cell proliferation correlates with the modulation of cell cycle–associated genes and growth factor synthesis; and (5) cGMP’s effects on apoptosis appear to be mediated, at least in part, through regulation of Bcl-2-related genes. Gene expression profiling will likely contribute to the rapidly growing list of cGMP-regulated genes; however, the mechanisms of transcriptional and translational regulation by cGMP are only beginning to be understood. Some effects of cGMP on gene expression involve cross-talk with other signaling pathways, such MAP kinase, calcineurin, and RhoA pathways; other effects of cGMP may be directly attributed to PKG phosphorylation of specific transcription factors, such as CREB and TFII-I.

Acknowledgments

The authors were supported by NIH grant R01-GM55586.

References


Pilz and Casteel Cyclic GMP and Gene Expression 1043


64. Genaro AM, Hertelano S, Alvarez A, Martinez C, Bosca L. Spleenic lymphocyte programmed cell death is prevented by nitric oxide release...
140. Abdelaziz N, Colombo F, Mercier I, Calderone A. Nitric oxide attenuates the expression of transforming growth factor-β1 mRNA in rat cardiac fibroblasts via destabilization. *Hypertension.* 2001;38:261–266.
Regulation of Gene Expression by Cyclic GMP
Renate B. Pilz and Darren E. Casteel

Circ Res. 2003;93:1034-1046
doi: 10.1161/01.RES.0000103311.52853.48

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/93/11/1034

Data Supplement (unedited) at:
http://circres.ahajournals.org/content/suppl/2003/11/21/93.11.1034.DC1