Significance and therapeutic potential of the natriuretic peptides/cGMP/cGMP-dependent protein kinase pathway in vascular regeneration.

Abstract:
Natriuretic peptides (NPs), which consist of atrial, brain, and C-type natriuretic peptides (ANP, BNP, and CNP, respectively), are characterized as cardiac or vascular hormones that elicit their biological effects by activation of the cGMP/cGMP-dependent protein kinase (cGK) pathway. We recently reported that adenoviral gene transfer of CNP into rabbit blood vessels not only suppressed neointimal formation but also accelerated reendothelialization, a required step for endothelium-dependent vasorelaxation and antithrombogenicity. Accordingly, we investigated the therapeutic potential of the NPscGMPcGK pathway for vascular regeneration. In transgenic (Tg) mice that overexpress BNP in response to hindlimb ischemia, neovascularization with appropriate mural cell coating was accelerated without edema or bleeding, and impaired angiogenesis by the suppression of nitric oxide production was effectively rescued. Furthermore, in BNP-Tg mice, inflammatory cell infiltration in ischemic tissue and vascular superoxide production were suppressed compared with control mice. Ischemia-induced angiogenesis was also significantly potentiated in cGK type I Tg mice, but attenuated in
cGK type I knockout mice. NPs significantly stimulated capillary network formation of cultured endothelial cells by cGK stimulation and subsequent Erk12 activation. Furthermore, gene transfer of CNP into ischemic muscles effectively accelerated angiogenesis. These findings reveal an action of the NPscGMPcGK pathway to exert multiple vasculoprotective and regenerative actions in the absence of apparent adverse effects, and therefore suggest that NPs as the endogenous cardiovascular hormone can be used as a strategy of therapeutic angiogenesis in patients with tissue ischemia.