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Modulating cGMP in heart failure

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Heart failure (HF) represents a cardiovascular syndrome of major importance with increasing prevalence worldwide contributing to increased cardiovascular morbidity and mortality. The hallmarks of this syndrome in response to myocardial dysfunction are intense systemic and renal vasoconstriction, avid sodium and water retention and structural remodelling of the heart which all contribute to the symptoms and signs of this disease process. Both from a pathophysiological and therapeutic perspective, the cGMP pathway plays a central role with great opportunity for therapeutic modulation. Two interacting cGMP pathways are central to the emerging therapeutics of HF. One is the NO/sGC/cGMP system and the other is the Natriuretic peptide (NP)/pGC/cGMP system. Increasing evidence establishes that the intense vasoconstriction of HF involves a dysfunctional NO/sGC/cGMP with evidence for excessive oxidized and heme free sGC rendering this important vasorelaxing system markedly impaired. We have demonstrated the novel NO-independent and heme-independent sGC stimulator BAY 58–2667 has potent systemic and renal vasodilating actions, unloads the heart, increases cardiac output and preserves GFR and sodium excretion. Unlike conventional nitrovasodilators BAY 58–2667 is a selective sGC activator that has no cGMP-independent actions and lacking tolerance represents a landmark breakthrough as a novel new agent for HF via NO/sGC/cGMP signalling. With regard to the complementary NP/pGC/cGMP pathway, both cardiac peptides ANP and BNP that target the pGC-A receptor have been developed for HF. Due in part to distinct spatial and temporal localization of sGC versus pGC receptors and signalling in the kidney, NP/pGC/cGMP signalling in the kidney more importantly regulates GFR and sodium excretion whereas the NO/sGC/cGMP pathway more importantly controls renal vascular tone. Here however the full renal actions of ANP and BNP are limited by upregulation of renal type V phosphodiesterase (PDEV) and dual targeting of pGC-A with BNP together with PDEV inhibition with sildenafil results in marked restoration of NP/pGC/cGMP activation resulting in enhanced GFR and sodium excretion together with PDEV inhibition suppressing ventricular hypertrophy. Recognizing the recent report of pGC-A receptor downregulation in the kidney and heart in HF, novel new generation chimeric peptides of CNP that possess additional renal actions are emerging as complementary cGMP strategy to enhance cardiovascular and renal function in the syndrome of HF. Finally, the concept of activating both pGC with a NP and sGC with BAY 58–2667 is also emerging to optimize cardiorenal function and enhance cardiovascular structure. Clearly, cGMP modulation is proving to be a seminal advance in the therapeutics of HF which is a cardiovascular syndrome with major unmet therapeutic needs.