

Letter to the Editor

Beta-Endorphin Elevation: Another Mechanism of Action of Sacubitril/Valsartan in Heart Failure?

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We read with great interest the recent article entitled “A Novel Paradigm for Sacubitril/Valsartan: Beta-Endorphin Elevation as a Contributor to Exercise Tolerance Improvement in Rats With

Preexisting Heart Failure Induced by Pressure-Overload” by Maslov et al.¹ In their well designed paper, the authors compared effects of sacubitril/valsartan and monotherapies of sacubitril or valsartan on peptides up-regulated by neprilysin (NEP) inhibition. They induced a model of heart failure (HF) with reduced ejection fraction (HFrEF) by pressure-overload via constriction of the suprarenal abdominal aorta in rats. They found that sacubitril/valsartan therapy increases beta-endorphin (BE) concentrations and improves exercise tolerance. They suggested that BE elevation might be a potential mechanism of action leading to improvement in exercise tolerance seen with sacubitril/valsartan.

NEP is a neutral endopeptidase that metabolizes various vasoactive peptides, including natriuretic peptides, bradykinin, and Ang II. NEP inhibition also increases the levels of circulating angiotensin II and endothelin.² In addition, NEP is involved in the metabolism of more than 30 peptides with various biologic actions, including vasodilation, vasoconstriction, mitogenesis, and angiogenesis. NEP participates in the degradation of endogenous opioids, and early synthetic NEP inhibitors were developed as potential analgesic agents operating by enhancement of endogenous opioids.³ BE is the one of the main endogenous opioids that is increased in HF.^{3,4} Kawashima et al⁴ reported higher levels of circulating BE in patients with HFrEF, and circulating BE was closely correlated with functional class. Cozzolino et al⁵ evaluated whether an intravenous infusion of BE exerted any effect on cardiovascular function and on the neurohormonal status in patients with HF. In that study, patients received a 1-hour intravenous infusion of BE and on a separate occasion received placebo and underwent

echocardiographic and laboratory measurements at baseline and during infusions. Infusion of BE improved left ventricular ejection fraction and reduced systemic vascular resistance. Furthermore, it blunted the neurohormonal activation in patients with HF. These effects are similar to the effects of current guideline-directed medical therapy in HF. Based on the observations stated above, the findings of Maslov et al¹ become more intriguing. An increase in endogenous opioids seems to be another potential action of NEP inhibition in HF. In our opinion, BE has a further role in HF pathophysiology, and an increase in BE by means of NEP inhibition might have some extra beneficial effects in addition to relief of dyspnea and improvement of exercise tolerance.

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