News Release

## Title

Corticotropin releasing hormone receptor 2 exacerbates chronic cardiac dysfunction

## Key Points

- Corticotropin releasing hormone receptor 2 (Crhr2) is a G protein-coupled receptor highly expressed in cardiomyocytes.
- Plasma Crhr2 agonist levels were 7.5-fold higher in patients with heart failure compared to healthy controls.
- Treatment with a Crhr2 antagonist were resistant to the onset of heart failure in mice.


## Summary

Heart failure occurs when the heart is unable to effectively pump blood and maintain tissue perfusion. Despite numerous therapeutic advancements over previous decades, the prognosis of patients with chronic heart failure remains poor, emphasizing the need to identify additional pathophysiological factors. Here, we show that corticotropin releasing hormone receptor 2 (Crhr2) is a G protein-coupled receptor highly expressed in cardiomyocytes and continuous infusion of the Crhr2 agonist, Urocortin 2 (Ucn2) reduced left ventricular ejection fraction in mice. Moreover, plasma Ucn2 levels were higher in patients with heart failure compared to healthy controls. Additionally, cardiomyocyte-specific deletion of Crhr2 protected mice from pressure overload-induced cardiac dysfunction, while mice treated with a Crhr2 antagonist were resistant to maladaptive 3′-5′-cyclic adenosine monophosphate (cAMP) response element binding protein-mediated gene expression and the onset of heart failure. Collectively, our results indicate that constitutive Crhr2 activation causes cardiac dysfunction and suggests that Crhr2 blockade is a promising therapeutic strategy for patients with chronic heart failure.


## Research Background

Heart failure is a common cardiovascular disease with poor prognosis that develops when the heart is unable to pump blood and maintain tissue perfusion. Despite improvements in the treatment of cardiovascular diseases such as coronary heart disease and hypertension, the prognosis of heart failure remains poor. In the heart, GPCRs regulate cardiac function in response to extracellular stimuli such as catecholamine and angiotensin II and play a role in cardiac dysfunction and fibrosis. GPCR inhibitors are widely used to treat patients with heart failure. Although the heart expresses several GPCRs, only β adrenergic and angiotensin II receptors antagonists are clinically used as a long-term treatment for patients with chronic heart failure. Despite these available therapies, mortality and hospitalization rates have remained relatively high for over a decade, suggesting that additional uncharacterized factors may also mediate disease pathophysiology.

**Research Results**

The study report that the the GPCR corticotropin releasing hormone receptor 2 (Crhr2) is highly expressed in the heart and promotes in heart failure. Notably, constitutive Crhr2 activation incites cardiac dysfunction in mice and serum levels of the Crhr2 agonist Urocortin2 (Ucn2) were markedly higher in patients with heart failure as compared to healthy controls. Moreover, Crhr2 antagonist treatment mitigated pressure overload-induced cardiac dysfunction in mice and suppressed maladaptive gene expression mediated by 3′-5′-cyclic adenosine monophosphate (cAMP) response element binding protein. Thus, our results indicate that Crhr2 may be a promising therapeutic target for chronic heart failure.

**Research Summary and Future Perspective**

Crhr2 activation plays a critical role in the development of heart failure and that Crhr2 antagonist treatment prevents cardiac dysfunction in model mice. Clinical analysis showed significant elevations in plasma Ucn2 in patients with heart failure as compared to healthy subjects. Ucn2 may serve as a prognostic indicator for response to Crhr2 inhibitor treatment and facilitate the development of more effective therapies for chronic heart failure.

**Publication**

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