Cardiovascular Genetics: A News Round-Up

Glucagon-Like Peptide-1 Receptor–Atrial Natriuretic Peptide Axis
A Novel Mechanism for Blood Pressure Regulation

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Study Hypothesis
Population genetic studies have established the role of natriuretic peptide system in blood pressure (BP) regulation. The primary function of atrial natriuretic peptide (ANP) is to induce natriuresis through kidneys and promote vasodilatation in blood vessels. Clinical trials have shown that glucagon-like peptide-1 receptor (GLP-1R) agonists reduce BP and decrease cardiovascular risk. In the current study, Kim et al uncover a novel link between GLP-1R and ANP, possibly elucidating the mechanism behind the reduction of BP that is observed with the use of GLP-1R agonists in clinical trials.

How Was the Hypothesis Tested?
The authors used *Glp1r*−/− mice, *Nppa*−/− mice, and *Rapgef4*−/− mice (all on the C57BL/6 background) with the corresponding wild-type controls. Angiotensin II infusion and pressure overload secondary to transaortic constriction were used to induce hypertension in the mice. The authors tested whether liraglutide (GLP-1R agonist) infusion in the normotensive and hypertensive mice reduced BP, induced ANP secretion, and promoted aortic vasodilatation. Next, they determined the importance of ANP for hypertension in the mice. The authors tested whether liraglutide using ANP knockout null mice reduced BP, induced ANP secretion, and promoted aortic vasodilatation. Finally, the authors used *Rapgef4*−/− mice, which are deficient of the gene encoding the downstream effector, Rap guanine nucleotide exchange factor Epac2 (also known as Rapgef4), because plasma ANP levels failed to increase in *Rapgef4*−/− mice after treatment with liraglutide. Expression of adenosinergic Epac2 in atrial cardiomyocytes from hypertensive *Rapgef4*−/− mice restored the ability of liraglutide to induce ANP secretion from the cardiomyocytes. In addition, liraglutide significantly lowered both systolic and diastolic BP in hypertensive wild-type mice but had no effect on BP in hypertensive *Rapgef4*−/− mice. Taken together, these results suggest that liraglutide induces the release of ANP via a GLP-1R/Epac2 signaling pathway mechanism and regulates BP in a GLP-1R–ANP-dependent manner.

Implications
This study uncovers a novel gut-heart axis by which a gut hormone, GLP-1, regulates ANP secretion from cardiomyocytes and lowers BP. One could speculate that these findings can be translated to treating hypertension in humans especially in patients with coexisting diabetes mellitus. Further research directed at pharmacologically augmenting the activation of natriuretic peptide system through GLP-1R pathway is warranted.

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Disclosures
None.

Key Words: atrial natriuretic factor ■ blood pressure ■ glucagon-like peptide 1 ■ natriuretic peptides

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523
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