Apelin was identified in 1998 as the endogenous ligand for the then orphan G-protein–coupled receptor, APJ, now renamed the apelin receptor. Widely expressed in the central nervous system and peripheral tissues, the apelin system participates in a diverse array of processes, including glucose metabolism, immune function, and fluid homeostasis. However, its principal physiological role seems to be related to its cardiovascular actions.

Apelin is synthesized as a 77-amino acid prepropeptide that is cleaved into a mature 36-amino acid peptide. Shorter more active isoforms have also been identified, with the pyroglutamated 13-amino acid apelin, (Pyr1)apelin-13, being the more active isoforms have also been identified, with the pyroglutamated 13-amino acid apelin, (Pyr1)apelin-13, being the most potent and abundant form in cardiac tissue. The main source of plasma apelin is unclear although the vascular endothelium and the atria of the heart are likely to be significant contributors. Apelin has a brief plasma half-life of <5 minutes in humans, and its cardiovascular effects are relatively short lived. One enzyme that has long been implicated in the inactivation of apelin peptides is angiotensin-converting enzyme (ACE) type 2, a carboxypeptidase that negatively regulates the renin–angiotensin–aldosterone system by cleaving angiotensin II to the biologically inactive peptide angiotensin 1–9. Although ACE2 was previously reported to hydrolyze both apelin-13 and apelin-36 with high catalytic efficiency, its ability to inactivate these peptides and physiological significance was hitherto unclear (Figure).

In this issue of Hypertension, Wang et al present a comprehensive series of studies that confirm an important role for ACE2 in the metabolism of biologically active apelin isoforms and represent an important step toward the development of longer acting apelin receptor agonists. Building on elegant molecular modeling studies, the authors convincingly show, through a combination of in vitro and in vivo approaches, that ACE2 contributes to the degradation of both apelin-17 and (Pyr1)apelin-13. In mice, the loss of ACE2 function, through a combination of in vitro and in vivo approaches, that ACE2 contributes to the degradation of both apelin-17 and (Pyr1)apelin-13. In mice, the loss of ACE2 function, through either pharmacological inhibition or genetic knockout, prolonged circulating concentrations of both these isoforms after exogenous administration. Importantly, in both models, greater persistence of the apelin peptide was associated with a more sustained depressor response. The authors then proceeded to construct and test 2 apelin analogues designed to be resistant to proteolytic cleavage by ACE2. After confirming the inability of ACE2 to cleave these analogues in vitro, they concluded by demonstrating a prolonged hypotensive action of both analogues relative to the native isoforms.

This work could open up new avenues for exploring the therapeutic potential of apelin. In preclinical models, apelin receptor agonism mediates a nitric oxide–dependent fall in blood pressure, reduces ventricular preload and afterload, and potently increases myocardial contractility. These effects are paralleled in humans in whom apelin peptides induce peripheral and coronary vasodilatation while increasing cardiac output and contractility. Importantly, both the local vascular and systemic hemodynamic responses to apelin are preserved in patients with stable symptomatic chronic heart failure, maintained on contemporary medical therapy.

Given this favorable profile of physiological actions, the upregulation of apelin signaling may be beneficial in not only many cardiovascular disorders, most notably heart failure, but also vascular disease, hypertension, myocardial ischemia, and the metabolic syndrome. To date, detailed clinical research in this area has been severely hampered by a lack of available tools to study the effects of sustained apelin agonism.

One strategy to augment apelin signaling is to inhibit the breakdown of biologically active endogenous apelin peptides. The feasibility and efficacy of such an approach in the setting of heart failure have recently been demonstrated with the neprilysin inhibitor, sacubitril. Inhibition of neprilysin, a neutral endopeptidase, increases circulating concentrations and actions of endogenous natriuretic peptides, Bradykinin, and adrenomedullin by reducing their degradation. An alternative strategy is to develop long-acting orally available apelin analogues. One major barrier to progress on both of these fronts has been a poor understanding of the post-translational processing, cleavage, and inactivation of apelin peptides. The studies by Wang et al, therefore, represent an important step toward our ability to study the effects of chronic apelin agonism: a prerequisite for exploring its therapeutic potential.

These recent studies have several notable strengths. The use of multiple complementary approaches, including the measurement of cardiovascular responses, increases confidence in the principal findings and enhances their physiological relevance. The authors also used a high-performance mass spectrometry–based method for apelin quantification capable
of detecting low concentrations of apelin peptides and differentiating the various isoforms. This is particularly important as current commercially available enzyme-linked assays and radioimmunoassays for apelin are unreliable, are hampered by nonspecific protein binding, do not measure all isoforms, and tend to report inaccurately elevated apelin concentrations.

The work by Wang et al has extended our understanding of the field and is a major contribution. However, as with all excellent research, further questions arise. First, although ACE2 may contribute to the cleavage of biologically active apelin peptides, it is clear that apelin degradation also occurs through pathways that are independent of ACE2 and involve proteases yet to be identified. Thus, although genetic knockout of ACE2 prolongs the increases in circulating apelin concentration after exogenous administration, the plasma half-life of the peptides is still <5 minutes. Accordingly, despite demonstrating resistance to cleavage by human recombinant ACE2, one of the synthetic apelin analogues was completely degraded after 60 minutes of incubation with human plasma.

The potentiation of blood pressure responses to apelin in the setting of reduced ACE2 activity would seem to support the physiological importance of this enzymatic pathway for apelin inactivation. However, the extent to which the observed increase in hypotensive action can be attributed to persistence of active apelin isoforms is uncertain. As the authors acknowledge, ACE2 is an important regulator of other vasoactive peptide systems, including the renin–angiotensin system and, as such, its inhibition will have broader effects than simply altered apelin degradation. Indeed, the prolongation of physiological response to apelin observed with ACE2 inhibition would seem to be exceed its expected effects on plasma apelin concentrations alone given the relatively modest effect on plasma half-life. Closer examination of the correlation between pharmacokinetic and pharmacodynamic data in these studies and exploring the effects of ACE2 inhibition on other responses to apelin, such as glucose metabolism, may help to clarify this issue. The application of larger animal models will allow more detailed pharmacokinetic modeling and will also help to address many of these issues.

In summary, the studies by Wang et al represent an important step forward in our understanding of the enzymatic degradation of apelin peptides and offer proof of concept for an approach to augmenting apelin agonism through the generation of synthetic long-acting analogues. It also suggests that inhibition of apelin metabolism is a worthwhile endeavor and that this approach could have major therapeutic potential especially if more apelin-specific peptidases are identified. The development of clinically efficacious strategies is likely to depend on a greater understanding of the fundamental biology of the apelin system and in particular a more comprehensive elucidation of the pathways responsible for the post-translational processing and inactivation of apelin peptides. The current study is one of the first steps along the way to unlocking the therapeutic potential of apelin.

Sources of Funding
A.G. Japp and D.E. Newby conducted research in apelin supported by Chest Heart and Stroke Scotland and the British Heart Foundation (FS/06/64, FS/09/19, and PG/11/11/13).

Disclosures
A.G. Japp was supported by National Health Service (NHS) Research Scotland Fellowship through NHS Lothian. D.E. Newby was supported by the British Heart Foundation (CH/09/002 and RE/13/3/30183) and is the recipient of a Wellcome Trust Senior Investigator Award (WT103782/AIA).

References


Unlocking the Therapeutic Potential of Apelin
Alan G. Japp and David E. Newby

Hypertension. 2016;68:307-309; originally published online May 23, 2016; doi: 10.1161/HYPERTENSIONAHA.116.07057

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/68/2/307

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/