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STATE-OF-THE-ART REVIEW

Cardiac Endocrinology

Heart-Derived Hormones in Physiology and Disease

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HIGHLIGHTS

- **The heart uses an endocrine mechanism to communicate with the rest of the body.**
- **Heart-derived hormones, such as GDF-15, myostatin, and ANP/BNP, share common features, including synthesis, regulation, and function, and they coordinate the functions of the heart and target organs.**
- **Additional heart-secreted factors play important autocrine and/or paracrine roles in local cardiac remodeling.**
- **Future studies in the field of cardiac endocrinology will further advance the understanding of the intricate communications between the heart and the rest of the body.**

SUMMARY

The heart plays a central role in the circulatory system and provides essential oxygen, nutrients, and growth factors to the whole organism. The heart can synthesize and secrete endocrine signals to communicate with distant target organs. Studies of long-known and recently discovered heart-derived hormones highlight a shared theme and reveal a unified mechanism of heart-derived hormones in coordinating cardiac function and target organ biology. This paper reviews the biochemistry, signaling, function, regulation, and clinical significance of representative heart-derived hormones, with a focus on the cardiovascular system. This review also discusses important and exciting questions that will advance the field of cardiac endocrinology. (J Am Coll Cardiol Basic Trans Science 2020;5:949–60) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The vital function of the heart has been known for thousands of years. The heart beats continuously to pump blood that carries oxygen and nutrients to every cell of our body. An unhealthy heart, such as one with heart failure, has significantly reduced contractile function that reduces its ability to perform such a task. As a result, cells in our body receive less oxygen, nutrients, and other factors critical for their survival, growth, and normal function. In contrast, during exercise, the heart needs to elevate its rate and capacity to satisfy the increased whole body oxygen and energy demand. Therefore, it is of paramount importance that the heart communicates its functional status to the rest of the body to coordinate nutritional needs and functions.

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ABBREVIATIONS AND ACRONYMS

ActR = activin receptor

ANP = atrial natriuretic peptide

BNP = brain natriuretic peptide

CNP = C-type natriuretic peptide

FGF = fibroblast growth factor

FSTL = follistatin-like

GDF = growth differentiation factor

GFRAL = GDNF family receptor α-like

NPR = natriuretic peptide receptors

PCSK = proprotein convertase subtilisin/kexin type

ST2 = suppression of tumorigenesis-2

TGF = transforming growth factor

Such heart-derived signals can take many forms and can be neuronal or endocrine in nature. Neuronal signals tend to be fast-acting, whereas endocrine signals can stimulate long-term changes. The heart can signal its functional status to the brain through sensory nerves; the brain then integrates and relays this information to the rest of the body through efferent nerves or endocrine signals (e.g., change in growth hormone level). Alternatively, the heart can secrete signals into the circulation that travel to distant sites of the body to directly affect their biology, thus functioning as heart-derived hormones. Such heart-derived hormones can be proteins, lipids, metabolites, or other forms of molecules. Most cell types routinely secrete many factors into the extracellular space, but most of them are often trapped there without going into the systemic circulation, or they go into circulation as mere biomarkers without specific biological functions through activating distinct receptors on specific target organs. Due to space limitations, this review mainly focuses on heart-derived endocrine hormones with systemic effects.

Compared with adipose tissue, liver, or muscle, the endocrine function of the heart is much less understood, with few heart-derived hormones identified and studied. The most well-established heart-derived hormones are atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), discovered almost 40 years ago (1–3), which play critical roles in vasodilation and natriuresis. Recent work from many laboratories, including ours, have identified or indicated new heart-derived hormones, such as growth differentiation factor (GDF)-15 and myostatin (4,5). A shared theme has emerged through these studies, which has helped define heart-derived hormones despite their biochemical diversity (**Figure 1, Central Illustration**): 1) they are synthesized and secreted from specific heart cells and enter the circulatory system; 2) their synthesis, maturation, secretion, and circulating levels are highly regulated in response to altered internal cardiac function or external cardiac demand; and 3) they act through specific receptors and signaling mechanisms in specific distant target organs and execute distinct biological functions to coordinate changes of cardiac function and demand (e.g., reduction of blood pressure by ANP/BNP, inhibition of body growth by GDF-15). Therefore, we refer to the study of these heart-derived hormones in physiology and disease as cardiac endocrinology.

We review known heart-derived hormones, focusing on GDF15, myostatin, and ANP/BNP, and their biology in the cardiovascular system. We also briefly summarize additional heart-secreted factors with significant clinical relevance that largely function in an autocrine or paracrine manner to regulate local cardiac function. Last, we discuss important and exciting questions that remain to be answered in the field of cardiac endocrinology.

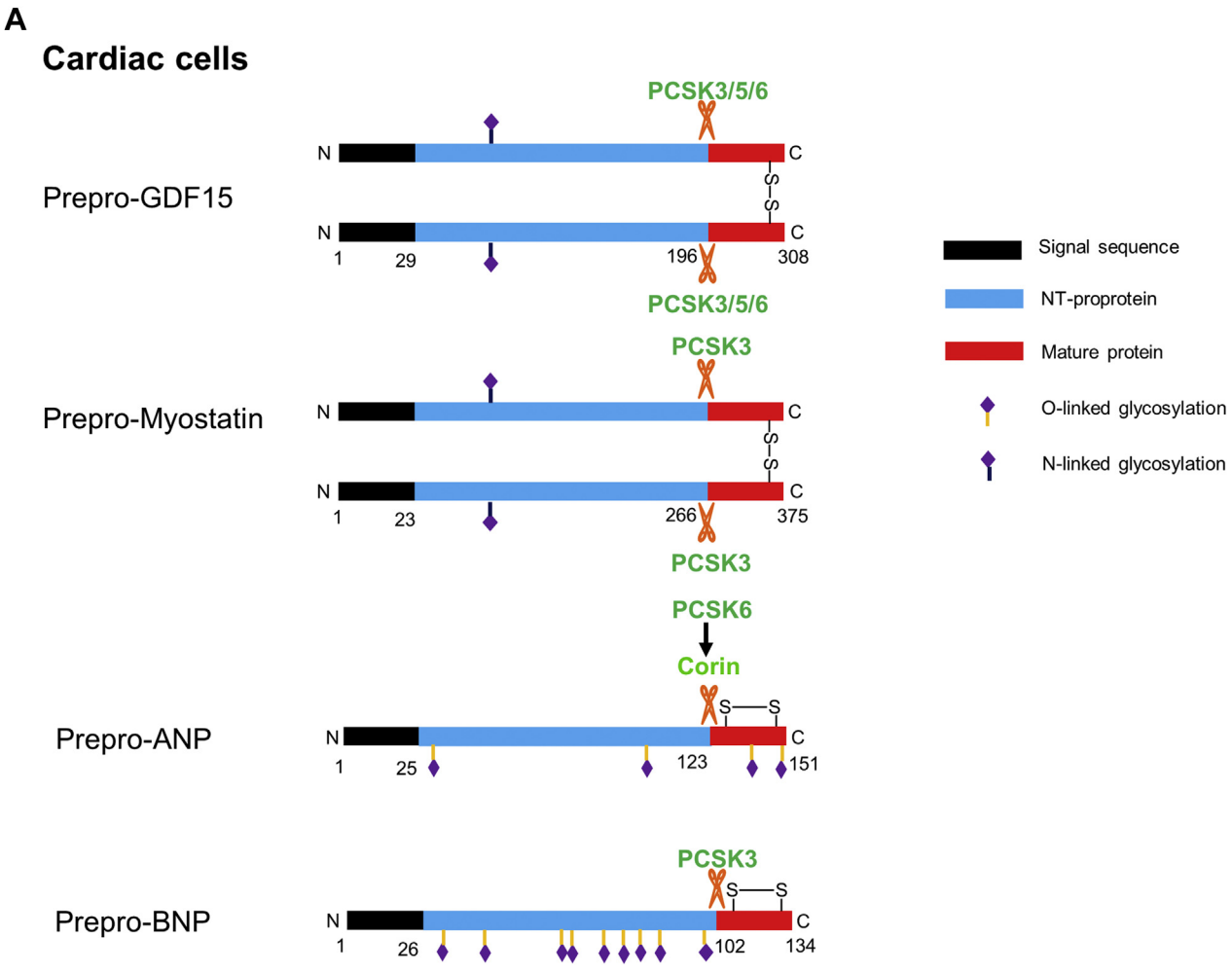
GDF15

GDF-15 is a divergent member of the transforming growth factor (TGF)-β family. GDF-15 was first discovered by several independent groups and was designated as macrophage inhibitory cytokine 1, placental bone morphogenetic factor, placental TGF-β, or prostate-derived factor (6–9). *Gdf15* expression is low in most tissues under physiological conditions (8) but can be induced in the heart and other organs under pathological conditions, often with concomitant elevation of the circulating GDF-15 protein level (4,10–12). In the cardiovascular system, cardiac synthesis and secretion of GDF-15 are substantially increased in various cardiovascular diseases (e.g., heart failure) (13–15). In addition to serving as a useful serum biomarker of cardiovascular disease, heart-secreted GDF-15 was recently shown to slow pediatric body growth by inhibiting liver growth hormone signaling, thus functioning as a heart-derived hormone (4).

BIOCHEMISTRY. Human prepro-GDF-15 has a well-conserved N-terminal signal sequence of 29 amino acids and a C-terminal glycosylated pro-GDF-15 of 279 amino acids that tends to form a homodimer through an intermolecular disulfide bond (**Figure 1A**) (16). Three members of the proprotein convertase subtilisin/kexin (PCSK) family, PCSK3 (also known as furin), PCSK5, and PCSK6 have been shown to cleave pro-GDF-15 right after the conserved RXXR sequence both in vitro and in vivo, generating the mature GDF-15 dimer (17,18), which is the major circulating form of GDF-15 (19). The secretion of GDF-15 is little understood, and it is unclear whether GDF-15 exists in cellular granules before being secreted. Pro-GDF-15 has been observed in the extracellular matrix in studies of tumor cell lines, indicating that pro-GDF-15 can be secreted and that PCSK-mediated maturation can occur extracellularly (20,21). It remains to be discovered how circulating GDF-15 is cleared or degraded.

RECEPTOR AND SIGNALING. The receptor and signaling of GDF15 has long been elusive and debated, partly due to the high concentration of GDF-15 used in

FIGURE 1 Shared Features of GDF-15, Myostatin, and ANP/BNP Biochemistry, Regulation and Signaling



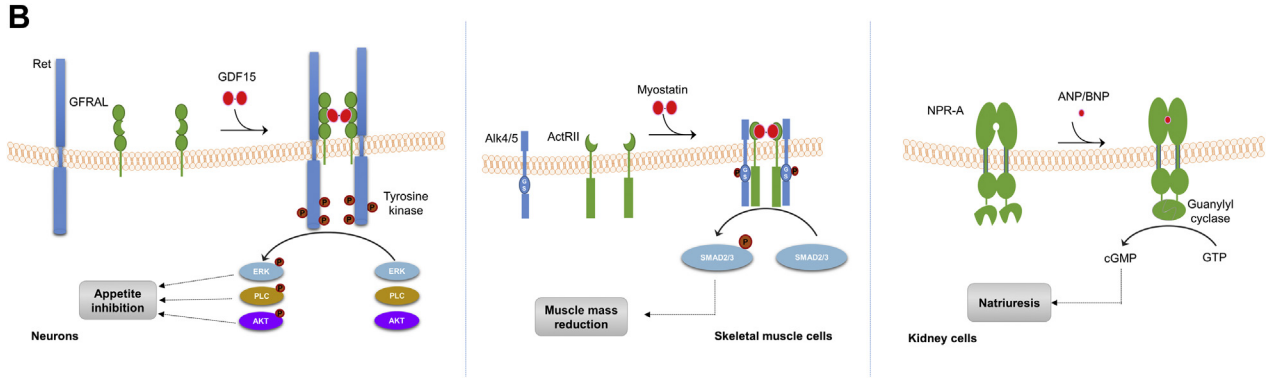
(A) Structure and maturation of human growth differentiation factor (GDF)-15, myostatin, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) in cardiac cells. GDF-15, myostatin, ANP, and BNP are all synthesized as prepro-peptides and undergo similar post-translational modifications, including: 1) glycosylation; 2) cleavage by proprotein convertase subtilisin/kexin types (PCSKs) to mature; and 3) forming intramolecular or intermolecular disulfide bond from cysteine residues. **(B)** Signaling of GDF15, myostatin, ANP, and BNP. GDF-15 dimer binding triggers GDNF family receptor α-like (GFRAL) homodimerization and recruits receptor tyrosine kinase RET, which results in appetite inhibition in area postrema neurons. Myostatin dimer binding with activin receptor II (ActRII) induces its heterodimerization with ActRI (Alk4/5), which results in the reduction of muscle mass in skeletal muscle cells. ANP or BNP binding triggers a conformational change of natriuretic peptide receptor-A (NPR-A) homodimer and then activates the guanylyl cyclase domain catalyzing cyclic guanosine monophosphate (cGMP) production, which results in natriuresis in kidney cells.

Continued on the next page

most in vitro experiments (often hundred- to thousand-fold greater than physiological or pathological levels observed in vivo) and that some commercial sources of GDF-15 contain significant amount of contaminating TGF-β (22).

The recent identification of GDNF family receptor α-like (GFRAL) as a bona fide GDF-15 receptor represents a significant advance in our understanding of GDF-15 biology (23-26). These studies convincingly show that a GDF15 homodimer binds to a GFRAL homodimer, which then recruits and activates the receptor tyrosine kinase RET for downstream intracellular signaling (24,26) (**Figure 1B**). GFRAL contains a large extracellular domain (~330 amino acids) and a single transmembrane helix but has a short intracellular C-terminus without characterized kinase

FIGURE 1 Continued



activity. GFRAL is reportedly expressed only in certain neurons located in the area postrema and nucleus of the solitary tract of the brainstem.

REGULATION, FUNCTION, AND CLINICAL SIGNIFICANCE. Numerous clinical studies have shown that the circulating GDF-15 level is increased in various heart diseases, including acute coronary syndromes and heart failure, and serves as a valuable diagnostic and prognostic biomarker for these diseases (13–15). The cardiac GDF-15 level is regulated at multiple levels, including synthesis and processing. The gene regulatory network that induces cardiac *Gdf15* transcription was revealed using single-nucleus RNA-Seq in a genetic mouse model of heart disease (27), which indicated involvement of multiple factors (GATA4, unfolded protein response, and so on) in controlling GDF-15 synthesis. Heart disease also increases the transcription and protein level of PCSK5, thus promoting GDF-15 maturation at the same time (18). Furthermore, recent studies revealed that GDF-15 executes important cardiovascular functions beyond serving as a biomarker. GDF-15 exhibits protective effects in mouse models of cardiac ischemia/reperfusion injury and hypertrophy induced by pressure overload (28,29), presumably acting via autocrine or paracrine mechanisms locally in the heart.

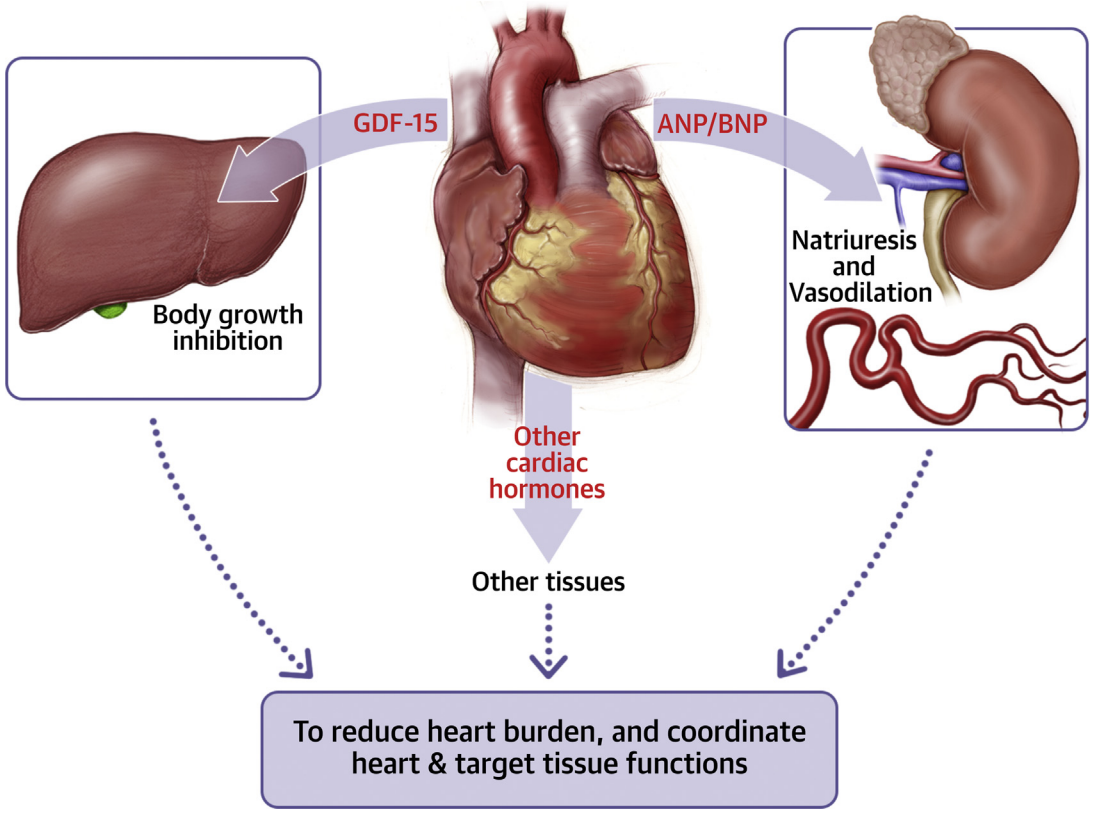
GDF-15 can also function as a heart-derived endocrine hormone that regulates pediatric body growth (4). Pediatric heart disease induces cardiac GDF-15 synthesis and secretion. Circulating GDF-15, in turn, acts on the liver to inhibit growth hormone signaling and body growth. Blocking cardiac production of GDF-15 via the AAV-delivered *Gdf15* shRNA specifically expressed in cardiomyocytes normalizes circulating GDF-15 levels and restores liver growth hormone signaling, establishing GDF15 as a bona fide heart-derived hormone that regulates pediatric body growth. Plasma GDF-15 is further increased in children with concomitant heart disease and failure to thrive (FTT), providing a potential mechanism for the well-established clinical observation that children with heart diseases often develop FTT. Therefore, GDF-15 functions as a crucial endocrine signal for heart–body communication.

Outside of the cardiovascular system, GDF-15 produces strong appetite-suppressing and nausea-like effects that are completely dependent on GFRAL (23–26,30,31) and was proposed to mediate metformin's effect on body weight and energy balance (32,33). Accordingly, genome-wide association studies and other genetic studies identified several loci next to the *Gdf15* gene that are associated with hyperemesis gravidarum (rs16982345) (34), obesity (rs17724992) (35), and prostate cancer (rs1058587) (36), in addition to the risk of left ventricular hypertrophy (rs4808793) (37), highlighting the clinical significance related to GDF-15 biology. GDF-15-GFRAL is currently under extensive studies for 2 major therapeutic applications: activating GDF-15-GFRAL for treating metabolic disorders, including obesity, diabetes, and fatty liver disease (38,39); and inhibiting GDF-15-GFRAL for treating anorexia and cancer cachexia (31,40). Clinical trials for these implications are currently ongoing.

MYOSTATIN

Myostatin is another member of the TGF-β superfamily and was first discovered through screening in a mouse skeletal muscle library (5). A well-established negative regulator of muscle mass, myostatin is primarily expressed in skeletal muscle (5). Low levels of

CENTRAL ILLUSTRATION **Shared Theme of Heart-Derived Endocrine Hormones in Coordinating Functions of Heart and Their Target Organs**



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ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; GDF-15 = growth differentiation factor-15.

myostatin can be found in normal hearts and are largely localized in Purkinje fibers (41).

Similar to GDF-15, myostatin is synthesized as a prepro-protein, which then undergoes glycosylation and homodimerization via an intermolecular disulfide bond (**Figure 1A**). Upon removal of the N-terminal signal sequence, the remaining pro-myostatin is further proteolytically processed by PCSK3 and the metalloproteinase bone morphogenetic protein 1 sequentially to become active (42,43). Although pro-myostatin can be cleaved by PCSK3 inside the cell, most pro-myostatin is believed to be secreted and processed extracellularly (44). After PCSK3 cleavage at the RXXR site, the myostatin dimer is associated with the remaining N-terminal region noncovalently as a latent complex until a second cleavage by bone morphogenetic protein 1 that generates the active form. It remains largely unknown how circulating myostatin is removed or degraded.

The receptors for myostatin are activin receptors (ActR), shared by other members of TGF-β family, including GDF-11 and activin-A. ActR includes 2 heteromeric single transmembrane serine/threonine kinases: type I (ActRI) and type II (ActRII). ActRII binds directly to myostatin, then recruits and phosphorylates ActRI (ALK4 or ALK5) at its cytosolic glycine/serine-rich (GS) domain which, in turn, phosphorylates and activates SMAD2/3 proteins (**Figure 1B**). Activated SMAD2/3 then inhibits skeletal muscle cell proliferation and protein synthesis through multiple mechanisms, including gene expression regulation and mTOR inhibition. Myostatin binds to both ActR type IIA (ActRIIA) and type IIB (ActRIIB) in vitro (45). However, transgenic mice that expressed a

dominant-negative form of ActRIIB mimicked the muscle phenotype of myostatin-deficient mice (42), which indicated ActRIIB is sufficient for myostatin inhibition on skeletal muscle growth in vivo.

Loss-of-function mutations of *Mtsn* (myostatin gene) led to widespread increase of skeletal muscle mass in both animals and humans (5,46), whereas overexpression of myostatin induced profound muscle loss in mice (47), which established myostatin as an essential regulator of muscle mass. A genome-wide association study identified several single nucleotide polymorphisms near *Mtsn* associated with racing performance in horses, and variations at ActRIIB gene *Acvr2b* were associated with handgrip strength in humans (48,49).

In the cardiovascular system, myostatin levels in both the heart and circulation are elevated in myocardial infarction or heart failure (50–53). The myostatin processing enzyme bone morphogenetic protein 1 activity was also increased in patient hearts with ischemic or dilated cardiomyopathy (52). Clinical studies showed that plasma myostatin level was positively correlated with heart disease biomarker N-terminal pro-BNP in patients with congestive heart failure and with infarct size in acute myocardial infarction, which indicated that myostatin is a potential biomarker for these heart diseases.

Cachexia and muscle wasting are often observed in severe heart disease (e.g., heart failure). Nkx2.5-cre–mediated, cardiac-specific deletion of *Mtsn* prevented skeletal muscle atrophy caused by heart failure (50), which suggested that cardiac-derived myostatin functions as an endocrine hormone acting on skeletal muscle. Therefore, myostatin-ActR signaling emerged as a promising target for muscle atrophy associated with heart failure. To this end, inhibition of myostatin-ActRIIB binding with an anti-myostatin blocking antibody JA-16 was shown to reverse skeletal muscle atrophy in mouse heart failure (50).

ANP AND BNP

Largely synthesized and secreted from the heart myocardium, ANP and BNP have a well-established endocrine function that regulates whole body water and electrolyte balance (1–3). Similar to GDF-15 and myostatin, ANP and BNP are synthesized as prepro-peptides and cleaved by protease Corin or PCSK3, respectively, to release the mature active form (**Figure 1A**). Corin is, in turn, activated by PCSK6 (54).

The essential physiological function of ANP and BNP in regulating whole body hemodynamics is mediated through their specific receptors expressed in target tissues, including kidney, adrenal, brain, and vascular smooth muscle (55–57) (**Figure 1B**). Three types of natriuretic peptide receptors (NPRs) are known in mammals: NPR-A, NPR-B, and NPR-C. Upon natriuretic peptides binding, NPR-A or NPR-B catalyzes the production of the second messenger cyclic guanosine monophosphate, which further activates the broad downstream targets in different tissues (58–60). In contrast to NPR-A/B, NPR-C has a short intracellular domain that results in no guanylyl cyclase activity and no effect on intracellular cyclic guanosine monophosphate levels. NPR-C thus functions as a “clearance receptor” through internalization and balances the activities of circulating ANP and BNP (61–63). In addition, circulating ANP and BNP are cleared by the membrane-bound protease neprilysin (64,65).

Although ANP and BNP are constitutively released under basal conditions primarily from the heart, their circulating levels are substantially induced in heart diseases via regulation at multiple levels: synthesis, processing, secretion, and degradation (66–68). ANP/BNP and their degradation enzyme neprilysin have emerged as clinically important biomarkers and/or therapeutic targets for cardiovascular disease (69,70). A combination drug of the neprilysin inhibitor sacubitril and the angiotensin II receptor inhibitor valsartan (Entresto, Novartis, Basel, Switzerland) was recently approved for patients with heart failure. In clinical trials, Entresto demonstrated further reduction of cardiovascular death, hospitalization, and all-cause mortality than widely used angiotensin-converting enzyme inhibitors alone (69,71,72).

OTHER HEART-DERIVED HORMONES

Additional heart-derived factors may potentially function in an endocrine manner. Mice with cardiomyocyte-specific loss of the transcriptional mediator complex protein MED13 gained more weight on a high-fat diet, although they exhibited no body weight change on a chow diet (73). Cardiomyocyte-specific overexpression of MED13 in mice conferred a lean phenotype by enhancing metabolism in white adipose tissue and the liver (74). Parabiosis experiments suggested that endocrine factors mediate such metabolic changes (74). Similarly, cardiomyocyte-specific overexpression and knock-out of G-protein–coupled receptor kinase 2 also altered adipose metabolism potentially through endocrine mechanisms (75). In both cases, the exact identities of possible heart-derived endocrine factors

TABLE 1 Heart-Derived Hormones and Autocrine/Paracrine Factors

	Pathophysiological Role	Clinical Relevance	Ref. #
Endocrine hormones			
ANP	Natriuresis and vasodilation	HF Therapeutic target (sacubitril)	(67,71)
BNP	Natriuresis and vasodilation	HF, biomarker Therapeutic target (Sacubitril)	(70,71)
GDF-15	Inhibiting body growth	Biomarker for ACS, HF	(13-15)
Myostatin (GDF-8)	Reducing skeletal muscle mass	HF, AMI, cardiac cachexia	(50,52,76,77)
Autocrine/paracrine factors			
Activin A	Protecting cardiomyocyte	MI	(78)
CNP	Vasodilation	HF, CH	(79–83)
CTRP9	Cardioprotection	CH, MI, HF	(84–86)
ET-1	Promoting cardiomyocyte survival	HF	(87)
FGF-2	Inhibition of excessive autophagy and increase of ubiquitinated protein clearance	MI	(88–90)
FGF-9	Preserving systolic function	MI	(91)
FGF-16	Preventing cardiac hypertrophy and fibrosis	CH	(92)
FGF-21	Regulating cardiac metabolism; antihypertrophic	AMI, CHD, HF, DCM	(93,94)
FGF-23	Promoting fibrosis and diastolic dysfunction	CH, MI	(95,96)
FSTL1	Cardioprotection	HF, ACS, CH	(97–101)
FSTL3	Antagonizing Activin A cardioprotection	MI, CH	(78,102)
IL-33/sST2	Antihypertrophic and antifibrosis	AMI, HF, CH sST2 is a biomarker for HF and AMI	(103,104)
MANF	Cardioprotection	MI, CH	(105,106)
miRNA-1/208a(b)/499/30a	Post-transcriptional regulation	AMI	(107–111)
PI16	Inhibiting hypertrophy	HF, CH	(112)
sFRP2	Antagonist of Wnt signaling	MI	(113,114)
sFRP3	Antagonist of Wnt signaling	HF, MI, ACS	(115,116)

AMI = acute myocardial infarction; ACS = acute coronary syndrome; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; CH = cardiac hypertrophy; CHD = coronary heart disease; CNP = C-type natriuretic peptide; CTRP9 = C1q/tumor necrosis factor-related protein-9; DCM = diabetic cardiomyopathy; ET = endothelin; FGF = fibroblast growth factor; FSTL1 = follistatin-like 1; GDF = growth differentiation factor; HF = heart failure; IL = interleukin; MANF = mesencephalic astrocyte–derived neurotrophic factor; MI = myocardial infarction; miRNA = microRNA; PI16 = protease inhibitor 16; sFRP = secreted frizzled-related protein; sST2 = soluble suppression of tumorigenesis-2.

that mediate reported metabolic effects remain to be discovered.

HEART-DERIVED AUTOCRINE AND/OR PARACRINE FACTORS

Cardiac cells such as cardiomyocytes, fibroblasts, and endothelial cells can secrete a large number of factors in various forms from proteins, lipids, and small molecules to exosomes. In addition to GDF-15, myostatin and ANP/BNP, some of these factors have been reported to enter systemic circulation. However, it remains unknown whether the strictly heart-derived portion of these factors in circulation (e.g., in a heart-specific knock-out setting) have specific biological functions on distinct target organs. In contrast, many of the cardiac cell–secreted factors enter the local extracellular environment without going into systemic circulation. Many of them have been shown to function in local cardiac remodeling by acting in an autocrine or paracrine manner. Their functions are summarized in **Table 1**, and we focus our discussion on those with significant clinical relevance.

C-TYPE NATRIURETIC PEPTIDE. Unlike ANP and BNP, C-type natriuretic peptide (CNP) is widely expressed and not heart-specific (117,118). However, cardiac synthesis of CNP is substantially elevated in patients with chronic heart failure (79), and CNP regulates cardiac function through its receptor NPR-B in the heart (119-121). Cardiac-specific overexpression of CNP in rats had no effect on the infarct size upon ischemia/reperfusion injury but prevented the following hypertrophy (80). Systemic infusion of CNP significantly reduced hypertrophy and fibrosis after myocardial infarction in mice (81). Cardiomyocyte-specific deletion of CNP showed deteriorated heart function in a pressure-overload injury model (82).

FOLLISTATIN. The follistatin family of proteins are a group of secreted glycoproteins that bind and neutralize TGF-β family factors. Cardiac synthesis of follistatin-like 1 (FSTL1) and 3 (FSTL3) are elevated in human heart failure and in rat models of hypertrophic cardiomyopathy induced by pressure overload (97). Serum FSTL1 is increased in patients with heart failure and acute coronary syndrome (98,99); therefore, it is a potential biomarker for cardiovascular diseases (98,100). FSTL1 administration has been shown to reduce myocardial infarct size in ischemia/reperfusion injury models through suppressing TGF-β family protein BMP4 proinflammatory signaling (101). In addition, FSTL1 overexpression specifically in mouse hearts leads to resistance to pressure overload–induced hypertrophy. Cardiomyocyte-specific loss of FSTL1 exacerbates cardiac hypertrophy and heart dysfunction while not altering the basal phenotype (122). In contrast to the beneficial role of FSTL1, FSTL3 binds activin A and antagonizes its cardiac protective function. As a result, cardiac-specific loss of FSTL3 attenuates ischemia/reperfusion injury and pathological hypertrophy (78,102).

FIBROBLAST GROWTH FACTOR-21. Several fibroblast growth factors (FGFs), along with their receptors, are detectable in multiple cardiac cell types, and they regulate cardiac development and function in an autocrine/paracrine manner in mice and humans (123). Among them, a high level of circulating FGF-21 has been observed in human heart diseases, including acute myocardial infarction, coronary heart disease, heart failure, and diabetic cardiomyopathy (124–126); thus, FGF-21 is a potential biomarker for cardiovascular diseases. FGF-21 also plays an important role in cardiac metabolism and function through autocrine and/or paracrine mechanisms. Whole-body loss of FGF-21 reduced cardiac fatty acid oxidation and resulted in exacerbated hypertrophy induced by isoproterenol that was reversed by FGF-21 administration, which indicated the cardioprotective effect of FGF-21 in pathological hypertrophy (93). Beyond the cardiovascular system, FGF-21 is a well-established regulator of metabolic signaling in other tissues, including brown fat and the brain (127–130), and is being evaluated in metabolic disorders, including obesity and diabetes. An analog of FGF-21, LY2405319, demonstrated improvement in dyslipidemia and body weight in obese patients with type 2 diabetes (131).

INTERLEUKIN-33. Inflammatory response is one of the most notable processes occurring in many forms of heart disease and involves numerous inflammatory cytokines. Among them, cardiac interleukin-33 synthesis and secretion is induced mostly in cardiac fibroblasts by biomechanical stimuli, and it activates its receptor, suppression of tumorigenesis-2 (ST2), which is expressed on cardiomyocytes in a paracrine manner. Disruption of interleukin-33 signaling by deleting ST2 systemically or cardiac specifically exacerbates hypertrophic and fibrosis phenotypes induced by pressure overload injury (103,104). A soluble isoform of ST2 generated by alternative splicing was reported to be released into circulation and can function as a decoy receptor for interleukin-33 in the myocardium (103). The circulating soluble isoform of ST2 has emerged as a biomarker for multiple heart diseases, including acute myocardial infarction and heart failure (132–134), and the corresponding soluble isoform of ST2 immunoassay has been widely used clinically.

MicroRNA. Micro-RNAs (miRNAs) are noncoding RNAs of 18 to 25 nucleotides that are involved in post-transcriptional regulation by binding to the 3' untranslated region of the target mRNA. miRNAs produced by cardiac cells can be encapsulated into exosomes or microvesicles and mediate cell–cell communication in hearts in an autocrine or paracrine fashion (135–138). Several cardiac-enriched miRNAs that exist predominantly in exosomes are highly elevated in the serum of patients with heart diseases. Circulating miRNA-1, miRNA-208a/b, miRNA-499, or miRNA-30a have been shown to be significantly increased in both mouse models and patients with acute myocardial infarction, thus emerging as potential biomarkers for cardiovascular diseases (107–111).

CARDIAC ENDOCRINOLOGY: KEY QUESTIONS AND FUTURE DIRECTIONS

Since the original discoveries of ANP/BNP, recent studies of GDF-15 and other possible heart-derived hormones have reinforced the importance of the endocrine function of the heart. Looking back, this probably should not be surprising. The heart is such a vital organ for the survival of an individual organism, that its health and functional status should be closely monitored and signaled to the rest of the body. Moreover, the heart occupies the best “real estate” in the whole circulatory system, and endocrine hormones are effective ways for the heart to communicate with other organs.

The striking similarity among various cardiac-derived endocrine hormones in terms of their biochemical modification, regulation, function, and clinical relevance illustrates the common features

of heart-derived hormones (**Figure 1, Central Illustration**). Among these features, the most important include: 1) their cardiac synthesis, maturation, secretion, and circulating levels are regulated in response to changing external cardiac demand or internal cardiac function (e.g., heart disease); and 2) their biological functions involve coordinating changes of cardiac function and demand—including vasodilation by ANP/BNP to reduce cardiac resistance and inhibition of body size by GDF-15 to mitigate cardiac burden, which are both used to cope with decreasing cardiac function due to disease and help prevent further deterioration of heart health (**Central Illustration**). Such coordination and homeostatic functions may well represent the fundamental biology of heart-derived hormones.

We believe that many additional heart-derived hormones remain to be discovered. The identification of new cardiac hormonal signals and further investigation of their regulation, signaling, function, and clinical significance will continue to provide novel biological insights into the many intricate communication mechanisms between the heart and other organs underlying their "symbiotic" relations. As demonstrated by GDF-15, myostatin, and ANP/BNP, these additional heart-derived hormones will also likely be of significant clinical importance as therapeutic targets or biomarkers of certain disease. We propose that the insights learned from GDF-15, myostatin, and ANP/BNP will guide the discovery and understanding of additional heart-derived hormones. An unbiased systemic screen can identify heart cell–secreted factors that match these common features (**Central Illustration**). Functional studies using approaches such as cardiac cell-specific transgenic/knock-out animal models and parabiosis can further demonstrate their biological significance and endocrine nature. Last, their clinical significance and therapeutic value can be explored based on their biological function and regulatory mechanisms.

Recent single-cell/nucleus transcriptomic analysis has revealed that only a portion of cardiomyocytes or other cardiac cell types synthesize cardiac hormones (27). This raises a few fundamental questions in cardiac endocrinology: are there specific populations of cardiac cells that tend to gain significant hormone synthesizing and secreting capabilities? If so, what are the internal genetic components and external signals that drive their endocrine-like functions? Just as our understanding of insulin is incomplete without studying pancreatic β cells, studies of potential cardiac endocrine cells will significantly enhance our understanding of heart-derived hormones and advance the field of cardiac endocrinology. We think that the fast-developing single-cell multiomics techniques (139–141) will be instrumental in moving the field forward. Single-cell transcriptome analysis will identify cells that show increased expression of hormones, processing enzymes (e.g., PCSK proteins), and even secretory machineries (endoplasmic reticulum, Golgi, and so on) following various stimuli; single-cell epigenome analysis will further discover the regulatory mechanisms and extracellular signals that promote the endocrine function of these cells.

CONCLUSIONS

In summary, historical and recent discoveries revealed the importance of the endocrine function of the heart. Studies of various heart-derived hormones highlighted their shared fundamental features and pointed to a unified endocrine mechanism that the heart uses to communicate with the rest of the body. The answers to many exciting basic and translational questions will further advance the field of cardiac endocrinology.

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