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Hormone treatments in congestive heart failure

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Abstract

The common ultimate pathological feature for all cardiovascular diseases, congestive heart failure (CHF), is now considered as one of the main public health burdens that is associated with grave implications. Neurohormonal systems play a critical role in cardiovascular homeostasis, pathophysiology, and cardiovascular diseases. Hormone treatments such as the newly invented dual-acting drug valsartan/sacubitril are promising candidates for CHF, in addition to the conventional medications encompassing beta receptor blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists. Clinical trials also indicate that in CHF patients with low insulin-like growth factor-1 or low thyroid hormone levels, supplemental treatment with growth hormone or thyroid hormone seems to be cardioprotective; and in CHF patients with volume overload the vasopressin antagonists can relieve the symptoms superior to loop diuretics. Furthermore, a combination of selective glucocorticoid receptor agonist and mineralocorticoid receptor antagonist may be used in patients with diuretic resistance. Finally, the potential cardiovascular efficacy and safety of incretin-based therapies, testosterone or estrogen supplementation needs to be prudently evaluated in large-scale clinical studies. In this review, we briefly discuss the therapeutic effects of several key hormones in CHF.

Keywords

Congestive heart failure, treatment, hormone

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Introduction

The common ultimate pathological feature for all cardiovascular diseases, congestive heart failure (CHF), is now considered as one of the main public health burdens that is associated with grave implications.[1] It is estimated that approximately 5.3 million

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people suffer from CHF (2.5% of adult Americans) and that approximately $60 billion per year is spent on the management of CHF in the US.[2,3] Despite advancements in pharmaceutical treatments and medical devices for CHF, the long-term mortality and morbidity of CHF is still unacceptably high, and the median 5-year survival is below 50%.[4]

Neurohormonal systems play a critical role in cardiovascular homeostasis, pathophysiology, and cardiovascular diseases. A large number of studies have established the crucial role played by the activated sympathetic nervous system in the decompensatory progression of CHF. Meanwhile, sympathetic suppressants, from peripheral beta receptor blockers to central sympatholytics that block sympathetic activation, can mitigate or protect the failing heart.[5] In terms of the parasympathetic nervous system, vagus nerve afferent activation from the periphery can modulate efferent adrenergic and cholinergic neurons centrally and cholinergic neurons exert tonic inhibition of adrenergic neuron activation and of norepinephrine release from nerve terminals.[5] Clinically, vagus nerve stimulation therapy, combined with chronic beta receptor blocker therapy, has been shown to further improve left ventricle (LV) function and reverse remodeling beyond what is achieved with beta receptor blockers alone.[5,6] Furthermore, endothelin-1 (ET-1) is the most abundant isoform of endothelin in the human cardiovascular system and this peptide induces vasoconstriction mainly via the endothelin A receptor.[7] Experimental studies identified ET-1 as a regulator of the interaction between sympathetic neurons and cardiac myocytes that may be of clinical importance.[7] However, nonselective and selective endothelin A receptor antagonists have not yet been approved for use due to lack of effectiveness in clinical trials for CHF.[7]

The renin–angiotensin–aldosterone system (RAAS) was the first neurohormonal system studied in CHF.[8] Overactivation of the RAAS leads to increased cardiac injury and vascular endothelial damage, which predisposes to CHF.[8] In addition to the direct hemodynamic effects, an imbalanced RAAS may cause heart dysfunction through mechanisms including inflammation, oxidative stress, and cardiac remodeling.[8] The crucial finding that blockade of the RAAS significantly improves survival of CHF has formed the basis of current professional guidelines, which uniformly recommend inhibition of RAAS with an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blockers (ARBs), and/or mineralocorticoid receptor antagonists (MRAs) as the standard treatment for CHF.[8]

To date, other hormones such as natriuretic peptides, incretins, growth hormone, vasopressin, glucocorticoids, thyroid hormone, and sex hormones have been intensively studied in an experimental animal model of CHF and in clinical trials. In this review, we briefly discuss the current understanding regarding the therapeutic effects of these key hormones in CHF.

Natriuretic peptides and neprilysin

Natriuretic peptides

Natriuretic peptides (NPs), encompassing atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), have demonstrated beneficial effects in CHF such as vasodilatation via suppressing the sympathetic activity and the RAAS.[9] NPs also promote natriuresis via inhibiting the reabsorption of sodium and water in the distal and proximal nephron.[9] Among the NPs, ANP is synthesized and secreted in the atria in response to distension, BNP is

primarily synthesized and secreted by ventricular myocytes in response to volume overload-induced ventricular stretch, and CNP is synthesized by endothelial cells under the stimulation of acetylcholine, cytokine receptor agonists, or shear stress.[9]

Nesiritide is a recombinant human BNP that has undergone clinical trials in patients with acute decompensated heart failure (ADHF). Nesiritide acutely reduced heart failure symptoms and pulmonary capillary wedge pressure in these patients.[10,11] However, although nesiritide slightly reduced dyspnea, it did not alter mortality or rehospitalization, but significantly increased rates of hypotension in a large randomized controlled trial.[12] One meta-analysis encompassing three randomized controlled trials found that patients receiving nesiritide treatment had a trend toward increased 30-day mortality,[13] but this was not confirmed by a later meta-analysis encompassing seven randomized controlled trials.[14]

Urodilatin, a 32-amino acid peptide that shares a similar structure to ANP, is differentially processed from pro-ANP.[15–17] Secreted by distal renal tubule cells, urodilatin decreases sodium and water reabsorption at the level of the collecting duct.[15,18] Ularitide is a synthesized analogue of human urodilatin. In animal models and clinical trials, ularitide relieved CHF symptoms and preserved renal function.[19] In a phase III clinical study (TRUE-AHF), the ularitide group had greater reductions in systolic blood pressure and in levels of N-terminal pro-BNP than the placebo group.[20] However, short-term treatment did not affect a clinical composite endpoint or reduce long-term cardiovascular mortality.[19,20]

Neprilysin

Neprilysin (NEP) is a neutral endopeptidase mainly expressed in the kidneys.[21] It degrades NPs and other vasoactive peptides such as angiotensin (ANG) II, ET-1, substance P and bradykinin.[21] Consequently, the net physiological effect of NEP depends on the balance of its actions on vasodilators and vasoconstrictors.[21] Valsartan/sacubitril (LCZ696), a combination of a NEP inhibitor (sacubitril) and an ARB (valsartan), is a newly US Food and Drug Administration approved drug for CHF.[22] In comparison with enalapril, the PARADIGM trial showed valsartan/sacubitril reduced cardiovascular mortality and rehospitalization in patients with heart failure with reduced ejection fraction (HFrEF).[22] In patients with heart failure with preserved ejection fraction (HFpEF), valsartan/sacubitril also reduced the N-terminal pro-BNP levels and improved the patients' symptoms.[22] Therefore, in addition to the conventional medications such as ACE inhibitors, ARBs, MRAs, and beta receptor blockers, valsartan/sacubitril is another promising medication for CHF.[22]

Incretins

In a blood glucose-dependent manner, incretins can stimulate the pancreatic secretion of insulin.[23] Therefore, incretin-based therapies are now widely used in patients with diabetes mellitus, such as glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase (DPP)-4 inhibitors.[23] Notably, GLP-1 can act on the heart and vasculature as well, and its receptors are expressed on cardiomyocytes, coronary smooth muscle cells and endothelial cells, and human umbilical vein endothelial cells.[24–27]

Incretin-based therapies exert cardioprotective effects in animal studies.[23] In dogs with pacing-induced dilated cardiomyopathy (DCM), the administration of recombinant GLP-1, GLP-1 (7-36) or GLP-1 (9-36) reduced the plasma levels of norepinephrine, decreased the LV end-diastolic pressure, heart rate (HR), and systemic

vascular resistance, and improved LV function represented by stroke volume (SV), cardiac output (CO), and the LV dP/dt values.[28,29] In rats with spontaneous hypertension, GLP-1 administered for 3 months reduced cardiomyocyte apoptosis, preserved LV contractility, and further improved the survival rates.[30] In pigs with pacing-induced DCM, administration of a DPP-4 inhibitor sitagliptin for 3 weeks also increased SV, reduced HR, and preserved renal function.[31]

In patients with CHF after myocardial infarction (MI) or percutaneous coronary intervention, infusion of GLP-1 improves both the LV ejection fraction (LVEF) and wall motion.[28,32] In a single-center nonrandomized study, infusion of GLP-1 agonist for 5 weeks improved the LVEF, oxygen consumption, 6-min walk test (6MWT) scores, and quality of life in 12 patients with CHF (New York Heart Association [NYHA] class III/IV).[33] However, in a double-blind placebo-controlled trial, infusion of GLP-1 agonist for 48 hours had no significant effect on LV function in 15 patients with CHF (NYHA class II–III and LVEF $< 40\%$).[34] A long duration of GLP-1 agonist infusion might be required to improve heart function.

Compared with these studies, large-scale clinical trials failed to show the cardioprotective roles for GLP-1 agonists and DPP-4 inhibitors beyond glucose regulation. For example, the SAVOR-TIMI 53 study is a randomized trial in patients with a history of, or those at risk of, cardiovascular events.[35] Within 2.1 years of follow-up, saxagliptin did not alter the incidence of cardiovascular events, whereas it increased the rates of CHF hospitalization by 27%.[35] The EXAMINE study, another randomized trial among patients with type 2 diabetes and a recent history of acute coronary syndrome, found that alogliptin had no significant effect on cardiovascular events during 18-months of follow-up.[36] The TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) trial revealed that sitagliptin had neutral effects on cardiovascular risk and CHF hospitalization among older patients with type 2 diabetes and cardiovascular disease.[37] Until other ongoing clinical trials such as the FIGHT (The Functional Impact of GLP-1 for Heart Failure Treatment) and CAROLINA (Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes) studies publish their results, the clinical benefit of incretin-based therapies in CHF will remain unclear.

Growth hormone and ghrelin

Growth hormone

Growth hormone (GH) plays a crucial role for the maintenance of structure and function of normal adult hearts.[38,39] Since the myocardium and vessels secrete insulin-like growth factor-1 (IGF-1)[40–42] and express functional receptors for both GH[43–45] and IGF-1,[46,47] it is speculated that GH could directly act on the cardiovascular system as well as indirectly via the autocrine/paracrine effects of IGF-I. GH/IGF-1 can stimulate cardiac growth and contractility, and regulate vascular tone and peripheral resistance.[48]

In a rat model with ischemic CHF, GH and IGF-I increased SV and CO.[49,50] In patients with CHF due to ischemia or idiopathic DCM, both short-term infusion and chronic therapy of GH improved LVEF, CO, and exercise performance.[51–53] Additionally, GH treatment in patients with CHF promoted endothelial function and nonendothelium-dependent vasodilation,[54] and decreased the levels of circulating cytokines and apoptotic agents.[55] However, in other studies in patients with CHF, although GH treatment significantly increased IGF-1 levels, it did not improve cardiac performance.[56–58] Meanwhile, in a further subgroup analysis with those that had higher serum IGF-I levels in response

to GH treatment, the LVEF was also significantly increased by GH treatment.[59]

Acquired GH resistance may explain these controversial results.[56] An acquired GH-resistant state has been described in CHF, with a typical pattern of high GH levels and low IGF-1 levels.[60] GH levels were increased three-fold in CHF patients with significant weight loss compared with healthy subjects and noncachectic patients; in contrast, IGF-1 levels were reduced, particularly in patients with cachexia.[61] It has been shown that GH infusion produced less cardiovascular beneficial effects in patients with a lower baseline serum IGF-1.[62] In a meta-analysis including 12 clinical trials, beneficial effects of GH treatment on LVEF and exercise parameters correlated with the extent of increased levels of serum IGF-1.[63] Recently, in a randomized, single-blind study, only CHF patients with GH deficiency were selected and treated with GH for 6 months.[64] GH treatment significantly increased peak oxygen uptake, exercise duration, and flow-mediated vasodilation, and improved quality of life.[64] Moreover, GH treatment led to a significant increase in LVEF and a reduction in circulating N-terminal pro-BNP levels.[64] Hence, the benefit of GH treatment in selected CHF patients, especially those with GH deficiency, might be the future direction; however, these findings need further validation in more robust clinical trials.

Ghrelin

Ghrelin, a growth hormone-releasing peptide, is an endogenous ligand of growth hormone secretagogue receptors (GHSRs).[65] The high expression of GHSR1a in the heart and large vessels provides evidence of its cardiac activity, indicating ghrelin is a promising new therapeutic agent for cardiovascular diseases.[66]

In rats with chronic heart failure, ghrelin treatment attenuates the development of LV remodeling and improves LV dysfunction as indicated by the increases in CO and LV fractional shortening.[67] Activation of cardiac sympathetic nervous activity (SNA) and maladaptive remodeling is also manifested in ghrelin-deficient mice with CHF at 2 weeks after MI, accounting for the high mortality, particularly in cases that have been caused directly by HF.[68,69] Chronic treatment with metoprolol or ghrelin, which were associated with cardiac SNA inhibition and a decrease in plasma catecholamine levels, improved heart dysfunction and mortality.[68] In patients with CHF, ghrelin administration significantly decreases systemic vascular resistance and increases the CO and SV.[70,71] Furthermore, intravenous administration of ghrelin (2 μg/kg, twice a day for 3 weeks) significantly improved LVEF from 27% to 31% and increased peak workload and oxygen consumption during exercise, while dramatically decreasing plasma norepinephrine.[72] Taken together, these findings indicate that both exogenous and endogenous ghrelin are crucial in balancing the autonomic nervous system, protecting cardiac function, and improving prognosis in CHF.[73] However, these effects have not been confirmed by large-scale controlled clinical trials.

Vasopressin-receptor antagonists

Arginine vasopressin (AVP) is a neurohypophysial hormone secreted from the posterior pituitary in response to decreased blood pressure and increased plasma osmolality. AVP regulates vascular tone via the nonosmotic AVP V1a receptor on vascular smooth muscle cells, and modulates volume homeostasis via the osmotic AVP V2 receptor on principal cells of the renal collecting duct.[74,75] Further, AVP contributes to cardiac fibrosis and hypertrophy at the later stages of CHF.[74]

Arginine vasopressin V2 receptor selective antagonists, like tolvaptan and lixivaptan, have been studied in animal and human CHF.[76–79] In patients with CHF and preserved renal function, single doses of tolvaptan (30 mg) or furosemide (80 mg) led to a similar urine output.[78] In rats with CHF, tolvaptan dose-dependently increased the concentration of plasma sodium, whereas furosemide almost decreased it.[80] Notably, furosemide increased plasma renin activity and aldosterone concentration, whereas tolvaptan did not, implying that tolvaptan is superior to furosemide in the treatment of CHF with volume overload.[80] In addition, without inducing renal injury, the progression of LV dysfunction was halted by chronic tolvaptan treatment in rats with CHF.[81] In rats with MI, chronic tolvaptan treatment also improved LVEF and reduced MI-induced remodeling such as macrophage infiltration, interstitial fibrosis, and mineralocorticoid receptor (MR) expression in the LV.[82–84] These studies indicated that tolvaptan is cardioprotective for CHF, which may be mediated by the suppression of the RAAS and inflammation.

However, neither short- nor long-term morbidity/mortality has been improved by these agents in large-scale clinical trials. For example, the ACTIV in CHF trial (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure) evaluated the short- and intermediate-term effects of tolvaptan in symptomatic HFrEF patients.[85] Compared with the standard therapy group, the tolvaptan therapy group had a lower body weight and higher net fluid loss.[85] Although it did not affect blood pressure, HR, or electrolytes, tolvaptan did not reduce the exacerbation rate of CHF.[85] The EVEREST trial (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) evaluated the short- and long-term effects of tolvaptan in CHF patients when added to standard therapy within 48 hours of hospitalization.[86] A 60-day tolvaptan treatment period symptomatically improved heart failure without any serious side-effects, but did not improve mortality.[86] The ECLIPSE trial (Effect of Tolvaptan on Hemodynamic Parameters in Subjects with Heart Failure) evaluated the hemodynamic effects of tolvaptan in symptomatic HFrEF patients.[87] Tolvaptan dose-dependently increased urine output and levels of serum sodium without changing blood pressure (BP), HR, pulmonary and systemic vascular resistance, or cardiac index.[87]

To explain the discrepancy between basic studies and clinical trials, as most clinical trials evaluated the effects of AVP antagonists in CHF patients who had been taking diuretics, these results can be confounded. Therefore, head-to-head studies are warranted to directly compare the effects of AVP antagonists with standard diuretics in the clinical setting.

Glucocorticoids and urocortins

Glucocorticoids

Stresses play a significant role in the exacerbation and progression of CHF. Glucocorticoids are the primary hormones in the response to a vast array of stresses. The actions of glucocorticoids are mediated by their glucocorticoid receptors (GR). In certain cells such as cardiomyocytes, the MRs may also be activated by glucocorticoids.[88]

Acute increases in glucocorticoids can enhance cardiomyocyte contractility and promote survival under stresses; whereas sustained high levels of glucocorticoids due to chronic stress or therapeutic intervention could be hazardous to the cardiovascular system through their systemic and local effects.[88] An association between supraphysiological levels of glucocorticoids and the incidence of CHF has been demonstrated in epidemiological studies.[89,90]

Patients who have sustained high levels of glucocorticoids such as those with Cushing's syndrome will develop hypertension and metabolic syndrome, two well recognized risk factors for CHF.[88] Acute glucocorticoid administration in healthy volunteers can reduce heart rate,[91] and chronic use can induce cardiac hypertrophy.[92–95] The local effects of glucocorticoids are mediated by over-activation of cardiomyocyte MR and cardiomyocyte GR, both of which lead to metabolic impairment, and translate into tissue damage, impairment of exercise capacity, and worsening symptoms.[88] Results from transgenic mice suggest that GR signaling in cardiomyocytes is critical for the normal heart function, while MR signaling participates in the development and progression of heart dysfunction.[88] Therefore, a combination of a selective GR agonist and MR antagonist might be a new therapeutic target.

Further, diuretic resistance is very common in CHF and associated with poor outcomes. Recent evidence showed that glucocorticoids may help to overcome diuretic resistance.[96,97] In a study in patients with refractory ADHF, adding prednisone (1 mg/kg per day, maximum dosage of 60 mg/day) to standard treatment doubled daily urine output, and improved CHF symptoms in 80% of patients.[98] In addition, the levels of serum creatinine were reduced in patients who received prednisone whereas unchanged in patients who received standard treatment.[98]

Urocortins

Urocortin 1, 2 and 3 are a group of endogenous peptide hormones belonging to the corticotropin-releasing hormone (CRH) family.[99] The effects of urocortins are mediated by activation of central CRH receptor 1 (CRH-R1) and peripheral CRH-R2.[99] It has been shown that urocortins produce vasodilation and positive inotropic effects, and exert cardioprotective effects against ischemia-reperfusion injury.[99] They can also regulate the sympathetic nervous system and the RAAS.[99] In eight HFrEF patients, an intravenous urocortin 1 infusion was associated with high adrenocorticotropic hormone and cortisol levels and no changes in the levels of ANP or ghrelin, or any significant hemodynamic or renal effects compared with the placebo group.[100] In eight HFrEF patients (six with non-ischemic etiology and two with ischemic cardiomyopathy) who received low and high doses (25 μg and 100 μg) of intravenous urocortin 2, the urocortin group had increases in CO and LVEF that proportionally correlated with urocortin dose, accompanied by a reduction in mean arterial pressure, systemic peripheral resistance, and cardiac work.[101] In a phase II study, administration of urocortin 3 in patients with HFrEF (LVEF $< 35\%$) caused dose-dependent increases in cardiac index and reduction in systemic vascular resistance, without any effects on pulmonary capillary wedge pressure, HR or systolic BP.[102] The above reports suggest that urocortins may be potential therapeutic targets of CHF.

Testosterone and estrogen

Testosterone supplementation

Low testosterone levels are common in men with CHF and are an independent risk predictor for decreased exercise capacity and poor prognosis in these patients.[103–105] Furthermore, intravenous testosterone administration in patients with CHF acutely reduces peripheral vascular resistance and increases CO.[106] A meta-analysis revealed that in patients with HFrEF, testosterone supplementation for 12–52 weeks was associated with an increase of exercise capacity represented by 6MWT;[107] although the sample size was modest and the routes of

testosterone administration were different.[108–111] This degree of improvement is greater than that seen with other therapies that are currently used for morbidity and mortality reduction in patients with CHF such as ACE inhibitors, beta receptor blockers, and cardiac resynchronization therapy.[112–114] Furthermore, there was an improvement in NYHA functional class; 35% of patients in the testosterone group (versus 10% in the placebo group) had an improvement of at least 1 class.[107] However, this improvement occurred in the absence of cardiac structure or functional change on echocardiography; hence the improvement in exercise capacity was likely achieved via peripheral mechanisms.[115] Nevertheless, testosterone therapy can cause water and salt retention and pose a potential safety concern. The TOM (Testosterone in Older Men with Mobility Limitations) trial was discontinued early due to significantly higher cardiovascular events in the testosterone group.[116]

Hormone replacement treatment

Several large-scale clinical trials have been conducted in examining the effects of postmenopausal hormone replacement treatment (HRT) on cardiovascular health. For example, in a primary prevention trial with 16 608 women and a mean of 5.2 years follow-up, HRT did not reduce the incidence of stroke, coronary heart disease (CHD), and pulmonary embolism.[117] In a secondary prevention clinical trial in women with CHD, HRT did not decrease the cardiovascular events.[118] However, recent studies proposed a timing-related benefit of HRT on CHD. When HRT was initiated in younger women (<60 years) and at an earlier stage of menopause (<10 years after onset), it reduced the total mortality and cardiovascular events; but when HRT was initiated in older women (>60 years) or at a later stage of menopause (>10 years after onset), it had no effect or a possible adverse effect on these endpoints.[119–121] A large meta-analysis including 23 randomized controlled clinical trials and 39 000 women confirmed a 32% reduction of CHD incidence in women initiating HRT before 60 years of age and <10 years after menopause.[122] This risk reduction was lost in women older than 60 years of age or in those for whom HRT was initiated > 10 years after the menopause.[122] These results support the timing-related benefit hypothesis.[123] Although none of these clinical trials examined the impact of HRT on heart function or dysfunction, its involvement is nearly certain as ischemia precedes both diastolic and systolic CHF.

Thyroid Hormones

Many critical cardiovascular functions such as heart contraction, relaxation, and coronary blood flow are regulated by thyroid hormones.[124] The proper balance of thyroid hormones is necessary to maintain cardiovascular homeostasis, as both hyperthyroidism and hypothyroidism result in pathological cardiac conditions.[125]

A large body of evidence suggests an increase of cardiovascular events with borderline low thyroid hormones conditions such as subclinical hypothyroidism,[126–130] which were improved after thyroid hormone treatment.[129–132] In fact, recent studies in CHF patients have also shown an increased mortality with low thyroid function.[133–135] However, this association is controversial, as one meta-analysis did not reveal a link[136] and two others did.[137,138] Moreover, no studies have examined the effects of thyroid hormone treatment on mortality in CHF patients.

Notably, the high incidence of borderline low thyroid hormone conditions implies that nearly half of CHF patients could suffer from this condition.[128] Animal

Table 1. Overview of hormone therapeutics in patients with congestive heart failure (CHF).

Hormones	Mechanism of action	Hemodynamic effects	Clinical outcomes	Other notes
Natriuretic peptides	Natriuresis; vasodilatation; suppressing the sympathetic activity and the RAAS[9]	Reduced pulmonary capillary wedge pressure; improved heart failure symptoms[10,11]	Did not alter mortality or rehospitalization[12]	
Neprilysin inhibitor	Neprilysin degrades natriuretic peptides and other vasoactive peptides[21]	Reduced N-terminal pro-BNP levels; improved symptoms[22]	Reduced cardiovascular mortality and rehospitalization[22]	
Incretin-based therapies (GLP-1 receptor agonists and DPP-4 inhibitors)	Incretin acts on receptors of the heart and vasculature[23–26]	Decreased systemic vascular resistance; improved LV function[28,29]	Neutral or increased the rates of CHF hospitalization[35–37]	
Growth hormone	Acts on receptors of the heart and vasculature[43–47]	Promoted cardiac growth and contractility; regulate vascular tone and peripheral resistance[48]	Unknown	Better effects of GH treatment on LV function in selected CHF patients with GH deficiency[63,64]
Ghrelin	Receptors in the heart and large vessel; SNA inhibition[66]	Increased the cardiac output[71,72]	Unknown	
Vasopressin receptor antagonists	Vasopressin modulates volume homeostasis; regulates vascular tone[74,75]	Preserved renal function; increased urine output[76–81]	Not improve in short- nor long-term morbidity/mortality[85–87]	
Glucocorticoids	Via glucocorticoid receptors[88]	Promoted cardiomyocytes contractility; induced cardiac hypertrophy[88]	Cardiovascular hazardous[88–90]	Overcome diuretic resistance[96–98]
Urocortins	Activation of central CRH receptors; regulates the SNA and the RAAS[99]	Vasodilation and positive inotropic effects[99,101,102]	Unknown	
Testosterone supplementation	No improvement in cardiac function or structure; via peripheral indirect mechanisms[115]	Reduced peripheral vascular resistance; increased cardiac output[106]	Higher cardiovascular events[116]	

(continued)

Table 1. Continued

Hormones	Mechanism of action	Hemodynamic effects	Clinical outcomes	Other notes
Estrogen replacement	Via receptors in cardiovascular systems	Unclear	Reduced the total mortality and cardiovascular events when initiated in younger women (<60 years) and earlier stage of menopause (<10 years); possible adverse effect when initiated in older women (>60 years) or later stage of menopause (>10 years)[119–123]	
Thyroid hormones	Via thyroid hormone receptors[124]	Improvement of LV function[139,141]	Unknown	

RAAS, renin–angiotensin-–aldosterone system; BNP, brain natriuretic peptide; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; LV, left ventricle; GH, growth hormone; SNA, sympathetic nervous activity; CRH, corticotropin releasing hormone.

experiments in CHF have indicated that low cardiac tissue triiodothyronine (T3) levels may be present even in the background of normal serum thyroid hormones.[139,140] The restoration of cardiac tissue T3 levels was associated with an improvement of LV function in rats.[139,141] However, the doses of thyroid hormone treatment needed to fully restore cardiac tissue T3 levels and improve LV function resulted in higher than normal levels of serum thyroid hormone.[141] The actual incidence of low cardiac tissue T3 levels in CHF patients remains unknown.

Future directions

Other hormones have been studied in patients with CHF that might point to future directions. For example, serelaxin is the recombinant form of human relaxin-2, a naturally occurring peptide hormone that mediates systemic hemodynamic and renal adaptive changes during pregnancy.[142] In the RELAX-AHF study, serelaxin was found to significantly improve symptoms and signs of ADHF, prevent in-hospital worsening heart failure, as well as significantly improve 180-day cardiovascular and all-cause mortality after a 48-hour infusion commenced within 16 hours of presentation.[142] Sodium-glucose cotransporter-2 (SGLT2) is a protein that facilitates glucose reabsorption in the kidney.[143] SGLT2 inhibition can promote natriuresis and osmotic diuresis, leading to plasma volume contraction and reduced preload, and decreases in blood pressure, arterial stiffness, and afterload, thereby improving sub-endocardial blood flow in patients with CHF.[143] The EMPA-REG OUTCOME trial demonstrated that empagliflozin significantly reduced mortality and heart failure (HF) hospitalization risk in patients with type 2

diabetes.[144] The CANVAS trial subsequently reported that canagliflozin treatment reduced major adverse cardiovascular events and HF hospitalization risk in patients with type 2 diabetes using insulin.[145] The mechanisms responsible for the cardioprotective effects of SGLT2 inhibitors remain incompletely understood.[143] Large clinical trials with SGLT2 inhibitors are now investigating the potential use of SGLT2 inhibition in patients who have HF with and without type 2 diabetes.

In addition, HFpEF is a form of CHF where the patients presenting with HF have a normal LV ejection fraction. Although approximately 50% of patients with HF have HFpEF, there is still very little evidence regarding hormone treatments for HFpEF.[146] The findings of some recent studies are highlighted here. Serelaxin was well tolerated and effective in relieving dyspnea and had a similar effect on short- and long-term outcomes, including survival improvement in ADHF patients with HFpEF compared with those with HFrEF.[147] Treatment with a selective endothelin receptor A antagonist in HFpEF patients increased exercise tolerance but did not improve any of the secondary end-points such as LV mass or diastolic function.[148] In patients with pulmonary hypertension and HFpEF, endothelin receptor blockade may have no beneficial effects and could even be detrimental in comparison with a placebo.[149] On the other hand, in high-risk patients with HFpEF, a strategy of N-terminal pro-BNP-guided therapy (target to less than 1000 pg/ml) was not more effective than the usual care strategy in improving outcomes.[150]

Conclusion

The prevalence of CHF has increased in the past several decades. Despite considerable advances and innovations in both medications and medical devices, the prognosis of CHF remains very poor. There is an unmet need to develop alternative or additional treatment modalities. Hormonal imbalance is a key finding and common feature in CHF, such as the over-activated RAAS, which translates into progression of the underlying disease, development of cardiovascular comorbidities, and increases in major adverse cardiovascular events. Hormonal modulation is therefore an important therapeutic strategy for CHF.

An overview of hormone therapeutics in patients with CHF is summarized in Table 1.[9–12,21–26,28,29,35–37,43–48,63,64,66,71,72,74–81,85–90,96–99,101,102,106,115,116,119–124,139,141]

Among the discussed hormones in this review, neprilysin inhibitor is a promising drug candidate for the treatment of CHF on the top of current conventional medications. Secondly, by using an approach in the selection of CHF patients with low IGF-1 levels or low thyroid hormone levels, supplemental treatment with GH or thyroid hormone seems to be reasonable and cardioprotective. Nonetheless, there have been no clinical trials examining the long-term effects of GH or thyroid hormone treatment on cardiovascular mortality in CHF patients. Moreover, in the clinical settings of CHF with volume overload or edematous status, the AVP antagonists can relieve the symptoms without sympathetic system or the RAAS activation superior to loop diuretics. A combination of selective GR agonist and MR antagonist may represent an improved approach for glucocorticoids in the treatment of CHF, specifically in patients with diuretic resistance. Finally, the potential cardiovascular efficacy and safety of incretin-based therapies, testosterone supplementation, or HRT needs to be prudently evaluated in large-scale clinical studies.

Declaration of conflicting interests

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