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Recent Advances in Pharmacotherapy for Heart Failure: Future Directions

[1]Pitchai Balakumar and [2]Manjeet Singh
[1]Department of Pharmaceutical Sciences and Drug Research, Punjabi University
Patiala, Punjab, India
[2]I.S.F. Institute of Pharmaceutical Sciences and Drug Research
Moga, Punjab, India

Abstract: Heart failure is a significant clinical challenge associated with high morbidity, mortality and economic burden in developing countries and the prevalence of chronic heart failure is continuously increasing. Heart failure is characterized by exercise intolerance, fatigability, dyspnea and volume retention occurring as a consequence of myocardial dysfunction. The drug therapies employed to treat heart failure like diuretics, vasodilators and inotropics have improved functional status of heart; but not decreasing long-term mortality. Recognition of neurohormones as important substances in the pathogenesis of heart failure has resulted in several treatment modalities including Angiotensin Converting Enzyme (ACE) inhibitors and β blockers that yield improvements of heart failure patients. But, heart failure is still a progressive disease with high morbidity and mortality. It suggests that vital pathogenic mechanisms remain active and unchanged by the present therapeutic strategies. Therefore, the need of new effective treatments for heart failure is mandatory. In this article, we review potential therapies insighted from recent studies of therapeutic interventions which may play as future drugs for heart failure.

Key words: Emerging drug therapies, novel target sites, heart failure

INTRODUCTION

Heart failure is a major clinical problem associated with high morbidity and mortality in industrialized nations (Miller and Missov, 2001). Heart failure is a condition in which cardiac muscles become weak and fail to pump blood efficiently to meet the metabolic requirements of body. It is a complex neurohumoral and inflammatory syndrome (Balakumar and Singh, 2005, 2006). The drugs like diuretics, vasodilators, inotropic agents, Angiotensin Converting Enzyme (ACE) inhibitors and β adrenoceptor blockers have been presently employed to improve functional status of heart failure (Eichhorn, 1998; Murray and Dugan, 2000). In spite of effective drugs available to treat heart failure, it is still a progressive syndrome with high morbidity and mortality (Balakumar and Singh, 2006). Various pharmacological target sites have been identified and implicated in pathogenesis of heart failure.

Angiotensin-II AT_1 Receptor Blockers

Angiotensin-II AT_1 Receptor Blockers (ARB_s) have been developed to block RAAS more completely and they are less prone to produce dry cough and angioedema as compared to ACE inhibitors (Papademetriou and Dunlap, 2003). The candisartan has been shown to improve diastolic dysfunction and reduce progression of cardiac remodeling (Wake *et al*., 2005). Olmesartan has been reported to produce cardioprotection by suppressing inflammatory cytokines (Yuan *et al*., 2005). The clinical trials such as ELITE (Evaluation of Losartan In The Elderly), CHARM (Candisartan in Heart

Corresponding Author: Dr. Pitchai Balakumar, Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala- 147002 India Tel: +91-9815557265 Fax: +91-175-2283073

failure Assessment of Reduction in Mortality and Morbidity) and Val-HeFT (Valsartan-Heart Failure Trial) have demonstrated that ARBs are better alternative agents for heart failure in patients who are unable to tolerate ACE inhibitors (Pitt *et al*., 1997, 2000; Granger *et al*., 2003; McMurray *et al*., 2003; Yusuf *et al*., 2003). Moreover, combination of ARBs with either ACE inhibitors or β-blockers may be beneficial; but triple therapy with combination of ARBs, ACE inhibitors and β blockers is harmful due to excessive neurohormonal blockade (Cohn and Tognoni, 2001; Granger *et al*., 2003; McMurray *et al*., 2003; Yusuf *et al*., 2003; Bhakta and Dunlap, 2004).

Arginine Vasopressin Receptor Antagonists

Arginine Vasopressin (AVP) acts on V_2 receptor and stimulates biosynthesis of aquoporin-2 (AQ_2), a water channel protein which is involved in free water reabsorbtion (Nielsen *et al*., 1999). Administration of OPC-31260, a V_2 receptor antagonist, has been shown to produce diuresis by mechanistically attenuating upregulation of AQ_2 water channels (Xu *et al*., 1997). In contrast to a loop diuretic such as furosemide, the OPC-31260 has been shown to stimulate free water excretion with little or no sodium loss (Ohnishi *et al*., 1995). Tolvaptan (OPC-41061), a synthetic analogue of OPC-31260 has produced diuresis and reduced oedema, dyspnea and jugular venous pressure (Udelson *et al*., 2002). The clinical trial named ACTIVE in CHF study (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure) has suggested that tolvaptan relieves systemic congestion in patients of heart failure (Cleland *et al*., 2004; Gheorghiade *et al*., 2004). AVP increases systemic vascular resistance, venous pressure, Pulmonary Capillary Wedge Pressure (PCWP) and left ventricular filling pressure and produces cardiac remodeling through V_{1a} receptor (Goldsmith, 1987; Walker *et al*., 1988; Fujisawa and Lijima, 1999; Goldsmith and Gheorghiade, 2005). Conivaptan (YM-087), a dnal V_{1a}/ V_2 receptor antagonist has been shown to inhibit pressor response and stimulate aquaresis in rats and dogs (Tahara *et al*., 1997; Yatsu *et al*., 1997). In patients with severe symptomatic heart failure, conivaptan has significantly reduced both PCWP and right atrial pressure (Udelson *et al*., 2001). In summary, AVP antagonists may be useful in treatment of patients with volume-overload heart failure. AVP antagonists appear to produce effective reduction in congestion without worsening renal function (Lee *et al*., 2003; Sanghi *et al*., 2005; Costello-Boerrigter *et al*., 2006).

Aldosterone Receptor Antagonists

The use of aldosterone antagonists is emerging as an attractive treatment for patients with severe heart failure (Coca and Perazella, 2005; Dieterich *et al*., 2005; Kamath *et al*., 2005; Tang *et al*., 2005). The spironolactone has inhibited fibrosis by decreasing procollagen (type III). Further spironolactone has reduced hospitalizations and increased survival rate (30%) in RALES study (Randomized ALdactone Evaluation Study) (Pitt *et al*., 1999; Zannad *et al*., 2001). In EPHESUS study (Eplerenone Neurohormonal Efficacy and Survival study), eplerenone, an aldosterone receptor antagonist has reduced mortality, sudden death and duration of hospitalizations due to heart failure (Pitt *et al*., 2003). Moreover, spironolactone and eplerenone are life saving agents in patients with advanced heart failure (Marcy and Ripley, 2006).

Natriuretic Peptides

The family of natriuretic peptides consists of 3 isoforms including Atrial Natriuretic Peptide (ANP), Brain Natriuretic Peptide (BNP) and C-type Natriuretic Peptide (CNP) (Struthers, 1994). ANP and BNP are circulating peptides produced principally by right atrium and ventricles, respectively where as CNP is produced by endothelial cells (Chen and Burnett, 1999). The BNP is documented to produce natriuresis, diuresis, vasodilation and decrease the activation of RAAS and sympathetic nervous system (Bhalla and Maisel, 2004; Richards *et al*., 2006; Strunk *et al*., 2006;

Tsutamoto *et al*., 2006). Nesiritide is a recombinant form of human BNP (Richards *et al*., 2006; Strunk *et al*., 2006). In PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with DobutaminE or NaTrecor) trial, infusion of nesiritide reduces PCWP and peripheral vascular resistance in patients with decompensated heart failure (Mills *et al*., 1999). The major problems with natriuretic peptides are their peptidic nature and short half-life (Corti *et al*., 2001).

Neutral Endopeptidase Inhibitors

Natriuretic peptides are degraded in body by enzyme known as Neutral Endopeptidase (NEP) (Ronco *et al*., 1988; Corti *et al*., 2001). Hence agents that inhibit NEP and consequently block the metabolism of endogenously generated natriuretic peptides are developed. Candoxatril and ecadotril are highly specific inhibitors of NEP which have been noted to prevent the degradation of natriuretic peptides and thus increase their biological activity (Corti *et al*., 2001). The candoxatrilat is an active metabolite of candoxatril and has produced diuresis and natriuresis in patients of heart failure (Northridge *et al*., 1999). Further, it produced vasoconstriction rather than vasodilation in some subjects (Ferro *et al*., 1998) which is still controversial. The ecadotril (sinorphan) has decreased PCWP (Kahn *et al*., 1990) and it has been noted to produce severe pancytopenia and death in patients of heart failure (Cleland and Swedberg, 1998). Hence the development of NEP inhibitors has been discouraged.

Vasopeptidase Inhibitors

Vasopeptidase inhibitors have combined effect of Neutral Endopeptidase (NEP) and Angiotensin Converting Enzyme (ACE) inhibition and have produced vasodilation, diuresis and enhancement of myocardial function (Corti *et al*., 2001). Omapatrilat, sampatrilat, fasidotrilat, MDL 100 240, Z13752A, BMS 189921 and mixanpril are vasopeptidase inhibitors which have been developed for treatment of heart failure (Basuray, 2003). The inhibition of vasopeptidase with omapatrilat has improved cardiac geometry (Trippodo *et al*., 1995). The omapatrilat is superior to ACE inhibitors to increase glomerular filtration rate, sodium excretion and decrease PCWP (Chen *et al*., 2001; Abassi *et al*., 2005). The OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) trial has demonstrated that omapatrilat improves ventricular function in patients of heart failure (Solomon *et al*., 2005).

Endothelin Receptor Antagonists

Plasma concentration of endothelin-1 (ET-1) is elevated in patients with heart failure (McMurray *et al*., 1992). ET-1 produces vasoconstriction, cardiac remodeling through ET_A receptors and induces vasodilation through ET_B receptors by generating nitric oxide and prostacyclin (Haynes and Webb, 1993; Verhaar *et al*., 1998). FR 139317, a selective ET_A receptor antagonist has decreased cardiac pressures and increased cardiac output, glomerular filtration rate and renal blood flow. On the other hand, RES-701-1, a selective ET_B receptor antagonist has increased cardiac pressures and decreased cardiac output as well as renal blood flow (Ohnishi *et al*., 1998). Thus, blockade of ET_B receptors may not be useful in heart failure (Cowburn *et al*., 2005). Infusion of bosentan, a nonselective ET_A/ET_B receptor antagonist did not demonstrate any improvement in heart failure (Packer *et al*., 1998). Further, RITZ-4 (Randomized Intravenous TeZosentan study) trial has investigated tezosentan, a non-selective ET_A/ET_B receptor antagonist and it is reported not to improve functional status of patients with heart failure. Moreover, RITZ-4 study has reported that tezosentan has produced proischemic effect in patients with decompensated heart failure and acute coronary syndrome (O'Connor *et al*., 2003). Thus, non-selective ET_A/ET_B receptor antagonists are ineffective in heart failure and thereby selective ET_A receptor antagonists are evaluated clinically because activation of ET_B receptors produce nitric oxide mediated vasodilation. The darusentan, a selective ET_A receptor antagonist has not improved symptoms of heart failure and it has increased the mortality (Luscher *et al*., 2002). The earlier pre-clinical studies with endothelin receptor antagonists gave promising result; but recent clinical trials have not substantiated them.

DA_2-α_2 Receptor Dual Agonist

The nolomirole has been shown to have selective dopamine2-alpha2 (DA_2-α_2) receptor agonistic property. Treatment with nolomirole inhibits catecholamine release from sympathetic nerve endings (Masson *et al*., 2001) and inhibits the release of tumor necrosis factor-alpha (TNF-α) to improve ventricular function (Rossoni *et al*., 2003). Nolomirole significantly reduces cardiac hypertrophy, attenuates signs and symptoms of monocrotaline-induced heart failure (Pasini *et al*., 2004).

Dopamine β-Hydroxylase Inhibitor

Dopamine β-hydroxylase (DBH) catalyses the conversion of dopamine (DA) to norepinephrine (NE) in sympathetic nerves. Nepicastat is a DBH inhibitor which has been reported to reduce norepinephrine synthesis. Nepicastat has attenuated ventricular remodeling and prevented systolic dysfunction (Sabbah *et al*., 2000). Moreover, inhibition of DBH may augment the levels of DA that act via dopamine receptors to produce renal vasodilation.

Adenosine Receptor Antagonists

Adenosine constricts glomerular afferent arterioles by activating A_1 receptors and thereby decrease Glomerular Filtration Rate (GFR). Adenosine induces sodium reabsorbtion via A_1 receptors (Gottlieb *et al*., 2002; Doggrell, 2005). BG 9928, a selective A_1 receptor antagonist has increased GFR, urine flow and sodium excretion (Ticho *et al*., 2003).

Positive Inotropic Agents

Levosimendan is inotropic and vasodilator agent which has been developed to treat heart failure (Perrone and Kaplinsky, 2005). The inotropic effect of levosimendan is due to calcium sensitizing action and vasodilatory effect is mediated by opening ATP-sensitive potassium channels (Nicklas *et al*., 1999; Nieminen *et al*., 2000; Perrone and Kaplinsky, 2005). Levosimendan has produced positive inotropic effect, vasodilation and reduced dyspnea and fatigue in patients with severe heart failure (Nieminen *et al*., 2000; McLean *et al*., 2005). In LIDO (Levosimendan Infusion versus DObutamine) trial, levosimendan has reduced PCWP and mortality (Follath *et al*., 2002). Pimobendan has calcium sensitizing effect with PDE-III inhibition and it has been noted to improve hemodynamics and exercise tolerance in patients of heart failure (Watanabe *et al*., 2003). Xanthine Oxidase Inhibitors (XOIs) are shown to reduce mechanoenergetic uncoupling in failing heart (Minhas *et al*., 2006). Oxypurinol, the active metabolite of allopurinol and potent XOI, has been demonstrated to improve cardiac performances in heart failure (Hajjar and Leopold, 2006). Oxypurinol has positive inotropic effect and it ameliorates endothelial dysfunction in patients with heart failure (Freudenberger *et al*., 2004).

Inhibitors of pFOX and CPT-1

Ranolazine, an inhibitor of partial fatty acid oxidation (pFOX), suppresses oxidation of fatty acids and improves mechanical efficiency and ventricular function in heart failure (Chandler *et al*., 2002) and it has been recently approved by FDA. Increase in glucose oxidation can also be obtained by etoxomir, an inhibitor of Carnitine Palmitoyl Transferase-1 (CPT-1). The etoxomir reverses fetal gene expression, preserves cardiac function and prevents ventricular dilation (Turcani and Rupp, 1999). Etoxomir has improved ventricular function and reduced PCWP in patients with heart failure (Schmidt-Schweda and Holubarsch, 2000). Oxfenicine is another inhibitor of carnitine palmitoyl transferase-I and it has prevented ventricular remodeling in heart failure (Lionetti *et al*., 2005).

Novel Target Sites for Heart Failure

Recently, we have shown that inhibition of Rho-kinase (Balakumar and Singh, 2006a), poly (ADP-ribose) polymerase (Balakumar and Singh, 2006b, c) and caspase-3 (Balakumar and Singh,

2006d) prevent remodeling and improve the left ventricular function in rats subjected to pressure overload induced by partial aortic constriction. Treatment with SB207266, a $5HT_4$ receptor antagonist has been noted to improve cardiac function in heart failure rats, suggesting a possible beneficial effect of 5-HT_4 receptor antagonist in heart failure (Birkeland *et al*., 2006). The enhanced expression of Matrix Metalloproteinases (MMPs) trigger cardiac remodeling and inhibition of MMPs prevents ventricular dysfunction and progression of heart failure (Lindsay and Lee, 2000; Jugdutt, 2003; Moshal *et al*., 2005). Batimastat, ilomastat, marimastat and prinomastat are inhibitors of MMP which have been developed for heart failure. PG-53072, a selective inhibitor of MMP has attenuated left ventricular dysfunction and cardiac remodeling in experimental heart failure (Morita *et al*., 2006). Celacade™ is an immune modulator which has prevented chronic inflammation and apoptotic cell death by activating IL-10 mediated anti-inflammatory process. A clinical trial of Celacade™ has been shown to improve the symptoms of heart failure (Torre-Amione *et al*., 2005). Recently, a phase II clinical trial of celacade™ has been shown to reduce the risk of death and hospitalization due to chronic heart failure (Torre-Amione *et al*., 2004).

CONCLUSIONS

Despite the fact that major advances in lifesaving treatment have been made; our ability to recognize and optimally treat heart failure is limited. Novel emerging pharmacotherapy such as aldosterone receptor antagonists, AVP receptor antagonists, natriuretic peptides, vasopeptidase inhibitors, adenosine A_1 receptor antagonists, xanthine oxidase inhibitors, pFOX inhibitors, MMP inhibitors and immune modulation therapy like celacade may be prospective candidates in future for heart failure. Further advances in understanding of pathophysiology of heart failure will probably help to identify novel therapeutic agents for patients with poor prognosis of heart failure.

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