Recent Advances in Pharmacotherapy for Heart Failure: Future Directions

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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, fatigue, dyspnea and volume retention occurring as a consequence of myocardial dysfunction. The drug therapies employed to treat heart failure like diuretics, vasodilators and inotropes have been shown to 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 inspired 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 Missow, 2001). Heart failure is a condition in which cardiac muscles become weak and fail to pump blood efficiently to meet the metabolic requirements of the 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-adrenergic receptor 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 AT1, Receptor Blockers

Angiotensin-II AT1, Receptor Blockers (ARB1) 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 Duraiswami, 2003). The candesartan 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 (Candesartan in Heart
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; Biakha and Dunlap, 2004).

**Arginine Vasopressin Receptor Antagonists**

Arginine Vasopressin (AVP) acts on V2 receptor and stimulates biosynthesis of aquaporin-2 (AQ2), a water channel protein which is involved in free water reabsorption (Nielsen et al., 1999). Administration of OPC-31260, a V2 receptor antagonist, has been shown to produce diuresis by mechanistically attenuating upregulation of AQ2 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 (Ohrishi 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; Gheorghide 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 V1a receptor (Goldsmith, 1987; Walker et al., 1988; Fujisawa and Ilijima, 1999; Goldsmith and Gheorghide, 2005). Conivaptan (YM-087), a dual V1a/ V2 receptor antagonist has been shown to inhibit pressor response and stimulate aquarexis 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 Parazzolla, 2005; Dieterich et al., 2005; Kallath 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 (Marchy 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 (Bhatta 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 NaTreron) 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 peptide nature and short half-life (Corti et al., 2001).

Neutral Endopeptidase Inhibitors

Natriuretic peptides are degraded by body 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. Candesartan and ecazutril 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 candesartan is an active metabolite of candesartan 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 ecazutril (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, lampratril, fasidranil, 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 (McMurry et al., 1992). ET-1 produces vasoconstriction, cardiac remodeling through ET_{\alpha} receptors and induces vasodilation through ET_{\beta} receptors by generating nitric oxide and prostacyclin (Haynes and Webb, 1993; Verhaar et al., 1998). FR 139317, a selective ET_{\alpha} 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_{\beta} receptor antagonist has increased cardiac pressures and decreased cardiac output as well as renal blood flow (Ohnishi et al., 1998). Thus, blockade of ET_{\beta} receptors may not be useful in heart failure (Cowburn et al., 2005). Infusion of bosentan, a nonselective ET_{\alpha}/ET_{\beta} 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_{\alpha}/ET_{\beta} 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_{\alpha}/ET_{\beta} receptor antagonists are ineffective in heart failure and thereby selective ET_{\alpha} receptor antagonists are evaluated clinically because activation of ET_{\beta} receptors produce nitric oxide mediated vasodilation. The darusentan, a selective ET_{\alpha}, 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.
DA₂-α Receptor Dual Agonist

The nolomirole has been shown to have selective dopamine2-alpha2 (DA₂-α₂) 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 noradrenaline (NE) in sympathetic nerves. Nefinastat is a DBH inhibitor which has been reported to reduce noradrenaline synthesis. Nefinastat 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 A₁ receptors and thereby decrease Glomerular Filtration Rate (GFR). Adenosine induces sodium reabsorption via A1 receptors (Gottlieb et al., 2002; Doggett, 2005). BG 9928, a selective A₁ receptor antagonist has increased GFR, urine flow and sodium excretion (Tricke et al., 2003).

Positive Inotropic Agents

Levosimendan is inotropic and vasodilator agent which has been developed to treat heart failure (Perrone and Kaplan, 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 Kaplan, 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 mechanocnertic uncoupling in failing heart (Minhas et al., 2006). Allopurinol, the active metabolite of allopurinol and potent XO, has been demonstrated to improve cardiac performances in heart failure (Hajjar and Lepoldt, 2006). Allopurinol 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 (Chand et al., 2002) and it has been recently approved by FDA. Increase in glucose oxidation can also be obtained by etomoxir, an inhibitor of Carnitine Palmitoyl Transferase-1 (CPT-1). The etomoxir reverses fetal gene expression, preserves cardiac function and prevents ventricular dilation (Turceni and Rupp, 1999). Etomoxir has improved ventricular function and reduced PCWP in patients with heart failure (Schmidt-Schweda and Holmursch, 2000). Oxifenicine is another inhibitor of carnitine palmitoyl transferase-1 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 5HT4 receptor antagonist has been noted to improve cardiac function in heart failure rats, suggesting a possible beneficial effect of 5-HT, 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; Juddt, 2003; Moshal et al., 2005). Bimatrop, ilonastat, 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). Celadate 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 Celadate has been shown to improve the symptoms of heart failure (Torre-Amione et al., 2005). Recently, a phase II clinical trial of celadate 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 pharmacotheraphy such as aldosterone receptor antagonists, AVP receptor antagonists, natriuretic peptides, vasopeptidase inhibitors, adenosine A1 receptor antagonists, xanthine oxidase inhibitors, pFOX inhibitors, MMP inhibitors and immune modulation therapy like celadate 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.

REFERENCES


