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Cytokines in chronic heart failure: possible involvement in the neurohormonal and the cytokine systems at the cAMP level?



Abstract

In recent years, the pathophysiological concept of chronic heart failure (CHF) has changed from an isolated hemodynamic view to a more complex concept involving neuroendocrine and inflammatory pathways. New therapeutic strategies, such as b-blocker therapy, are based on these new concepts and provide clinical evidence for a clinical benefit in patients with CHF. The survival benefit of b-blocker therapy in CHF has been related to neurohumoral regulation. Thus, evidence evolved showing that following b-blocker therapy cytokine levels in CHF patients are altered. We have shown that the levels of soluble TNF receptor type 2 correlated well with cAMP in leukocytes. Data from clinical studies in adult and infant CHF patients have demonstrated that b-blocker therapy is accompanied by altered cytokine, cytokine antagonist, and/or soluble cytokine receptor levels. These alterations may result from a dysregulated interaction of b-adrenergic pathways and the cytokine system, and are possibly related to cAMP-dependent regulation of the release or shedding of these mediators.

Full text

Introduction

In recent years the pathophysiological concept of chronic heart failure (CHF) has changed from the hemodynamic view to more complex concepts involving neuroendocrine and inflammatory pathways. Early during the development of heart failure, cytokines may act protectively in response to myocardial stress, and provide a stimulus for heart cell growth, while during the development of chronic heart failure, cytokines may become deleterious. It has been suggested that, in addition to increased neurohormonal activity in CHF patients, proinflammatory cytokines may be involved in impaired cardiac function. Cytokine plasma levels, in particular interleukin-6 (IL-6) and tumor necrosis factor- α (TNF), are of diagnostic and prognostic value in CHF. More recently, soluble TNF receptors (sTNF-R) have been identified as strong predictors of increased mortality in CHF patients, with sTNF-R1 being the strongest parameter [1]. There is growing evidence that some of the beneficial effects of β -blocker therapy in CHF may result from their impact on the cytokine network. This overview summarizes present data from clinical studies related to cytokine production in adult, β -blocker-treated CHF patients and in β -blocker-treated infants with congenital heart disease. These studies indicate that - despite the differences in terms of etiology of CHF, and age of these patients - β -blocker therapy is accompanied by a lower expression of distinct circulating cytokines in treated patients. We suggest that cAMP may be involved in the regulation of this cytokine expression.

Role of cytokines in developing heart failure

Although several cytokines appear to be involved in CHF, particular interest has been directed towards the role of TNF in CHF. Thus, it has been shown *in vitro* that IL-1 and TNF may be involved in cardiovascular disease by reducing the contractility of the vessel wall or myocardial cells. In animals, TNF causes dilatation and remodelling of the left ventricle, and transgenic mice over-expressing TNF develop left ventricular dilatation and dysfunction. Despite this paradigm of TNF being harmful, some studies have revealed that TNF has a protective, inotropic action on the failing heart by stimulating the production of heat shock proteins, which enables the cells to resist transient stress, for example ischemia. Furthermore, injection of TNF improves survival of TNF^{-/-} knockout mice infected with encephalomyocarditis virus, in a dose-dependent manner, by increasing viral clearance. Further interest has been focused on IL-6 in CHF. IL-6 may exert endocrine effects such as a decrease of left ventricular contractility by nitric oxide production. The IL-6/IL-6 receptor complex, including gp-130, may play an important role in ventricular hypertrophy and ventricular remodeling. IL-6 is produced not only in leukocytes, but also in endothelial cells, vascular smooth muscle cells, cardiomyocytes and fibroblasts in various cardiovascular organs and the lung.

The response of the immune system to initial hemodynamic disturbances, possibly caused by myocardial dysfunction or congenital heart defects, may include secretion of various cytokines that promote inflammation, resulting in necrotic cardiomyocyte damage and endothelial

activation, thereby triggering production of secondary inflammatory mediators.

Simultaneously, counteracting mechanisms are stimulated that promote secretion of anti-inflammatory cytokines and peptides. Among them, IL-10 for example inhibits the respiratory burst in phagocytes and prevents the induction of monocyte coagulant activity. The secretion of the various cytokines depends on the normal function of traditional immune cells. After acute myocardial damage patients show remarkably increased IL-10 plasma levels, which are negatively correlated to the TNF release of monocytes. Thus, during CHF, the function of the immune cells seems to be disturbed resulting in an imbalance between pro- and anti-inflammatory cytokines.

Impact of b-blockers on cytokines in CHF

In some studies, the hypothesis that anti-cytokine therapy in CHF may be of clinical benefit has been addressed. However, in one prospective randomized trial, vesnarinone, a phosphodiesterase inhibitor which reduces the level of TNF in heart failure patients, increased mortality [2]. More recently a specific anti-cytokine therapy, using a TNF receptor fusion protein (etanercept), showed disappointing clinical results in a large clinical trial and had to be stopped prematurely because of futility [3]. These effects are not well understood, however, we may speculate that the dosage or the pharmacokinetics of the drug may have been a limiting factor. Furthermore, we need to take into account that blocking a single cytokine (i.e. TNF) may not result in clinical benefit owing to the redundancy and counter-regulatory pathways present in the cytokine network.

On the other hand, recently published studies have shown that the beneficial effect of b-blocker therapy in patients with CHF is paralleled by altered levels of inflammatory and anti-inflammatory cytokines (Table 1): Gullestad and coworkers [4] measured an increase of soluble IL-2 receptor in the plasma of CHF patients that was reversed after treatment with the selective b₁-blocker metoprolol after 3 months of application. In contrast, the elevated plasma levels of IL-6, IL-8 and TNF were not reversed in the metoprolol-treated patients. On the other hand, Ohtsuka and colleagues [5] described enhanced levels of TNF, sTNF-R2 and IL-10 in CHF patients. After selective blockade of the b₁-adrenoceptors with metoprolol they found a reduction of these cytokine levels. Reduction of IL-6 levels in CHF patients treated with diverse b-blockers has been observed in other clinical studies [6, 7]. We have measured numerous cytokines and found that the enhanced sTNF receptor and IL-10 plasma levels observed in the CHF patients with standard medication, were not present in patients additionally treated with metoprolol [8]. In contrast, the enhanced levels of IL-6, IL-8 and IL-1RA were not significantly reduced. We did not find enhanced levels of IL-2, TNF, or sCD14.

Children with congenital heart disease, presenting with clinical signs of CHF due to left-to-right shunts (despite preserved myocardial function), also show alterations of the "neuroendocrine" and "inflammatory" pathways, as discussed above for adults with myocardial dysfunction. Accordingly, also in infants, unspecific immune-modulatory effects influenced by b-blocker therapy may play an important role in the clinical benefit of b-blocker therapy [9]. However, at present the number of infants studied under these conditions is still very low.

In addition to clinical studies, experimental studies with animals have shown that b-blocker therapy prevented the increase of myocardial expression of IL-1b and TNF in a rat model of developing heart failure. A similar result was obtained in another study, showing that after experimental myocardial infarction in the rat, the myocardial overexpression of TNF and IL-1b, but not that of IL-6, was attenuated by the b-blocker metoprolol.

Taken together, treatment of heart failure patients with b-blocker appears to result in alterations within the cytokine system. The resulting "normalization" of the cytokine system, or parts thereof, as indicated by the reversal of cytokine, cytokine antagonist or soluble cytokine receptor levels towards levels in healthy controls, may contribute to the beneficial effects of b-blockers in the treatment of CHF.

Interaction of the neurohormonal and the cytokine system at the level of cAMP

During the pathogenesis of CHF, the neurohormonal and the cytokine system may interact. A possible mediator of this involvement is cAMP. This hypothesis is supported by the finding that cytokines are regulated by cAMP. Thus, production of cytokines by cytokine-producing cells, as well as the composition of blood cells, can be influenced by cAMP and thereby may contribute to the interaction of the neurohormonal and the cytokine system during the development and progression of CHF. Maisel and coworkers [10] have reported that circulating lymphocyte subpopulations are under adrenergic control. They demonstrated a decreased number of distinct circulating lymphocyte subpopulations in CHF patients. This alteration was reversed by metoprolol treatment. We have shown previously that cAMP levels in mononuclear cells (MNC) isolated from CHF patients and incubated with or without β_2 -adrenergic agonist were reduced, however, this reduction was reversed in CHF patients treated with the selective β_1 -blocker metoprolol [11]. Furthermore, we have described that sTNF-R2 levels were inversely correlated with basal leukocyte cAMP levels [8] (compare Figure 3 in [8]).

In summary, it is tempting to speculate that the observed changes of plasma cytokine, cytokine antagonist, or cytokine receptor levels in CHF patients treated with b-blocker therapy may result from a dysregulated interaction of the neurohormonal and the cytokine system. This may possibly be caused by altered cAMP levels in certain cells, in particular leukocytes. We suggest that as a consequence of altered cellular cAMP, an imbalanced production and/or release of cytokines, cytokine antagonists or soluble cytokine receptors may occur that is reversed by b-blocker therapy.

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Figures

Cytokine	b ₁ -selective blockers				Non-selective blockers			
	Result	Substance ¹	Study design ²	Reference	Result	Substance	Study design	Reference
sIL-2R	↓	meto	RCT	[4]				
IL-6	=	meto	RCT	[4]	↓	various	CS	[12]
	=	meto	CS	[8]	↓	various	CS	[6]
					↓	various	RCT	[13]
					↓	carv	CS	[7]
IL-8	=	meto	RCT	[4]				
	=	meto	CS	[8]				
IL-10	↓	meto-biso	CS	[5]				
	↓	meto	CS	[8]				
TNF	=	meto	RCT	[4]	=	various	RCT	[13]
	=	meto	CS	[8]	=	various	CS	[14]
	↓	meto-biso	CS	[5]	=	carv	CS	[7]

sTNF-R1	↓	meto	CS	[8]	↓	propranolol	CS	[9]
sTNF-R2	↓	meto-biso	CS	[5]	↓	propranolol	CS	[9]
	↓	meto	CS	[8]				
MCP-1	=	meto	CS	[4]				

¹ meto, metoprolol; meto-biso, metoprolol and bisoprolol; carv, carvedilol.

² RCT, randomized clinical trial; CS, clinical study.

³ lowered = unchanged

	Tableau 1 : Altered cytokine levels in CHF patients treated with b-blockers

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