Interaction Between Interleukin-1 Beta and Angiotensin II Receptor 1 in Hypothalamic Paraventricular Nucleus Contributes to Progression of Heart Failure

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The central mechanisms by which interleukin-1 beta (IL-1 β) and angiotensin II receptor 1 (AT1-R) contribute to sympathoexcitation in heart failure (HF) are unclear. In this study, we determined whether an interaction between IL-1 β and AT1-R in the paraventricular nucleus (PVN) contributes to progression of HF. Rats were implanted with bilateral PVN cannulae and subjected to coronary artery ligation or sham surgery (Sham). Subsequently, animals were treated for 4 weeks through PVN infusion with either vehicle, losartan (LOS, 200 μ g/day), IL-1 β (IL, 1 μ g/day), or IL-1 β along with LOS (LOS+IL). HF rats had higher levels of corticotropin-releasing hormone (CRH), norepinephrine (NE), and glutamate (Glu); lower levels of gamma-aminobutyric acid (GABA); and more positive fra-like activity in PVN when compared with Sham rats. HF rats also had higher levels of NE, epinephrine (EPI), and IL-1 β in plasma. PVN infusion of LOS attenuated the decreases in GABA and the increases in CRH, NE, and Glu in the PVN of HF rats. IL-1 β could further increase the expression of CRH, NE, Glu, EPI, and IL-1 β and decrease GABA expression. Treatment with IL-1 β along with LOS could eliminate the effects of IL-1 β . These findings suggest that an interaction between AT1-R and IL-1 β in the PVN contributes to progression in HF.

Introduction

ALTHOUGH CONTEMPORARY HEART FAILURE (HF) treatments have slowed improved survival, the overall incidences of morbidity and mortality continue to rise, which suggests that the current treatment programs still misses one or more important pathophysiologic mechanisms (Roger and others 2011). There is convincing evidence that inflammation plays an important role in the pathogenesis of HF (Hedayat and others (2010). In experimental animals, inflammatory cytokines promote left ventricular (LV) remodeling and acute contractile dysfunction (Finkel and others 1992; Pagani and others 1992). Proinflammatory cytokines (PICs), including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-18 (IL-18), have been reported as playing a pathogenetic role in HF. In HF rats, an increase in PICs is found not only in peripheral tissues but also in the hypothalamic paraventricular nucleus (PVN). Inflammation in this region has recently emerged as an important factor in the pathogenesis of HF (Yu and others 2012).

In HF animals, an increase in the components of renin-angiotensin system (RAS) is found not only in peripheral tissues but also in the PVN. Blocking brain RAS alleviated sympathetic activation in HF rats, which suggests the role of

brain RAS in inducing neurohumoral excitation in HF (Wang and others 2004). Excess amounts of both PICs and RAS are present in the PVN and contribute to neurohumoral excitation in HF (Zhang and others 2003).

Interleukin-1 beta (IL-1 β) is the prototypal inflammatory cytokine that becomes persistently elevated in plasma in patients with HF (Bujak and Frangogiannis 2009). Further studies identify a pathologic role for IL-1 β in ventricular remodeling and systolic dysfunction in HF rats (Abbate and others 2010; Van Tassell and others 2010). A recent study showed that IL-1 β was at a high level in PVN in HF rats (Kang and others 2006). However, the role that IL-1 β plays in the PVN and the relationship between IL-1 β and neurohumoral excitation are not well elucidated. The present study sought to determine the role of IL-1 β in the PVN and the correlation of IL-1 β and neurohumoral excitation in HF rats.

Materials and Methods

Animals

Male Sprague-Dawley rats (weighing 200–250 g) were housed in cages under standardized conditions 12 h light/dark cycle, 20–25°C ambient temperature and 40%–60% humidity with free access to rat chow and water. This investigation

conforms to the "Guide for the Care and Use of Laboratory Animals" published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). The animals were afforded by the laboratory animal center, the Shandong University of Traditional Chinese Medicine.

General experimental protocol

Rats underwent implantation of PVN cannulae; then, coronary artery ligation was performed to induce HF. Animals were divided into 5 groups: sham rats that received no treatment (Sham, $n=10$); HF rats which received angiotension II receptor 1 (AT1-R) antagonist losartan (LOS, 200 $\mu\text{g/day}$, $n=10$; Merck); HF rats that received IL-1 β (IL, 1 $\mu\text{g/day}$, $n=10$; Sigma-Aldrich); HF rats that received IL-1 β along with LOS (LOS+IL, $n=10$); and HF rats that received artificial cerebrospinal fluid (vehicle [VEH]). Drugs were given at 24 h after ligation lasting for 4 weeks. Osmotic mini-pumps were implanted subcutaneously and connected with the cannulae for the continuous infusion of LOS, IL-1 β , and LOS along with IL-1 β or artificial cerebrospinal fluid directly into the PVN. A stainless steel double cannula (Plastics One, Inc.) was implanted into the PVN. LV function was assessed by echocardiography at 24 h after recovery from surgery. At 4 weeks, rats were anesthetized for echocardiography examination and then euthanized to gather tissue and plasma for further analysis.

Implantation of PVN cannulae and coronary ligation

Alzet miniosmotic pumps (model 2004) were used to obtain a continuous infusion of the drug. Rats were placed into a stereotaxic apparatus after anesthesia (sodium pentobarbital, 50 mg kg^{-1} , ip.). The method for PVN cannulation has been previously described by others (Francis and others 2001). In brief, a stainless steel double cannula (Plastics One, Inc.) with a center-to-center distance of 0.5 mm was implanted into the PVN (2.0 mm posterior to the bregma and 8.5 mm ventral from the skull surface). HF was induced by ligation of the left anterior descending coronary artery as previously described (Liu and others 2012). For sham-operated rats (Sham), the surgery was done in the same manner without ligating the coronary artery. Post-surgical animals were given benzathine penicillin (30,000 U IM).

Echocardiographic assessment of LV function

Echocardiography was performed using an Acuson Sequoia clinical imager that was fitted with a 8-MHz sector-array probe, which generates 2-dimensional images at a rate of 100/s. Animals were sedated with sodium pentobarbital (25 mg kg^{-1} , ip.) to facilitate positioning for echocardiographic study. The animal was positioned in the left lateral recumbent position to optimize the windows for echocardiography. The anterior chest was shaved, and prewarmed acoustic coupling gel was applied. Short-axis images were acquired parallel to the mitral valve plane to obtain the largest cross-sectional image of the left ventricle (Francis and others 2001). Long-axis views were obtained perpendicular to the mitral valve plane. Images were stored for subsequent off-line analysis.

LV end-diastolic volume, LV end-systolic volume, LV ejection fraction, LV stroke volume, and LV mass were computed. The portion of the left ventricle that displayed akinesis was planimetered electronically and expressed as a

percentage of the total left ventricle silhouette to estimate the size of the ischemic zone. Only animals with large infarctions (ischemic zone $\geq 40\%$) were used in the study.

Tissue microdissection

The animals were sacrificed by decapitation, and their brains were quickly removed and frozen on dry ice. Serial sections (300 μm) of the brain were obtained using a cryostat maintaining at -10°C . The sections were transferred to coverslips that were placed on a cold stage set at -10°C . The PVN was microdissected out using Palkovits' microdissection technique (Mohan Kumar and others 1998).

Measurements of PVN tissue levels of glutamate, gamma-aminobutyric acid, and norepinephrine, and of plasma norepinephrine and epinephrine

High performance liquid chromatography with electrochemical detection (HPLC-EC, ECD-300; Eicom Corporation) was used for measuring plasma levels of norepinephrine (NE) and epinephrine (EPI), and PVN levels of NE, glutamate (Glu), and gamma-aminobutyric acid (GABA), as previously described by others (Mohan Kumar and others 1998; Barber and others 2003; Guggilam and others 2007). Briefly, it consists of an LC-4B amperometric detector, a glassy carbon working electrode, a phase II 5 μm ophthalaldehyde solution reverse phase 100 $\times$ 3.2 mm C-18 column, and a C-R6A Chromatopac integrator (Shimadzu). The mobile phase consisted of monochloroacetic acid (14.5 g/L), sodium hydroxide (4.675 g/L), octanesulfonic acid disodium salt (0.3 g/L), ethylenediaminetetraacetic acid (0.25 g/L), acetonitrile (35 mL/L), and tetrahydrofuran (14.5 mL/L). The mobile phase was made with pyrogen-free degassed water and filtered through a Milli-Q purification system (Millipore). The mobile phase was filtered and degassed, and its pH was adjusted to 3.1. The flow rate of the pump was 1.7 mL/min. The column and the working electrode were kept in an oven at a temperature of 37°C . At the time of HPLC-EC analysis, the samples were thawed at 60°C for 1 min. Each sample was homogenized and centrifuged at 12,000 rpm for 10 min. A mixture of 25 μL of the supernatant and 25 μL of the internal standard (0.45 mM isoproterenol) was injected into the HPLC system.

Western blot analysis

Protein was extracted from the PVN using cell lysis buffer (Cell Signaling Technology, Inc.). Protein level for corticotropin release hormone (CRH) was measured with western blotting analysis. The protein sample was mixed with an equal volume of 2 $\times$ 4% sodium dodecyl sulfate (SDS) sample buffer. The sample was boiled and then loaded onto the 7.5% SDS-polyacrylamide gel electrophoresis for electrophoresis at 40 mA/each gel for 50 min. The fractionated proteins on the gel were electrophoretically transferred onto the polyvinylidene difluoride membrane for 90 min. The membrane was incubated with 5% milk-Tris-buffered saline-Tween 20 solution for 30 min at room temperature. Then, the membrane was incubated with primary antibody (rabbit anti-rat CRH polyclonal antibody, 1:1,000; Santa Cruz, Inc.) at 4°C overnight. After being washed thrice, the membrane was incubated with secondary antibody [goat anti-rabbit immunoglobulin G (IgG),

TABLE 1. ECHOCARDIOGRAPHIC MEASUREMENTS

Measurement at	SHAM	VEH	LOS+IL-1 β	IL-1 β	LOS
24 h					
IZ (%)		46 $\pm$ 6	47 $\pm$ 5	46 $\pm$ 5	45 $\pm$ 7
LVEF	0.80 $\pm$ 0.08	0.39 $\pm$ 0.05 ^a	0.38 $\pm$ 0.06 ^a	0.37 $\pm$ 0.06 ^a	0.35 $\pm$ 0.05 ^a
LVEDV	0.34 $\pm$ 0.04	0.73 $\pm$ 0.07 ^a	0.76 $\pm$ 0.08 ^a	0.78 $\pm$ 0.08 ^a	0.75 $\pm$ 0.09 ^a
LVEDV/mass	0.52 $\pm$ 0.06	1.04 $\pm$ 0.08 ^a	1.06 $\pm$ 0.09 ^a	1.06 $\pm$ 0.08 ^a	1.09 $\pm$ 0.10 ^a
4 weeks					
IZ (%)		46 $\pm$ 7	48 $\pm$ 6	47 $\pm$ 5	46 $\pm$ 6
LVEF	0.79 $\pm$ 0.08	0.31 $\pm$ 0.05 ^{a,b}	0.42 $\pm$ 0.07 ^{a,c}	0.24 $\pm$ 0.04 ^{a,b}	0.40 $\pm$ 0.06 ^{a,c}
LVEDV	0.36 $\pm$ 0.04	1.39 $\pm$ 0.11 ^{a,b}	1.07 $\pm$ 0.12 ^{a-c}	1.68 $\pm$ 0.12 ^{a,b}	1.05 $\pm$ 0.09 ^{a-c}
LVEDV/mass	0.55 $\pm$ 0.06	1.70 $\pm$ 0.13 ^{a,b}	1.31 $\pm$ 0.11 ^{a-c}	1.91 $\pm$ 0.12 ^{a,b}	1.29 $\pm$ 0.13 ^{a-c}

Values are mean $\pm$ standard error of the mean.

^a P <0.05 versus SHAM group.

^b P <0.05, 4 weeks versus 24 h value.

^c P <0.05 versus Control group.

LOS, losartan; IL-1 β , interleukin 1 beta; IZ, infarction zone; LVEDV, left ventricular end diastolic volume; VEH, vehicle.

1:5,000] for an hour at room temperature. After being washed thrice, the membrane was treated with enhanced chemiluminescence reagent for 5 min and detected by exposing a film. The density of the bands was quantified with NIH image software.

Enzyme-linked immunosorbent assay studies

Plasma cytokine levels were measured using enzyme-linked immunosorbent assay (Biosource International) techniques, as previously described (Kang and others 2008).

Immunohistochemistry studies

Immunohistochemical studies were performed to assess PVN neuronal activation and the expression of Fra-like (Fra-LI) in PVN. Immunohistochemistry was performed in formalin-fixed sections of the brain as previously described (Guggilam and others 2008). The primary antibodies against Fra-LI (Santa Cruz; 1:100) were incubated overnight at 4°C. The sections were then washed twice in phosphate-buffered saline (PBS), and incubated with a peroxidase conjugated secondary IgG antibody for 30 min. Bound antibodies were detected with a streptavidin-peroxidase complex using 3,3'-diaminobenzidine tetrahydrochloride in PBS containing 0.003% hydrogen peroxide. Images were captured using a Diaphot 300 microscope (Nikon). For each animal, the positive neurons within the bilateral borders of the PVN were manually counted in 3 consecutive sections and an average value was reported.

Statistical analysis

All data are expressed as mean $\pm$ standard error of the mean. Data were analyzed by analysis of variance (ANO-

VA). Multiple testing was corrected using Tukey's test. The echocardiography data were analyzed by ANOVA, allowing for repeated measurement. A probability value of P <0.05 was considered statistically significant.

Results

Echocardiography

Two animals died during the procedure of the study, one in the IL group and the other in the VEH group. At 24 h, left ventricular end-diastolic volume (LVEDV), LVEDV/mass ratio or % infarction zone (IZ) was higher in LOS, IL, LOS + IL, or VEH groups than in the Sham group. There were no differences in these parameters among HF rats assigned to LOS, IL, LOS + IL, or the vehicle treatment. At 4 weeks, LVEDV and LVEDV/mass ratio was higher than the 24-h baseline values in the LOS, LOS + IL, and vehicle-treated HF rats, and which was higher in the IL-1 β -treated HF rats. At 4 weeks, LVEF was higher in the HF rats that received LOS or LOS along with IL-1 β when compared with the HF rats which received vehicle. LVEDV or LVEDV/mass in the HF rats which received LOS or LOS + IL-1 β was lower than that in the rats that received vehicle. Rats treated with IL-1 β showed lower LVEF and higher LVEDV or LVEDV/mass than rats treated with vehicle (Table 1).

Indicators of central neural activation in HF

Fra-LI activity. Fra-LI activity is an indicator of chronic neuronal activation in the PVN. Expression of Fra-LI activity increased in the PVN of HF rats compared with Sham rats (Fig. 1). Compared with rats treated with vehicle, rats

FIG. 1. Immunohistochemistry for Fra-like activity in paraventricular nucleus of hypothalamus ($\times 200$) in a coronal section. Fra-like activity is an indicator of chronic neuronal excitation. (A) Interleukin-1 beta (IL-1 β) group; (B) vehicle group; (C) losartan + IL-1 β group; (D) losartan group; (E) sham group.

FIG. 2. Western blot for corticotropin-releasing hormone protein in hypothalamus of IL-1 β , losartan, losartan + IL-1 β and vehicle treated heart failure (HF), and Sham rats. Primary antibody: rabbit anti-rat corticotropin-releasing hormone polyclonal antibody (1:1,000). Secondary antibody: goat anti-rabbit immunoglobulin G (1:5,000). * $P < 0.05$ versus Sham group; # $P < 0.05$, HF + treated versus HF + VEH.

that received LOS had fewer Fra-LI-positive PVN neurons ($P < 0.05$). HF rats treated with IL-1 β had more Fra-LI-positive PVN neurons than rats treated with vehicle ($P < 0.05$). However, HF rats that received LOS along with IL-1 β showed fewer Fra-LI-positive neurons ($P < 0.05$).

Corticotropin-releasing hormone. CRH protein expression in PVN was higher in HF rats than in Sham rats (Fig. 2). HF rats treated with LOS had less hypothalamic CRH expression than HF rats that received vehicle ($P < 0.05$). Compared with rats treated with vehicle, HF rats treated with IL-1 β had more hypothalamic CRH expression ($P < 0.05$). However, when HF rats were treated with LOS plus with IL-1 β , the hypothalamic CRH expression decreased significantly ($P < 0.05$).

PVN neurotransmitters. HF rats had higher levels of NE and Glu, and lower levels of GABA in the PVN compared with Sham rats (Fig. 3). Infusion of IL-1 β significantly decreased the GABA expression and increased the Glu and NE expression in HF rats. Treatment with infusion of LOS or

LOS along with IL-1 β attenuated the decrease in PVN GABA and the increases in Glu and NE in HF rats.

Plasma levels of PICs, EPI, and NE. Plasma levels of NE, EPI, and IL-1 β were higher in HF rats than in Sham rats ($P < 0.05$, Fig. 4). PVN infusion of IL-1 β increased the levels of NE, EPI, and IL-1 β in plasma than infusion of vehicle ($P < 0.05$). However, treatment with LOS or LOS plus IL-1 β significantly attenuated the increases in plasma levels of NE, EPI, and IL-1 β in HF rats.

Discussion

Neurohumoral and sympathoexcitation mechanisms play an important role in the pathophysiology of HF, which was considered the hallmark of HF. Plasma and PVN levels of PICs, such as TNF- α , IL-1 β , and IL-6, are increased in animals, with their levels rising concomitantly with cardiac dysfunction (Skyschally and others 2007; Schulz and Heusch 2009). Among the PICs, IL-1 β is an important mediator that is involved in hypothalamic regulation of the cardiovascular activities. However, the role that IL-1 β plays in the pathophysiology of HF is less studied. A novel finding of the present study is the interaction between IL-1 β and AT1-R taking place in PVN.

A growing body of evidence suggested that immune-mediated mechanisms play a key role in the pathogenesis of HF. Plasma PICs are increased in HF patients, and their levels increase with the severity of HF (Nozaki and others 1997). PICs are released from the injured site into the circulation after myocardial infarction. Simultaneously, the level of PICs in the central nervous system (CNS) is increased (Chappell and others 2009; Lacerda and others 2010). Overload of PICs in the CNS could induce sympathoexcitation, impact cardiac function, and contribute toward the pathophysiology of cardiovascular diseases (Kang and others 2008). Although increased PICs were found in the brains of HF rats and were considered contributors to exaggerated sympathetic activity, the mechanism by which PICs exert this effect is still unclear. The present study demonstrates that elevated PICs in PVN are accompanied by neurohormonal activation in PVN and elevation of components of RAS in plasma. It indicated that PICs in PVN has close contact with neurohormonal activation and RAS, which play an important role in the progression of HF.

IL-1 β is known to be an endogenous signaling molecule in the brain (Watt and Hobbs 2000). The expression of IL-1 β is increased in pressure and volume overload-induced cardiac hypertrophy (Dai and others 2004; Zhang and others 2007). IL-1 β has been classified as PICs that play important

FIG. 3. Level of norepinephrine, glutamate, and gamma-aminobutyric acid in paraventricular nucleus of hypothalamus of rats ($n = 10$). * $P < 0.05$ versus Sham group; # $P < 0.05$, HF + treated versus HF + VEH.

FIG. 4. Plasma levels of norepinephrine, epinephrine, and IL-1 β in rats ($n = 10$). * $P < 0.05$ versus Sham group; # $P < 0.05$, HF+ treated versus HF+ VEH.

roles in the process of HF. A cross-talk may exist between IL-1 β and neurohormonal activation in the PVN in HF. Intra-cerebroventricular administration of IL-1 β increased expression of CRH mRNA in the PVN (Schmidt and others 2003), as well as plasma adrenocorticotrophic hormone. The IL-1 β activation of targeted cells is known to mediate through functional IL-1 receptor type I (Martin and Falk 1997). IL-1 β is a potent activator of the hypothalamic-pituitary-adrenocortical axis; however, the CRH expressing neurons in the PVN lack IL-1R1 mRNA or IL-1R1-immunoreactivity (Ericsson and others 1995). Therefore, the actions of IL-1 β in the PVN may be indirectly exerted by PVN local circuits or through other modulators. In the present study, a microinjection of IL-1 β deteriorated the LV dysfunction, and increased the expression of PICs and neurohormones, which are in accordance with a previous study. However, treatment with LOS could alleviate the elevation of PICs and cardiac dysfunction. In addition, a microinjection of IL-1 β along with LOS eliminated the effects of IL-1 β . This indicated that angiotension II receptor may be a target of IL-1 β . Blockade of the angiotension II receptor interrupts IL-1 β signal transduction and then improves the presentation of HF. The results are in accordance with previous studies (Lu and others 2009). This is the first time we confirm the correlation between IL-1 β and angiotension II receptor in the process of HF. However, the exact mechanisms of how the interaction happens have not been well understood yet. Campese and others (2002) found that angiotension II and IL-1 β acted in a negative feedback loop. IL-1 β could stimulate the release of angiotension II, while angiotension II, in turn, might decrease the expression of IL-1 β in the brain.

The RAS is activated in HF and leads to vasoconstriction, volume accumulation, and exaggerated sympathetic nerve activity. The AT1-R is the primary receptor inducing the action of RAS. Previous studies have demonstrated that AT1-R is present in the PVN (Aguilera and others 1995) and mRNA levels for the AT1-R are high in the PVN. In addition, recent findings indicate that AT1-R is up-regulated in the PVN in HF (DiBona and others 1995). Blockade of AT1-R (Zhu and others 2004) or inhibition of angiotension II production by administration of angiotensin-converting enzyme inhibitors (Francis and others 2004) can effectively lower sympathetic activity that is concomitant with abatement of water retention and cardiac ventricular remodeling. In our study, a microinjection of IL-1 β deteriorated LV function and activated RAS and neuroendocrine. However, treatment with AT1-R antagonist LOS improved LV function and decreased plasma catecholamines alongside a de-

crease in cytokine levels. These results further confirm the cross-talk between cytokines and AT1-R in the PVN in HF.

To sum up, our study provides evidence for the fresh idea that an interaction between IL-1 β and AT1-R plays an important role in the progression of HF. This finding suggests a new approach to central therapy in HF, and so has important clinical implications.

Author Disclosure Statement

No competing financial interests exist.

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