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Central Mechanisms for Exercise Training-Induced Reduction in Sympatho-Excitation in Chronic Heart Failure

Karla K.V. Haack and **Irving H. Zucker**
Department of Cellular and Integrative Physiology, University of Nebraska Medical Center

Abstract

The control of sympathetic outflow in the chronic heart failure state (CHF) is markedly abnormal. Patients with heart failure present with increased plasma norepinephrine and increased sympathetic nerve activity. The mechanism for this sympatho-excitation are multiple and varied. Both depression in negative feedback sensory control mechanisms and augmentation of excitatory reflexes contribute to this sympatho-excitation. These include the arterial baroreflex, cardiac reflexes, arterial chemoreflexes and cardiac sympathetic afferent reflexes. In addition, abnormalities in central signaling in autonomic pathways have been implicated in the sympatho-excitatory process in CHF. These mechanisms include increases in central Angiotensin II and the Type 1 receptor, increased in reactive oxygen stress, up regulation in glutamate signaling and NR1 (N-methyl-D-aspartate subtype 1) receptors and others. Exercise training in the CHF state has been shown to reduce sympathetic outflow and result in increased survival and reduced cardiac events. Exercise training has been shown to reduce central Angiotensin II signaling including the Type 1 receptor and reduce oxidative stress by lowering the expression of many of the subunits of NADPH oxidase. In addition, there are profound effects on the central generation of nitric oxide and nitric oxide synthase in sympatho-regulatory areas of the brain. Recent studies have pointed to the balance between Angiotensin Converting Enzyme (ACE) and ACE2, translating into Angiotensin II and Angiotensin 1–7 as important regulators of sympathetic outflow. These enzymes appear to be normalized following exercise training in CHF. Understanding the precise molecular mechanisms by which exercise training is sympatho-inhibitory will uncover new targets for therapy.

Keywords

Sympathetic nerve activity; physical activity; angiotensin II; nitric oxide; oxidative stress

Corresponding Author: Irving H. Zucker, Ph.D., Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, Omaha, NE 68198-5850, izucker@unmc.edu, Phone: 402 559 7161, FAX: 402 559 4438.

Introduction

The syndrome of chronic heart failure (CHF) impacts every organ system including skeletal muscle both at rest and during exercise (Drexler et al., 1987; Hambrecht et al., 2000; Just, 1991; Magnusson, 1995; Musch et al., 1989; Parmley, 1989; Riley et al., 1990). Further, exercise was initially thought to worsen left ventricular dysfunction in CHF patients (McDonald et al., 1972). One of the most frequent complaints of patients with even mild CHF is the inability to exercise. One would think the mechanism at the root cause of exercise intolerance in CHF is simply a lack of cardiac reserve and an inability to adjust cardiac output to workload. However, because CHF impacts sympathetic outflow, endothelial function, peripheral vascular resistance and skeletal muscle protein synthesis and metabolism, the mechanism of exercise intolerance is multifactorial in this disease state. While the standard of care for CHF in the mid-20th century was bed rest and diuretic and/or cardiac glycoside therapy it has become increasingly accepted that all but the most severe CHF patients can carry out some form of exercise (Downing et al., 2011; McKelvie, 2008). In fact, the American Heart Association has advocated exercise training as a safe form of therapy (Piña et al., 2003). Several clinical studies now show substantial benefits of exercise training in patients with CHF including quality of life, a reduction in hospitalization, cardiac events and survival (Belardinelli et al., 1999; Chicco et al., 2008; Piepoli et al., 2000). The HF-ACTION trial demonstrated a decrease in all-cause mortality and hospitalization in CHF patients who underwent a moderate exercise training regimen (aerobic exercise of either cycling or treadmill walking for 40 minutes at 60% to 70% of heart rate reserve, five times per week) (O'Connor et al., 2009). These benefits are not limited to a single type of exercise modality; resistance training, aerobic exercise, and even calisthenics as tolerated after a cardiac event are all considered to be effective (Piepoli et al., 2000). In fact, a reduction of physical activity in this same CHF patient population may be a contributor to future exercise intolerance and impaired peripheral vascular resistance (Hunt et al., 2005). While there is consensus that exercise training is beneficial in the CHF state, the underlying mechanisms responsible for these effects are not at all clear. Pre-clinical experimental studies have been extremely useful in shedding light on potential pathophysiological mechanisms. This review will focus primarily on the effects of exercise training on sympathetic and cardiovascular reflex function in CHF however, it should be kept in mind that changes in sympathetic outflow is just one mechanism responsible for the beneficial effects of exercise training in CHF.

Sympatho-excitation in CHF

The neural control of cardiovascular function relies on an ancient controller dominated by classical negative feedback servo control systems scattered throughout the cardiovascular system. Normally, just the right amount of sympathetic nerve activity is provided to maintain peripheral vascular resistance and arterial pressure at a set point necessary for adequate tissue perfusion. The sensors are primarily located in the great vessels (baroreceptors), the heart, and in the carotid and aortic bodies (chemoreceptors). A large number of studies, both basic and clinical, have shown marked abnormalities in the ability of these sensors to correctly transmit information concerning arterial pressure, blood volume and oxygen tension (Eckberg et al., 1971; Ellenbogen et al., 1989; La Rovere et al., 2009;

Mohanty et al., 1989; Ponikowski et al., 1997; Zucker, 1991) in the setting of CHF. Early work suggested that depression in baroreflex gain mediated sympatho-excitation in patients and animals with CHF (Ferguson et al., 1984; Ferguson et al., 1992; Mancia et al., 1992). Reflexes mediated by sensory endings in the low pressure side of the circulation have also been shown to exhibit reduced gain and contribute to sympatho-excitation by removal of inhibitory restraint (Patel et al., 1996a; Pliquett et al., 2003; Zheng et al., 2006). Further studies also suggested that an increase in chemoreceptor sensitivity in CHF drives sympatho-excitation (Chua et al., 1996; Chua et al., 1997; Chugh et al., 1996; Ponikowski et al., 1997; Schultz et al., 2007; Sun et al., 1999a; Sun et al., 1999b). Finally, excitatory input from so called “cardiac sympathetic afferents” has also been shown to be augmented in the CHF state (Gao et al., 2007a; Gao et al., 2005a; Gao et al., 2004b; Wang et al., 2006; Zhu et al., 2004a; Zhu et al., 2004b; Zhu et al., 2002; Wang and Zucker, 1996). While there is little doubt that these reflexes contribute to sympatho-excitation in CHF the question still remains as to whether these abnormalities are initiating factors or a consequence of the CHF state?

In addition to dysfunction in cardiovascular sensory function there are many alterations in various components in the reflex arcs mediating autonomic outflow in CHF. Central changes in synaptic transmission and membrane sensitivity of pre-sympathetic neurons at several hypothalamic and medullary sites also participate in sympatho-excitation in CHF. Changes in discharge sensitivity of neurons in the rostral ventrolateral medulla (RVLM) and in the paraventricular nucleus (PVN) have been prominent in this regard (Gao et al., 2008; Patel et al., 2000). While it is beyond the scope of this review to detail all of the central changes that take place in CHF some of these changes will be highlighted below because exercise training profoundly influences them.

Does exercise training lower sympathetic outflow in heart failure?

Studies carried out on patients with CHF have shown a reduction in sympathetic outflow following a supervised exercise training regimen (stationary cycling 60 minutes 3 times per week), measured by either direct recording of muscle sympathetic nerve activity (Fraga et al., 2007; Roveda et al., 2003) or urinary norepinephrine excretion (Yousufuddin et al., 2000). Softer indices of sympatho-excitation such as heart rate variability and power spectral analysis have also pointed to a lowering of sympathetic outflow following exercise training in the CHF population (Coats et al., 1992; Colombo et al., 1999; Scalvini et al., 1998). These indices coincide with improvement in baroreflex and chemoreflex sensitivity in CHF (Gao et al., 2007b; Li et al., 2008; Liu et al., 2000; Liu et al., 2002; Negraõ et al., 2008a; Negraõ et al., 2008b). In a recent study by Rengo *et al.* (Rengo et al., 2014) it was shown that exercise training resulted in a decrease in heart rate, plasma norepinephrine, and brain natriuretic peptide (BNP) while increasing maximal oxygen consumption (MVO_2) and ejection fraction slightly. Importantly, these data were prognostic as to outcomes. Those patients with the greatest change in norepinephrine and BNP exhibited significantly better survival profiles. These data support earlier work showing that mortality was reduced in CHF patients that underwent and exercise training program (Belardinelli et al., 1999; Hagerman et al., 2005; Keteyian et al., 2012; O'Connor et al., 2009; Rosenwinkel et al., 2001; Smart et al., 2004). On the other hand, a recent analysis of the HF ACTION database by Ahmad et al. (Ahmad et al., 2014) showed no effect on BNP or cardiac function but an

improvement in hospitalizations and survival. In total however, it seems clear that exercise training does indeed impact sympathetic outflow and survival if not cardiac function *per se*.

What central mechanisms are responsible for sympatho-inhibition following exercise training in CHF?

The discharge sensitivity of pre-sympathetic neurons in the RVLM and of sympathetic projecting neurons in the PVN is determined ultimately by activity in membrane ion channel proteins and currents. In the CHF state alterations in several neuronal signaling pathways have been defined that impact channel activity and may be impacted by exercise training. The focus of this work has largely been in three areas; 1. The renin-Angiotensin II (Ang II) system, 2. Reactive oxygen stress (ROS) and 3. Nitric oxide synthase (NOS). In addition, exercise training impacts glutamate signaling in CHF (Kleiber et al., 2008; Llewellyn et al., 2012). Sympatho-excitatory neurons in the RVLM and PVN express Angiotensin II Type 1 receptors (AT1R) (Gao et al., 2005b; Gao et al., 2008; Liu et al., 2000; Wang et al., 2004) that modulate sympathetic discharge when stimulated with Ang II (Gao et al., 2008a). Experiments in various species and models of CHF have shown that AT1R protein and mRNA is increased in CHF in these sympatho-excitatory regions (Gao et al., 2005b). Signaling through the AT1R increases neuronal excitability, in part, by increasing superoxide production thorough activation of NADPH oxidase. Following an exercise training regimen rabbits with CHF exhibit a profound reduction in renal sympathetic nerve activity at rest, and normalization of plasma Ang II (figure 1)(Liu et al., 2000). In addition, exercise trained CHF rabbits exhibited a decrease in AT1R expression in the RVLM (Gao et al., 2004a; Gao et al., 2005b), a decrease in central oxidative stress (Gao et al., 2007b) and an increase in both CuZn and Mn superoxide dismutase (SOD) (Gao et al., 2004a). Importantly, the changes in central AT1R expression, baseline sympathetic nerve activity and the improvement in baroreflex function could be prevented by concomitant systemic infusion of Ang II in order to prevent the normalization of Ang II by exercise training (figure 1)(Mousa et al., 2008). These data fit with the idea that Ang II, derived either from *de novo* synthesis in the brain or from circulating Ang II that gains access to the central nervous system through the circumventricular organs or in areas with a disrupted blood brain barrier (Biancardi et al., 2014), activates the AT1R pathway. Exercise training, by abrogating AT1R expression and upregulating antioxidant enzymes in the brain reduces this angiotensinergic drive and decreases sympathetic nerve activity (Liu, et al., 2000; Mousa, et al., 2008; Gao, et al. 2007b).

The regulation of AT1R expression in neurons in the heart failure state and following exercise training is complex but appears to involve an NFkB (nuclear factor kappa B) – dependent cascade at the DNA level. NFkB is a protein dimer that is a transcription factor for a number of other pro-inflammatory cytokines and stress response genes (Kumar et al., J Mol Med (2004) 82:434–448). It is not clear if exercise training alters this pathway but data from our laboratory indicates that NFkB is reduced following exercise training in animals with CHF (figure 2)(Haack et al., 2012). In addition, the regulation of AT1R turnover may be affected by changes in the G-protein coupled receptor, GRK5 (Haack et al., 2012). Importantly, exercise training in heart failure also reduces cytokine levels, a major source of

NFkB activation (Conraads et al., 2002; Gielen et al., 2003; LeMaitre et al., 2004). A study by Nunes and others demonstrated that aerobic exercise in CHF rats decreased plasma levels of the inflammatory cytokines interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α) (Nunes et al., 2013). The reduction in plasma IL-6 and TNF-α following exercise training was also seen in CHF patients (Smart and Steele, 2011).

Current evidence suggests that nitric oxide (NO) is an important sympatho-inhibitory molecule in the medulla and hypothalamus (Ma et al., 1999; Wang et al., 2013; Zheng et al., 2011a; Zhu et al., 2004c). It has been known for some time that NO is reduced in the medulla and hypothalamus of animals with CHF (Patel et al., 1996; Zhang et al., 2001; Zhang et al., 1998). This is due, in part, to a reduction in NO synthase (NOS) (mostly neuronal NOS, nNOS) protein and mRNA and, in part, to a reduction in the bioavailability of NO due to increased superoxide production (Campese et al., 2004; Chan et al., 2012; Zanzinger et al., 2000). Exercise training has clearly been shown to increase nNOS in the kidney (Ito et al., 2013), vasculature (Kuru et al., 2009; Mayhan et al., 2011), skeletal muscle (Kingwell, 2000), in the carotid body (Li et al., 2008) and in the brain (Zheng et al., 2005). The sympatho-inhibitory effects of NO in animals with CHF are increased following upregulation of nNOS in the PVN or after exercise training. Another potential mechanism by which upregulation of nNOS and formation of NO may be beneficial in the heart failure state is by inhibition of glutamate signaling. In a study by Zheng *et al.* (Zheng et al., 2011a)) adenoviral gene transfer of the PVN with nNOS in rats with CHF inhibited the sympatho-excitatory response to the neurotransmitter N-methyl D aspartate (NMDA) and reduced NMDA receptor (NR1) expression. Furthermore, Kleiber et al. showed that exercise training in the CHF state reduced the response to NMDA in the PVN (Kleiber et al., 2008).

Another potential mechanism that can influence the sympatho-inhibitory action of NO is the balance between Angiotensin Converting Enzyme (ACE) and Angiotensin Converting Enzyme 2 (ACE2) in the central nervous system of animals with CHF. These two enzymes regulate the amount of pro-AT1R (Ang II and superoxide production) vs pro-mas receptor signaling (Ang 1–7 and NO production). In rabbits with pacing – induced CHF we showed increased ACE protein and decreased ACE2 protein in the rostral ventrolateral medulla (RVLM) and PVN (Kar et al., 2010). Importantly, those CHF rabbits that underwent an exercise training regimen exhibited normal levels of both proteins. Zheng et al. (Zheng et al., 2011b) showed that adenoviral overexpression of ACE2 in the PVN of rats with CHF increased NOS synthesis and reversed the abnormal hemodynamic and sympathetic responses to PVN L-NMMA (L-N-monomethyl arginine, a nonselective inhibitor of all NOS isoforms) microinjection, thereby mimicking the effects of exercise training. Additional data supporting an important role of Ang 1–7/Ang II balance in the CHF state comes from the use of transgenic mice that overexpress human ACE2 selectively in central neurons (Feng et al., 2009). When these mice develop CHF (infarction model) they exhibit lower renal sympathetic nerve activity and improved baroreflex function (Xiao et al., 2011). A similar effect is observed in rabbits with CHF in response if intracerebroventricular infusion of Ang 1–7 (Kar et al., 2011). Future studies are needed to examine the relative abundance of these pathways following exercise training in CHF patients.

Summary

Taken together, there is a wealth of information strongly suggesting that the benefits of exercise training are multiple in the CHF state. Every organ system is positively impacted by exercise training as is negatively impacted by heart failure. Those stimuli that have been shown to increase the discharge sensitivity of pre-sympathetic neurons in CHF are significantly ameliorated following an exercise training regimen. These include Ang II, ROS, glutamate, NOS/NO, ACE and ACE2 and antioxidant enzymes such as SOD. There are many other substances that have not been discussed in this short review (e.g. endothelin-1, vasopressin, etc.), all of which have been, or are targets for therapy in the CHF state. Figure 3 provides a summary of the beneficial effects of exercise training on sympathetic outflow and the neurohumoral mediators affected. Clearly the mechanisms by which exercise training operates to reduce sympatho-excitation in diseases such as heart failure and hypertension is complex and further research will be necessary to understand exactly how this paradigm translated to normalization of pre-sympathetic neuronal function.

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Highlights

- Although initially considered deleterious, exercise training in chronic heart failure (CHF) patients improves quality of life outcomes and decreases all-cause mortality.
- A hallmark of chronic heart failure is an increase in sympathetic drive; this is markedly reduced in both animal models and patients with CHF. In addition, exercise training restores baroreflex sensitivity and decreases chemoreflex sensitivity in CHF.
- Potential mechanisms underlying this improvement in autonomic imbalance following exercise training include: a reduction in reactive oxygen species and a concomitant increase in nitric oxide signaling, a reduction in Angiotensin II type 1 receptor signaling and a restoration of the imbalance of Angiotensin converting enzyme (ACE) and ACE2 expression, a decrease in circulating pro-inflammatory cytokines like NFkB, TNF-α, and IL-6, and a decrease in N-methyl D-aspartate (NMDA) receptor expression and signaling.

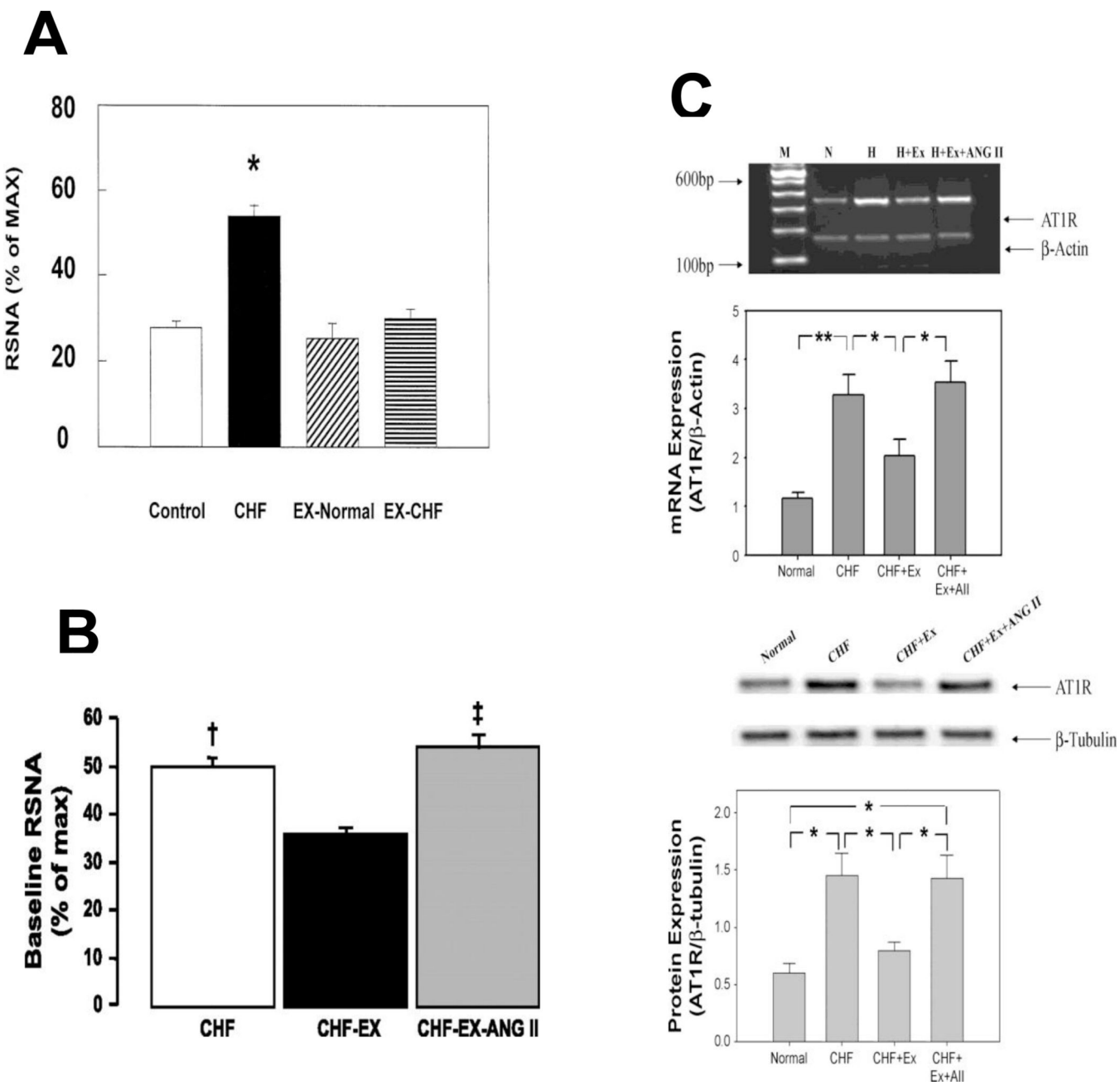

Figure 1.

Renal sympathetic nerve activity (A and B) and AT1 receptor expression (C) in the RVLM from rabbits with CHF that underwent an exercise training regimen or were sedentary. (A. from Liu, J.L. et al. 2000; B and C from Mousa, T.M. et al. 2008, with persmission.)

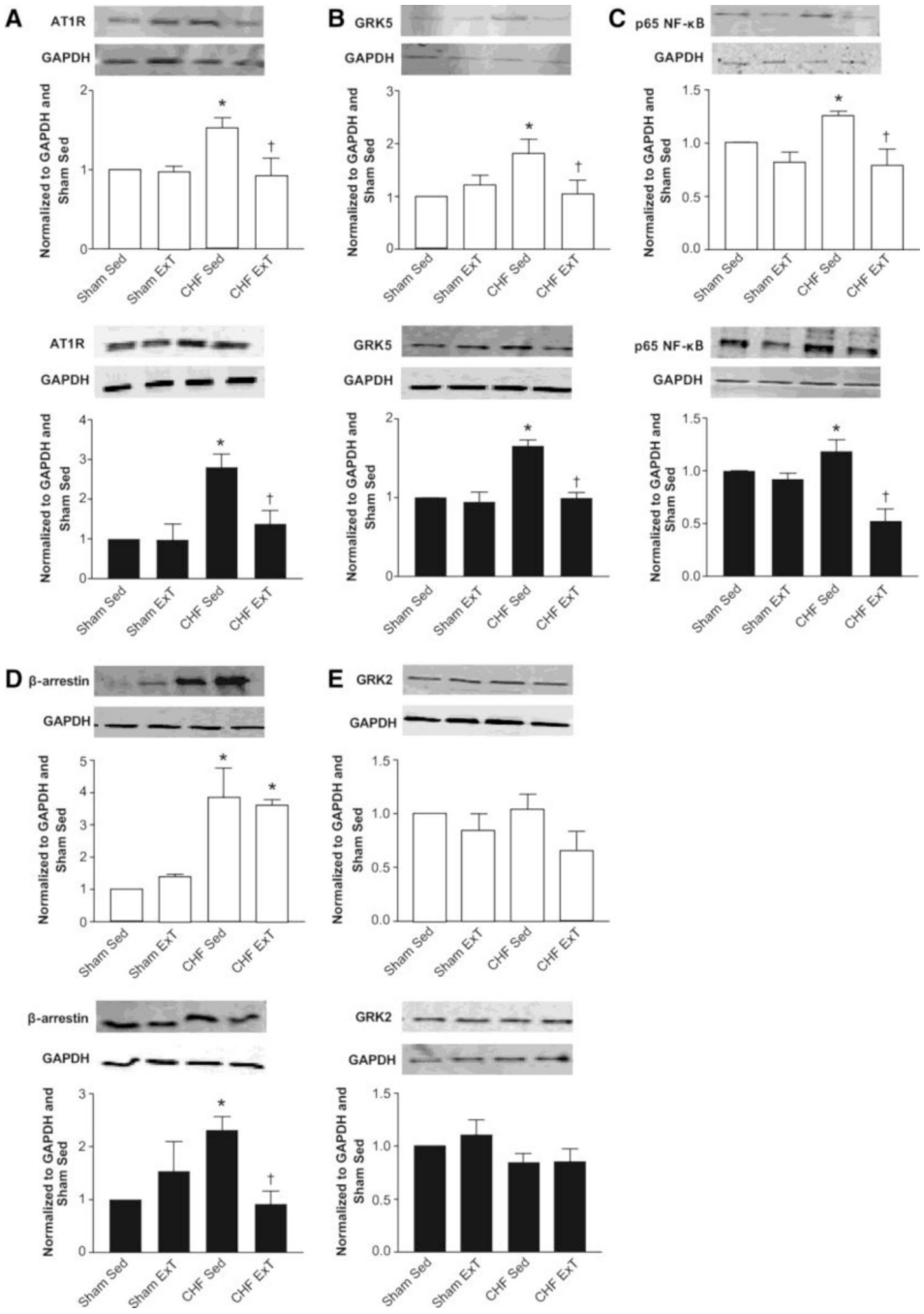

Figure 2.

Western blot data from rostral ventrolateral medulla and paraventricular nucleus in rats with heart failure and following exercise training. Exercise training reduces AT1R, GRK5, NFkB and β-arrestin in heart failure. (from Haack, KK. et al., 2012; with permission)

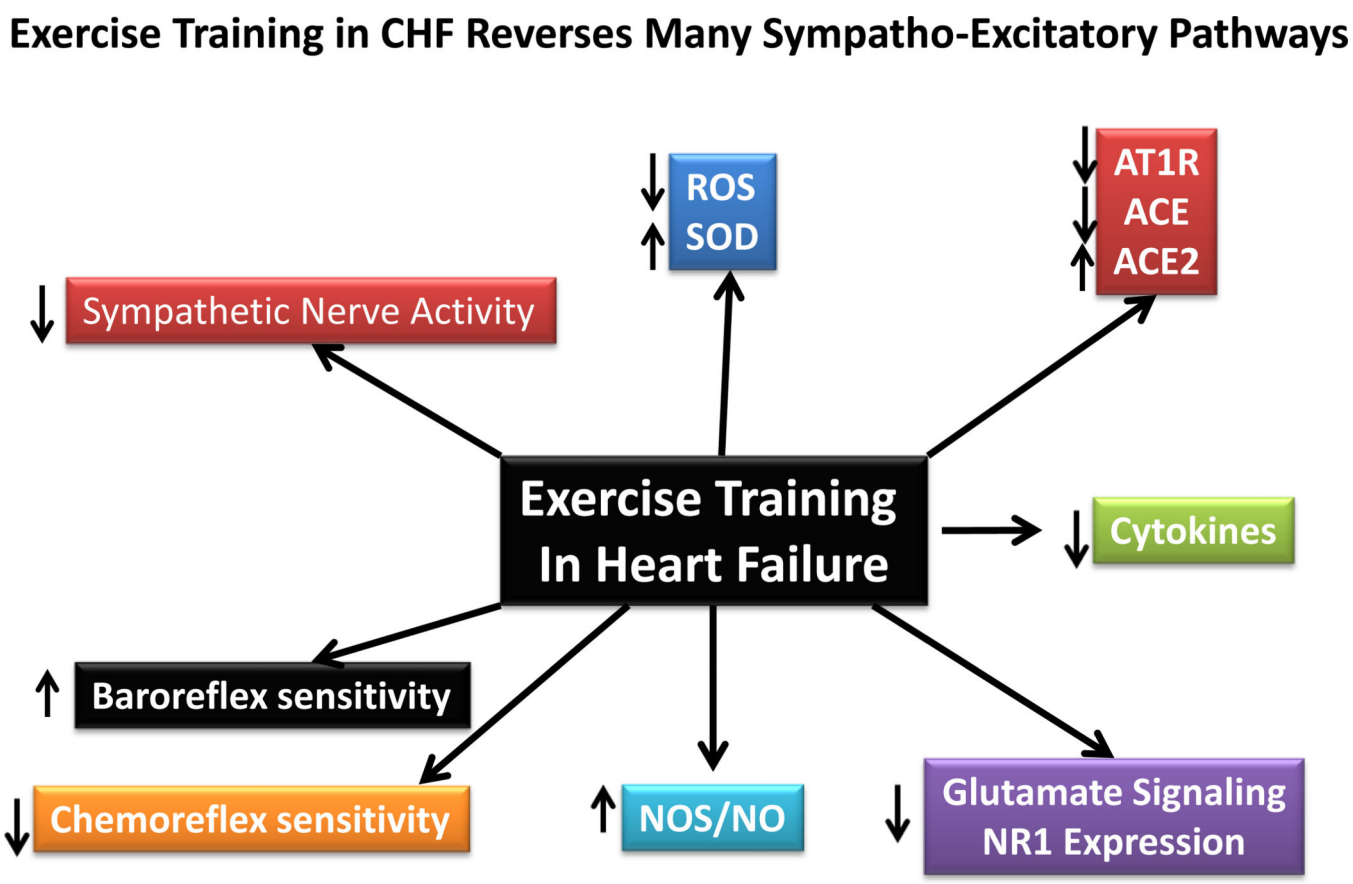

Figure 3.
A schematic overview of some of the factors impacted by exercise training in the heart failure state. Arrows denote the direction of the changes.