

Modulation of angiotensin II signaling following exercise training in heart failure

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Zucker IH, Schultz HD, Patel KP, Wang H. Modulation of angiotensin II signaling following exercise training in heart failure. *Am J Physiol Heart Circ Physiol* 308: H781–H791, 2015. First published February 9, 2015; doi:10.1152/ajpheart.00026.2015.—Sympathetic activation is a consistent finding in the chronic heart failure (CHF) state. Current therapy for CHF targets the renin-angiotensin II (ANG II) and adrenergic systems. Angiotensin converting enzyme (ACE) inhibitors and ANG II receptor blockers are standard treatments along with β -adrenergic blockade. However, the mortality and morbidity of this disease is still extremely high, even with good medical management. Exercise training (ExT) is currently being used in many centers as an adjunctive therapy for CHF. Clinical studies have shown that ExT is a safe, effective, and inexpensive way to improve quality of life, work capacity, and longevity in patients with CHF. This review discusses the potential neural interactions between ANG II and sympatho-excitation in CHF and the modulation of this interaction by ExT. We briefly review the current understanding of the modulation of the angiotensin type 1 receptor in sympatho-excitatory areas of the brain and in the periphery (i.e., in the carotid body and skeletal muscle). We discuss possible cellular mechanisms by which ExT may impact the sympatho-excitatory process by reducing oxidative stress, increasing nitric oxide, and reducing ANG II. We also discuss the potential role of ACE2 and Ang 1–7 in the sympathetic response to ExT. Fruitful areas of further investigation are the role and mechanisms by which pre-sympathetic neuronal metabolic activity in response to individual bouts of exercise regulate redox mechanisms and discharge at rest in CHF and other sympatho-excitatory states.

exercise training; heart failure; neural control; sympathetic; angiotensin II

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Chronic heart failure (CHF) is a disease that impacts every tissue and organ system. Many reviews have been written on the pathogenesis of CHF (21, 37, 47, 81, 107, 114, 127, 130, 229), and there is little doubt that the early compensation to cardiac dysfunction ultimately results in continued progression of the disease when the compensatory mechanisms are severe and prolonged. By the same token exercise training (ExT) also exerts effects on every tissue and organ system (29). Casual observers see the effects of ExT as an increase in endurance or muscle mass or even maximal oxygen consumption (VO_2max), but it is less obvious that ExT has major effects on neuronal function (36, 131, 135, 165, 172, 188), vascular function (41, 87, 168), renal function (97, 135, 215), and the immune system (3, 23, 59), even in the normal state.

Although patients with CHF show a small increase in VO_2max (about 10–20% similar to normal subjects) following

an ExT regimen (9, 106), their absolute VO_2max is below that of normal subjects. Nevertheless, multiple studies now show that ExT in the CHF state improves endurance, quality of life, and survival (10, 26, 115, 116, 123, 139, 140, 173). Numerous studies also have shown reductions in sympatho-excitation following ExT in CHF (82, 101, 124, 125, 135, 153, 217). Alterations in neurotransmitter release in various sympatho-excitatory areas of the brain have been demonstrated (84, 85, 120, 210), along with changes in neuronal discharge sensitivity (199, 206) in CHF. What has been somewhat of an enigma in this field is defining the precise cellular and molecular mechanisms that transduce ExT into reductions in sympathetic nerve activity in normal and disease states. For instance, ExT is well known to increase endothelial function because of an increase in shear stress that results in an increase in nitric oxide (NO) synthase (NOS) expression and activity (61, 111, 183) and ultimately more bioavailable NO. Although ExT has been shown to upregulate NOS and NO in the central nervous system (110, 214, 224) in disease states, the links between the act of ExT and a change in autonomic activity are still not completely understood.

Of all the mediators of sympathetic function, one that is closely implicated in the pathogenesis of CHF is angiotensin II (ANG II). Chronic heart failure is associated with increases in both peripheral and central ANG II (229) and plasma renin activity (184). In fact, many studies have documented activa-

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tion of multiple components of the central renin-angiotensin-aldosterone system in both clinical and experimental CHF (50, 51, 66, 79, 101). It is well established that ANG II can modulate sympathetic nerve activity at several loci in the neuraxis (148). This includes medullary and hypothalamic nuclei such as the rostral ventrolateral medulla (RVLM), the nucleus of the solitary tract (NTS), and the paraventricular nucleus (PVN). It is well known that high levels of ANG II decrease arterial baroreflex function and promote sympatho-excitation (11, 12, 17, 22, 69, 73, 92, 157, 159, 207), in part, through an action in the RVLM (58, 83, 113, 156). In the PVN ANG II can also evoke sympatho-excitation by increasing the discharge sensitivity of parvocellular neurons through its action on the angiotensin type 1 (AT₁R) receptor (85, 144, 217). Finally, ANG II is well recognized to evoke major effects at sympathetic ganglia (105, 149) and at the neuronal target-tissue interface via its potentiation of norepinephrine release (15, 90, 161, 186).

The ability of ANG II to evoke oxidative stress in many cell types, and certainly in neurons, has become a universal finding in the field of autonomic control (179, 185, 213, 222, 228). The fact that ANG II is elevated in CHF and is sympatho-excitatory has made it a prime candidate for pharmacological modulation, but it also may play an important role in the efficacy of nonpharmacological interventions such as ExT in the CHF state. Here we review the role of ExT on ANG II signaling and the regulation of sympathetic outflow (primarily renal) in CHF. Much of the data described comes from the author's laboratories, but the field is rapidly growing as the role of ExT becomes more widely accepted as a therapeutic modality in CHF becomes more widely accepted (80, 140, 143, 202).

ANG II Contributes to Sympatho-Excitation in Chronic Heart Failure

Clearly the renin-ANG II-aldosterone system is one of the prime therapeutic targets in the treatment of CHF. The recognition that ANG II participates in a major way to the progressive worsening of the CHF syndrome has made the use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) the first line of therapy for patients with this disorder. Although the efficacy of these agents is due, in part, to their effects on myocardial and vascular function, they also have effects on autonomic balance and have been shown to lower sympathetic outflow to the kidney and other tissues in CHF (16, 35, 72, 75, 146). Studies carried out in experimental CHF clearly show that central AT₁R signaling participates in the sympatho-excitatory process (48, 54, 85, 162, 225, 227). Intracerebroventricular infusion of the ARB losartan reduces renal sympathetic nerve activity in rabbits with pacing-induced CHF (102). In dogs with CHF, cerebrospinal fluid levels of ANG II are increased and are markedly higher than in plasma (229). The latter finding suggests either de novo synthesis of this peptide in the brain or entry and concentration of peripheral ANG II. In this regard, Biancardi et al. (13) have recently shown the ability of ANG II to pass the blood brain barrier and affect presympathetic neurons. Importantly, ANG II has ready access to receptors in circumventricular organs that are richly endowed with AT₁Rs (27, 30, 43, 112, 117, 154). AT₁R protein and mRNA are also markedly increased in the medulla and hypothalamus of ani-

mals with CHF (54, 66, 76, 103). An early landmark study demonstrating the pathophysiological relevance of these changes in central AT₁R expression in CHF was carried out in a rat myocardial infarction (MI) model of CHF (218). This study showed that intracerebroventricular administration of antisense oligonucleotides against the AT₁R resulted in a significant reduction in renal sympathetic nerve activity compared with administration of scrambled sense oligonucleotides.

ANG II, Abnormal Cardiovascular Reflexes, and Exercise Training in Heart Failure

Abnormal cardiovascular reflexes are thought to play a role in sympatho-excitation in the CHF state. These include a blunted arterial and cardiopulmonary baroreflex and enhanced cardiac sympathetic afferent reflex (CSAR) and arterial chemoreflex (32, 34, 40, 71, 104, 132–134, 163, 182, 194, 196, 197, 223). One of mechanisms by which ANG II causes sympatho-excitation in CHF is through its effects on these sympatho-excitatory and inhibitory reflexes. There is now convincing evidence that ANG II inhibits baroreflex function both acutely and chronically (55, 160). Earlier studies from this laboratory reported blockade of the AT₁R by intravenous infusion of the ANG II receptor antagonist L158809 reduced sympathetic tone and enhanced arterial baroreflex function in dogs and rabbits with pacing-induced CHF (121, 122). Subsequently, we have demonstrated that ExT enhances baroreflex sensitivity by an ANG II-dependent mechanism in a conscious CHF rabbit model (119).

Studies from our laboratories also suggest that a cardiogenic sympatho-excitatory reflex, the so-called CSAR, is significantly augmented and contributes to elevated renal and cardiac sympathetic outflow in CHF (104, 194, 197, 219). Furthermore, the CSAR increases sympathetic outflow and depresses baroreflex function, in part, via an NTS-AT₁R-dependent mechanism (198). However, whether ExT can attenuate the enhanced CSAR in CHF by an ANG II-dependent mechanism remains to be determined.

Many studies have also shown enhanced peripheral chemoreflex sensitivity in both experimental and human CHF (24, 25, 38, 94, 96, 128, 163, 182). Sympatho-excitation can be reduced by silencing input from these major sensory organs: the aortic and carotid bodies. This has been demonstrated in CHF following hyperoxia (5, 142, 205) or removal of the carotid bodies (32, 108). Similar studies have been carried out in hypertension following selective carotid body ablation (1, 136). Li et al. (94) showed normalization of peripheral chemoreflex sensitivity following ExT in rabbits with pacing-induced CHF. Importantly, these investigators also demonstrated that afferent discharge in response to hypoxia was reduced following ExT. Carotid bodies demonstrated increases in AT₁ receptor expression and reductions in neuronal NOS (nNOS) in the CHF state that were reversed following ExT. Finally, treatment with ANG II prevented the beneficial effects of ExT (94).

In addition to the abnormal reflex control of sympathetic outflow in CHF mediated by the reflexes discussed above, recent studies (126, 170, 175, 176, 195) have also demonstrated that an exaggerated exercise pressor reflex (EPR) contributes to the elevated sympathetic outflow in a coronary ligation-induced MI rat model. Studies from our laboratories

(190, 191) have shown that both peripheral afferent and spinal sensitization of the EPR contribute to the exercise-triggered sympatho-excitation in CHF rats. However, the detailed molecular mechanisms underlying peripheral afferent and spinal sensitization of the EPR in CHF remain largely unknown. It is of particular importance to understand if peripheral and central ANG II pathways play a critical role in mediating the sensitization of EPR in CHF. ExT initiated at an early stage of CHF largely prevents the exaggerated EPR-mediated sympatho-excitation and improves exercise intolerance in CHF rats (6, 192, 193). Other studies have also shown a reduction in plasma ANG II following ExT (2, 53, 152).

Exercise Training Reduces Central AT₁R Expression in Heart Failure

We and others (46, 101, 119, 124, 125, 141, 153, 217, 226) have shown that ExT reduces sympathetic nerve activity and circulating ANG II levels in both animals and humans with CHF. Furthermore, ExT in CHF normalizes arterial baroreflex and peripheral chemoreflex sensitivity, in part, due to suppression of an ANG II-dependent mechanism (119, 162). At the molecular level, several studies have shown increases in AT₁R expression (both protein and mRNA) in discrete presympathetic nuclei in the hypothalamus and medulla in animals with CHF (54, 57, 64, 66, 77, 119, 177) and in response to ANG II infusion (129, 201). Although this increase appears to be part of a positive feedback system that further exacerbates sympatho-excitation, the transcriptional regulation of AT₁R expression in the central nervous system is complex and little is known about the effects and mechanisms by which ExT reduces AT₁R expression. We do know, however, that this is an ANG II-dependent mechanism because clamping plasma ANG II at the levels observed in the CHF state abrogates the effects of ExT on AT₁R expression (119). In addition, blockade of the AT₁R reduces its upregulation in CHF (98, 99, 118, 201).

Because CHF is also an inflammatory state (81, 151), much interest has been generated on the role of cytokines and their downstream cellular mediators in mediating AT₁R expression. Exercise training may impact this pathway since it has been shown that ExT reduces cytokine expression in cardiovascular disease states (28, 59, 89, 124). In this regard, a major component of cytokine signaling is mediated by NF- κ B. Therefore, it is of interest to understand the role of this important transcription factor in mediating AT₁R expression in the central nervous system and the impact of ExT on this process. Central cytokine signaling in the CHF state contributes to sympatho-excitation, activation of NF- κ B, and upregulation of the AT₁R (49, 62, 109, 167, 212). Data from cultured neurons show that NF- κ B inhibition reduces AT₁R upregulation in CHF (67, 118). Because ExT reduces plasma ANG II and AT₁R expression in the CHF state (101), it is likely that the cellular signaling pathway involves NF- κ B and its cytosolic inhibitor I κ B. Although there is no binding sequence for NF- κ B on the AT₁R gene, there is a sequence for the transcription factor activator protein 1 (AP1) (14, 70, 200). AP1 is a dimer of c-jun and c-fos, and recent studies show that ANG II activates c-jun and p-JNK in the RVLM of animals and in neuronal cell culture (98, 99). Because NF- κ B mediates an increase in c-fos through the activation of Creb and Elk1 (67), it is likely that ExT impacts AT₁R expression by downregulation of the cytokine

and NF- κ B pathway. Consistent with the above concept, Llewellyn et al. (103) demonstrated decreased c-fos and AT₁R expression in the subfornical organ of rats with CHF following an ExT regimen.

The changes in AT₁R expression in the medulla and hypothalamus following ExT in CHF animals may mediate decreases in renal sympathetic outflow through an NO and reactive oxygen species mechanism. Although acute administration of ANG II in rats has been shown to stimulate NO release centrally (93), chronic ANG II signaling is likely to reduce central nNOS and the inhibitory effects of NO on sympathetic nerve activity in CHF (166). Similar mechanisms may be at play in peripheral organs (147). Because, in general, NO production in sympathetic nuclei is, in general, inhibitory (68, 158, 209, 211), the interaction between NO and ANG II signaling is important in understanding the central mechanisms regulated by ExT. The influence of reduced ANG II and increased NO signaling following ExT has been investigated in rats with CHF (214, 217). These data strongly suggest that ExT impacts specific molecular changes in presympathetic neurons in the setting of CHF through a mechanism that involves both ANG II and NO.

Although transcriptional regulation of the AT₁R may be an important mechanism in the sympatho-excitatory process and one that can be modulated by ExT, there are additional molecular and cellular mechanisms that need to be kept in mind and should be the target of future research. One such mechanism relates to the phosphorylation and turnover of the AT₁R and its modulation by ExT. In a recent study carried out in rats with CHF we showed that the AT₁R is phosphorylated by G protein receptor kinase 5 (GRK5) in the PVN and RVLM (66). GRK5 binds to the AT₁R and targets it for internalization by β -arrestin. Interestingly, although the AT₁R was upregulated in the CHF state and decreased following ExT, there were similar changes in GRK5 expression. At first this seems paradoxical because one would expect decreases in GRK5 to result in an increase in AT₁R expression and vice versa. On the other hand, we speculate that the increase in GRK5 in the CHF state represents an attempt by the system to limit uncontrolled increases in AT₁R expression; that is, it is a reaction to the primary event, which is the transcriptional upregulation of the AT₁R in CHF. In fact, this was clearly demonstrated in cell culture where exogenous ANG II evoked an upregulation in AT₁R expression that was completely inhibited by concomitant upregulation of GRK5. Importantly, overexpression of GRK5 also reduced the ANG II stimulation of NF- κ B. Importantly, suppression of GRK5 by short interfering RNA, on the other hand, evoked an increase in AT₁R expression in response to ANG II. Recent data in the heart also implicates GRK signaling in the nucleus, thereby potentially regulating AT₁R expression at the transcriptional level (60). These molecular changes may play an important role in the sensitivity of presympathetic neurons in CHF and their decrease following ExT.

ANG II and Oxidative Stress

The ability of ANG II to evoke an increase in oxidative stress, especially superoxide anion (O₂⁻) is well known (65, 185, 228). Animals and humans with CHF exhibit elevated reactive oxygen species (ROS) in the brain and periphery (33, 52, 54, 169, 208). Zimmerman et al. have demonstrated in-

creased $O_2^{\cdot -}$ production in the subfornical organ of mice infused intracerebroventricular with ANG II (220, 221). Schultz et al. have demonstrated increased ROS in the carotid body of animals with CHF (38, 39, 95). Overexpression of SOD1 but not extracellular SOD prevented the increase in ROS and the ANG II-induced pressor response (221). In animals with CHF central viral overexpression of either SOD1 or SOD2 reduced sympatho-excitation and enhanced baroreflex function (56) in response to ANG II. Increased levels of cellular ROS are thought to mediate changes in ion channel proteins, thereby contributing to an increase in discharge sensitivity of presympathetic neurons (18–20, 222). In the setting of CHF augmentation of many excitatory neurotransmitters coupled with intracellular ROS provide an important stimulus for increased sympathetic outflow. How does ExT impact this process? There are several possible scenarios. First, ExT provides a stimulus for the upregulation of antioxidant enzymes. In experimental CHF, ExT has been shown to increase the expression of SOD1, SOD2 in the brain, and other tissues (56, 88, 155, 181). However, the precise transduction mechanism that converts the act of ExT into changes in antioxidant enzyme expression and activity is not known. One possibility is that the increase in presympathetic nerve activity that accompanies the act of exercise conditions neurons to cope with increased oxidative stress (56, 86). This may actually be a more global phenomenon than appreciated. During exercise, skeletal mus-

cle generates large amounts of ROS (91, 138, 171) that may, through lipid peroxidation, provide a circulating stimulus to other tissues, including the brainstem, causing a reactive response to upregulate antioxidant enzymes. At the molecular level, there may also be important effects of ExT on cytokine and other pro-inflammatory molecules (23, 89, 174).

An intriguing pathway that may be important in the setting of CHF, hypertension, and other sympatho-excitatory disorders is the modulation of redox sensitive transcription factors such as NF- κ B and Nrf2 (100, 187, 189). These two transcription factors have been shown to regulate and to be regulated by ROS (100). Importantly, NF- κ B has been implicated as an important factor in the upregulation of the AT $_1$ R in cultured neurons and in animals with CHF as well as in response to chronic ANG II infusion. Preliminary data from this laboratory suggest that knockdown of p65 (a prime subunit of NF- κ B) in the RVLM using viral delivery of p65 shRNA normalizes the pressor response to systemic infusion of ANG II, suggesting the importance of ANG II-induced neurogenic hypertension and an important role for NF- κ B (Fig. 1). Recent data show that NF- κ B and Nrf2 compete for binding to the nuclear creb binding protein (100). Exercise training has been shown to modulate both proteins (7, 74, 150, 180). Although complete studies are not available to show that this competition may be one mechanism by which oxidative stress and AT $_1$ R expression is upregulated in sympatho-excitatory areas of the brain,

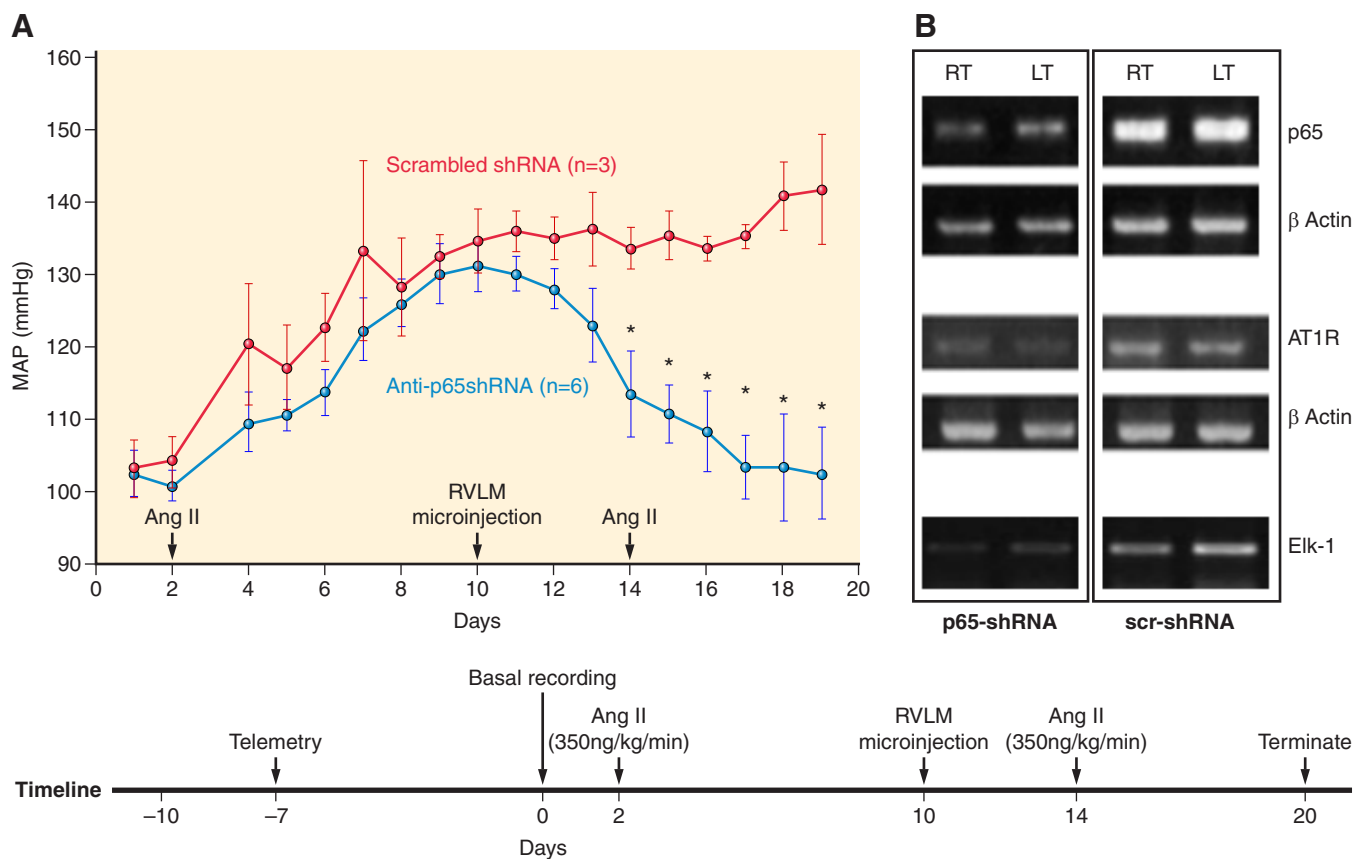


Fig. 1. *A*: effects of bilateral injection of p65 short hairpin RNA (shRNA) into the rostral ventrolateral medulla (RVLM) on the blood pressure response to systemic infusion of ANG II in conscious rats. *B*: Western blots show the suppressive effects of shRNA on p65, angiotensin type 1 receptor (AT $_1$ R), and Elk-1 protein. RT, right; LT, left. The time course of the experiment is shown below *A* and *B*. * $P < 0.05$ compared with scrambled shRNA (scr-shRNA) treatment. MAP, mean arterial blood pressure.

we speculate that in CHF and hypertension, NF- κ B-Nrf2 competition may be an important pathway.

Exercise Training Impacts Central ACE2

Mounting evidence over the past 10 years or so has pointed to the importance of ANG II metabolites in cardiovascular regulation. One of these, Ang 1–7, has risen to the forefront as an important peptide whose biological actions are opposed to that of ANG II by signaling through the Mas receptor (45, 131, 145). The balance between ACE and ACE2 determines the relative amount of each peptide in plasma and tissue. Chronic administration of Ang 1–7 is anti-hypertensive and anti-hypertrophic (63, 164). In the central nervous system it has been demonstrated that Ang 1–7 provides for sympatho-inhibition or at the very least a break on the sympatho-excitatory effects of ANG II (42, 78, 131). Furthermore, central ACE2 overexpression is sympatho-inhibitory in the CHF state (131, 204, 216); therefore, it is reasonable to examine the role of ACE and ACE2 in mediating the beneficial effects of ExT on sympathetic nerve activity in CHF.

Central infusion of Ang 1–7 clearly reduces renal sympathetic nerve activity and improves baroreflex function in conscious rabbits with pacing-induced CHF (78). This effect can be inhibited by co-infusion of the Mas receptor antagonist A779. In this same model of CHF, protein and mRNA expression of ACE2 was shown to be upregulated by ExT in the

RVLM and PVN (79). At the same time reciprocal changes in ACE expression were observed. These changes appear to be global since they occur in many organ systems and are potentially regulated by changes in microRNAs (8, 44, 137). Furthermore, ExT can reduce ACE2 shedding in the kidney by inhibition of ADAM 17 (178). Increased ACE2 can profoundly reduce oxidative stress in rats (203). In this regard, ExT has been shown to reduce ACE and increase ACE2 along with a decrease in oxidative stress in spontaneously hypertensive rats (4). The end result of this process is to mitigate the sympatho-excitatory effects of ANG II by a process that both enhances degradation of ANG II and increases the production of the sympatho-inhibitory peptide Ang 1–7.

Summary and Conclusions

There is little doubt that ExT is of benefit in patients with CHF (9, 29, 31, 80, 174). The mechanisms responsible for the effects of ExT in the setting of CHF are complex. Exercise training has profound effects on sympathetic and vagal outflow from the central nervous system, on inflammatory mediators, on ROS, and of course, on systemic hemodynamics, including endothelial function. All of these processes are abnormal in the CHF state. Interestingly, ANG II has been shown to be involved in activation of these processes primarily through the AT₁R. Figure 2 schematically summarizes these abnormal processes and indicates that ExT reduces or reverses many of

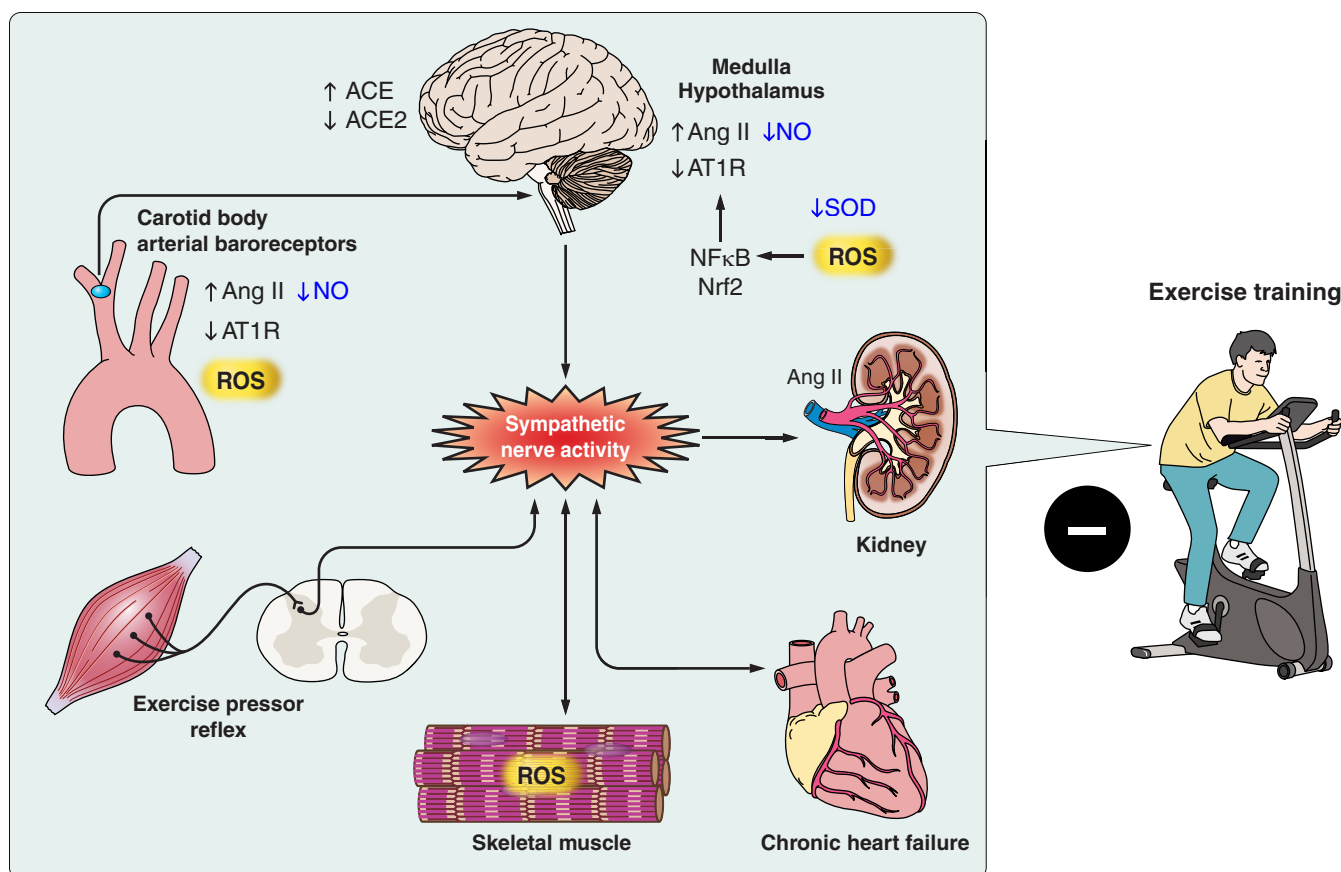


Fig. 2. A schematic depiction of some of the potential mechanisms by which exercise training (ExT) reduces sympathetic outflow in the heart failure state. Components of the renin ANG II system and reactive oxygen species (ROS) play important roles in this process in both the central nervous system and in the periphery. NO, nitric oxide.

these processes in the CHF state. Although ExT reduces circulating ANG II, AT₁R expressions, and oxidative stress in the CHF state, it also increases the central production of ACE2 and reduces ACE. It is still not completely clear how the act of ExT is transduced into a reduction in sympathetic outflow in CHF. Current data suggest, however, that modulation of the balance between NF- κ B and Nrf2 signaling and the modulation of antioxidant enzyme production and thus oxidative stress may also play an important role in this process.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

Author contributions: I.H.Z. conception and design of research; I.H.Z. prepared figures; I.H.Z. drafted manuscript; I.H.Z., H.D.S., K.P.P., and H.-J.W. edited and revised manuscript; I.H.Z., H.D.S., K.P.P., and H.-J.W. approved final version of manuscript.

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