Exercise pressor reflex in health and diseases: Animal studies

Satoshi Koba

Division of Integrative Physiology, Tottori University Faculty of Medicine, 86 Nishi-cho, Yonago, Tottori 683-8503, Japan

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Abstract A reflex originating in exercising skeletal muscle contributes to sympathoexcitation during exercise. This muscle-based reflex is termed the exercise pressor reflex (EPR). In this review, mechanisms underlying activation of the EPR are examined based on findings mainly obtained from cat studies. Specifically, roles played by chemical and mechanical stimuli due to contraction in increasing discharges of muscle afferent fibers are discussed. Roles metabolic byproducts play in stimulating and sensitizing muscle afferents are also examined. Central cardiovascular sites involved in activation of the EPR are investigated. In this review, moreover, mechanisms by which the EPR function becomes abnormal in heart failure and hypertension are discussed on the basis of experimental data mainly provided by rat studies. In heart failure, the muscle metaboreflex is attenuated while the mechanoreflex is enhanced. In hypertension, both the muscle metabo- and mechano- reflexes are enhanced. Peripheral factors leading to EPR dysfunction in these pathological conditions are examined.

Keywords: exercise, heart failure, hypertension, skeletal muscle contraction, sympathetic nervous system

Introduction

Sympathoexcitation seen during exercise is mediated by two distinct neural mechanisms: central command and a reflex originating in exercising skeletal muscle. Central command emanates from the rostral brain and radiates to neural circuits in the brainstem, thereby causing parallel activation of motor and sympathetic neurons. The muscle based reflex, termed ‘exercise pressor reflex’ (EPR), is evoked as thin fiber muscle afferents (groups III and IV) are stimulated by mechanical deformation of the afferents’ receptive fields, as well as by metabolic byproducts during exercise (muscle mechano- and metaboreflexes, respectively). In turn, afferent engagement stimulates the central cardiovascular pathways in the brainstem, thereby causing sympathoexcitation. In 1937, Alam and Smirk were the first to suggest that muscle afferent engagement during exercise has a pressor effect in humans. The authors found that a blood pressure increase during exercise in healthy subjects became augmented if the exercising skeletal muscle was ischemic, and that much of the increase in blood pressure was maintained when contractions stopped, but the muscle ischemia continued.

While roles played by the EPR in autonomic adjustments to exercise have been determined in human studies, our understanding of mechanisms by which the EPR is evoked has been largely dependent on outcomes from animal studies. In this article, how skeletal muscle contraction reflexly mediates autonomic and cardiovascular responses is discussed based on findings mainly obtained in cat studies. Moreover, data have accumulated demonstrating that the EPR function becomes abnormal under pathological conditions. In this article, mechanisms underlying the EPR dysfunction in heart failure and hypertension are also examined on the basis of data mainly collected from rat disease models.

Contribution of cat studies to understanding EPR mechanisms

Strong support for the concept that skeletal muscle contraction reflexly increases blood pressure came from experiments performed on anesthetized or unanesthetized decerebrated cats. In 1971, Coote et al. demonstrated that the blood pressure of anesthetized cats elevated while the triceps surae muscles were continuously (30-60 sec) and statically contracted by electrically stimulating the ventral roots. The pressor effect of contraction was a reflex because the response was prevented by sectioning the dorsal roots. Moreover, the EPR response to contraction (EPR response) became exaggerated when the arterial supply to the circulation of the contracting muscles was occluded, suggesting that metabolic byproducts due to contraction play a role in reflexly regulating the cardiovascular system.

McCloskey and Mitchell found that anodal blockade of the dorsal roots, which prevented impulses from group I and II muscle afferents, did not alter the EPR response in anesthetized cats. By contrast, topical application of...
a local anesthetic to the dorsal roots, which did not prevent impulses from group I and II afferents, attenuated the EPR response. These data suggest that stimulation of group III and IV muscle afferents, but not group I or II, during skeletal muscle contraction is responsible for the EPR generation. No role has been found for group I and II muscle afferents in evoking the EPR8. Recently, evidence in humans was provided demonstrating that stimulation of group III and IV muscle afferents is part of cardiovascular regulation during dynamic exercise. In healthy subjects, lumbar intrathecal fentanyl to block the central projection of μ-opioid-receptor sensitive group III/IV muscle afferents from the lower limbs reportedly reduced the pressor response to single leg knee-extensor exercise7).

Direct recordings of afferent impulses arising from endings in skeletal muscle while the muscle was contracted in anesthetized cats were taken8,9). Continuous contraction in skeletal muscle while the muscle was contracted directly recorded identified substances to stimulate and/or sensitize muscle afferents (Fig. 1). Intra-arterial infusion into cat hindlimb muscle circulation of ATP10, arachidonic acid11,12,13, and lactic acid14,15, all of which are byproducts of muscular contraction, were shown to increase discharges of group III and/or IV muscle afferents. Moreover, arachidonic acid15 and lactic acid16 infused intra-arterially enhanced the responses of group III muscle afferents to contraction, suggesting their role in sensitizing mechanically sensitive muscle afferents responding to contraction. Finally, a pharmacological blockade of muscle receptors for ATP (purinergic 2X)17, bradykinin (B2)18, and lactic acid19,20 or the cyclooxygenase inhibitor21 reportedly attenuated increases in cat muscle afferent activities in response to contraction.

The majority of group III and IV muscle afferent nerves makes their first synapse in the superficial dorsal horn of the spinal cord (Fig. 1). Neural transmitters/modulators which play a role in transmitting afferent signals from exercising skeletal muscle at this site were determined, including ATP19,20, glutamate21,22, NO23,24, and substance P25,26. For example, microdialyzing a purinergic 2X receptor blocker into the spinal dorsal horn reduced the EPR response, and microdialyzing α,β-methylene ATP into the dorsal horn augmented the EPR response in anes-

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**Exercise pressor reflex arc**

Fig. 1 Schema of the exercise pressor reflex (EPR) arc. Exercising skeletal muscle increases discharges of group III and group IV afferent fibers innervating skeletal muscle through its mechanical and chemical stimuli within the muscle. Metabolic byproducts of muscular contraction include ATP, arachidonic acid metabolites such as prostaglandin E2, bradykinin, and lactic acid, which play a role in stimulating and/or sensitizing muscle afferents responding to contraction. Group III muscle afferents are considered predominantly mechanically sensitive while group IV muscle afferents are chemically sensitive. Sensory signals from these afferents are processed within central cardiovascular sites. Nevertheless, central cardiovascular pathways involved in generation of the EPR have not been fully determined yet. In turn, sympathetic nerve activity is reflexly elevated, parasympathetic nerve activity is reduced, and the cardiovascular system is regulated. NTS: nucleus of solitarii tract, PAG: periaqueductal gray, RVLM: rostral ventrolateral medulla.
The medulla oblongata is required to generate the EPR (Fig. 1). Cats decerebrated at the midcollicular level reportedly exhibited a larger pressor response to continuous contraction of hindlimb skeletal muscle than cats decerebrated at 5-mm rostral to the obex\(^27\). Moreover, C1 spinal transection abolished the EPR response. By contrast, cerebellectomy had no effect on EPR response. Subsequently, it was shown in cats that 1) the EPR response was reduced by bilateral microinjections into the rostral ventrolateral medulla (RVLM) of an excitatory amino acid receptor antagonist, kynurenic acid\(^28\), and that 2) >70% RVLM neurons were stimulated during hindlimb skeletal muscle contraction\(^29\). These findings suggest that the RVLM, which contains presymptomatic neurons that have spontaneous activity and directly project to the spinal cord, is a key area to evoke the EPR. Specific areas of the medulla to be activated by skeletal muscle contraction were also studied by examining immunoreactivity of Fos, a marker of neuronal activation\(^30,31\). Continuous contraction of hindlimb skeletal muscle in barointact and barodenervated cats was followed by increases in Fos expression in several regions of the medulla, especially the RVLM and nucleus of solitary tract (NTS). The NTS is the first synaptic station of the cardiorespiratory afferent inputs including baroreceptors. The immunohistochemical data suggest that these medullary cardiovascular sites are activated by skeletal muscle contraction independently of concomitant arterial baroreflex activation.

Whether the rostral part of the brainstem is activated by skeletal muscle contraction was also investigated. A series of studies by Li and colleagues demonstrated in cats that 1) Fos expression was increased in the periaqueductal gray matter (PAG) after skeletal muscle contraction\(^32\), 2) glutamate was released in the PAG by contraction\(^33\), and 3) muscimol, a GABA receptor agonist microinjected into the PAG, reduced the pressor response to contraction\(^34\). Therefore, activation of the PAG likely contributes to activation of the EPR (Fig. 1). A human study, where local field potentials were directly recorded in patients having undergone neurosurgery, supports the notion that the PAG is activated by afferent engagement due to contraction\(^35\).

As stated, brainstem regions including the NTS, RVLM, and PAG have been identified to be involved in generation of the EPR (Fig. 1). Nevertheless, supraspinal pathways which functionally connect between afferent inputs originating in exercising skeletal muscle and sympathetic/parasympathetic efferent outputs have not been fully identified yet (Fig. 1).

Reflex sympathoexcitation caused by skeletal muscle contraction has been demonstrated in cats (Fig. 1). Sympathetic nerve activities (SNA) directed toward blood vessels in a variety of organs including kidney\(^36,37\), skeletal muscle\(^38\), and heart\(^39\), were increased when hindlimb skeletal muscle was continuously and statically contracted in anesthetized or unanesthetized decerebrate cats. Moreover, the roles played by the EPR-evoked sympathoexcitation in mediating renal vasoconstriction\(^40\) and tachycardia\(^39\) have been demonstrated. Of note, skin SNA was not reflexly increased by skeletal muscle contraction\(^41\), suggesting that the EPR-elicited sympathetic outflows are organ-specific.

Besides electrically stimulating motor nerves to induce skeletal muscle contraction, passively stretching skeletal muscle has often been done to stimulate skeletal muscle in animal and human studies. This is because passive muscle stretch is a maneuver to selectively excite mechanically sensitive muscle afferents, thereby allowing us to focus on roles for the muscle mechanoreflex. It was demonstrated in anesthetized cats that the blood pressure was reflexly elevated by passively stretching the triceps surae muscles, which did not generate any muscle metabolites\(^42\). Subsequent electrophysiological studies demonstrated stimulation of mechanically sensitive group III muscle afferents\(^43\), cardiac\(^39\) and renal\(^40\) SNA increases, as well as vagal withdrawal\(^44\), in response to muscle stretch in anesthetized or decerebrate cats. Human subjects also exhibited reflexly increased muscle SNA during passive muscle stretch\(^45\). Of note, however, passive muscle stretch in decerebrate cats reportedly stimulated a different population of mechanically sensitive group III muscle afferents than did static muscle contraction\(^46\).

Thus, when interpreting data collected with the muscle stretch protocol, we need to take it into account as a limitation that the mechanoreflex evoked by passive muscle stretch is not equal to the mechanical component of the EPR.

Development of rodent model for EPR studies

As discussed, cat studies have contributed to our understanding of mechanisms underlying activation of the EPR. In cats, however, experimental techniques to study cellular and molecular biology are not readily available. Moreover, although mechanisms for abnormal cardiovascular regulation during exercise in cardiovascular diseases such as heart failure\(^47\) and hypertension\(^48\) have recently attracted research attention, disease models have not been developed or are no longer cost effective in larger animals. Therefore, alternative animal models such as rodents need to be further developed to investigate the EPR function in health and diseases.

Attention needs to be paid to the fact that cardiovascular changes, seen during continuous contraction of skeletal muscle in anesthetized rats, have been reportedly different from those in cats and inconsistent between reports. Continuous contraction of hindlimb skeletal muscle in anesthetized rats elicited an increase\(^49\), a decrease\(^50\) or no change\(^51\) in blood pressure. These discrepancies could be due to unknown effects of anesthesia in this species\(^52\).
Thus, many researchers had avoided using rats for EPR studies.

An article\(^5\) was published in 2001, reporting that a reliable rat model for the study of the EPR was successfully developed. Smith and colleagues\(^5\) carried out decerebration at the precollicular level in rats, and electrically stimulated the cut ends of spinal ventral roots to induce continuous static contraction of the hindlimb skeletal muscle. In the decerebrate non-anesthetized rats, either contraction or passive stretch of hindlimb skeletal muscle reflexly elevated the blood pressure as seen in cats anesthetized or nonanesthetized decerebrated. The reliability of the decerebrate rat preparation to study the EPR function was readily supported by others\(^5\). Subsequently, it was also reported that the decerebrate rats exhibited increases in discharges in group III and IV muscle afferents\(^5\) and reflex sympathoexcitation in an organ-specific manner\(^5\) during contraction or passive stretch of skeletal muscle as did the cat preparations. In addition, a technical report that describes the surgical details to establish the decerebrate rat preparation has been published\(^5\). Currently, the decerebrate rat preparation has enabled us to investigate cellular and molecular mechanisms underlying the generation of the EPR in health and diseases.

In mice, transgenic and gene knockout techniques are readily available. Kramer and colleagues\(^5\) investigated in mice, transgenic and gene knockout techniques are currently, the decerebrate rat preparation has enabled us to investigate cellular and molecular mechanisms underlying the generation of the EPR in health and diseases.

**Contribution of rat studies to understanding mechanisms underlying EPR dysfunction in heart failure**

Heart disease is a global pandemic, which caused 15.5% of deaths in Japan in 2013 according to the statistics report by the Ministry of Health, Labour and Welfare of Japan. Heart failure (HF) is earmarked by low cardiac outputs for a given level of physical exertion that leads to reduced blood supply to metabolizing tissues. Moreover, SNA becomes overactive in this disease, which plays a role in disease progression. Supervised exercise training interventions in patients with HF not only improve quality of life and functional class but also decrease resting sympathetic overactivity\(^6\). However, HF includes abnormal autonomic adjustments to exercise. Specifically, sympathoexcitatory response to exercise is amplified in patients with HF\(^6\). As a result, renal vasoconstriction is enhanced\(^6\), and the increase in blood flow towards exercising skeletal muscle circulation is attenuated\(^6\). The amplified sympathoexcitation during exercise is a possible cause of exercise intolerance, a hallmark of HF\(^6\). Thus, understanding regulatory mechanisms of SNA during exercise in HF is clinically important.

Since skeletal muscle morphology and metabolism are altered in HF\(^6\), roles played by activation of the EPR in patients with HF have attracted research attention. Reportedly, isolated activation of muscle metaboreflex by postexercise circulatory occlusion of the exercising limb resulted in less elevation of muscle SNA\(^,6\) and less renal vasoconstriction\(^,6\) in HF patients than in healthy subjects. These observations suggest that the muscle metaboreflex is attenuated in HF. By contrast, the muscle mechanoreflex activation due to passive stretch of skeletal muscles evoked a significant elevation of muscle SNA\(^6\) and enhanced renal vasoconstriction\(^6\) in HF patients. These findings suggest that the muscle mechanoreflex is enhanced in HF. Nevertheless, the procedures of postexercise ischemia and passive stretch are not equal to induction of the chemical and mechanical components of the EPR, respectively, and are imperfect to assess the precise role played by the EPR activated by skeletal muscle contraction. In human studies, moreover, it is technically difficult to explore mechanisms underlying alterations in muscle metabo- and mechanoreflexes function in HF. Experiments performed on the decerebrate rat model overcame these limitations noticed in human studies.

Smith and colleagues\(^6\) tested if the EPR-mediated pressor response would be altered in rats with HF after myocardial infarction. In the decerebrate rats, activation of the EPR by electrically induced continuous muscle contraction resulted in a significantly larger pressor response in animals with HF compared to healthy controls. Comparable results were obtained with passive muscle stretch, as subsequently observed by Li and colleagues\(^7\). These results demonstrate that the EPR as well as mechanoreflex are augmented in HF, leading to the hypothesis that the muscle mechanoreflex contributes to EPR dysfunction that develops from this disease (Fig. 2). This hypothesis was supported by a subsequent study by Smith and colleagues\(^7\) demonstrating that the administration of gadolinium (a selective blocker of mechanoreceptors) within the hindlimb attenuated the EPR response to a larger degree in rats with HF than in healthy controls.

Koba and colleagues\(^7\) successfully recorded SNAs directed to kidney and hindlimb [renal SNA (RSNA) and lumbar SNA (LSNA), respectively] during 1-min intermittent bouts (1- to 4-s stimulation to relaxation) of static skeletal muscle contraction in decerebrate rats. Both the RSNA and LSNA responses to contraction in the rats with HF were significantly larger than those in healthy controls. It is noted that the intermittent bouts of contraction were considered to mainly evoke muscle mechanoreflex. This notion was made since RSNA and LSNA responded rapidly at the onset of muscle tension development with a short time delay (<0.5 sec) to reach the peak SNA response; RSNA and LSNA responses were synchronized as tension was developed for 1 sec during contraction, as seen during passive muscle stretch\(^6\). Therefore, the greater RSNA and LSNA responses in HF rats likely resulted
from the mechanical component of the EPR. Additionally, increases in discharges of group III muscle afferents in response to continuous contraction of hindlimb skeletal muscle were greater in rats with HF than in healthy controls\(^{54}\). These electrophysiological data also support the hypothesis that HF enhances the mechanical component of the EPR (Fig. 2).

Mechanisms by which the muscle mechanoreflex becomes enhanced in HF need to be elucidated. ATP rises in skeletal muscle interstitium with contraction\(^{73}\), and stimulates P2X receptors on thin fiber muscle afferents\(^{10}\), thereby not only stimulating chemically sensitive afferents, but also sensitizing mechanically sensitive afferents\(^{74}\). Li and colleagues\(^{70}\) found that α,β-methylene ATP infused intra-arterially into hindlimb circulation of the decerebrate rats enhanced the pressor response to passive stretch to a larger degree in rats with HF than in healthy controls. This finding suggested that ATP in skeletal muscle of HF has an effect to enhance the muscle mechanoreflex. The hypothesis of the role for ATP in HF was supported by another study demonstrating that intra-arterial infusion into the hindlimb circulation of PPADS, a P2X receptor antagonist, reduced the increase in group III muscle afferent activity, in response to contraction as well as stretch, to a greater extent in HF rats than in healthy controls\(^{54}\). Moreover, expression of the P2X receptors in rat dorsal root ganglion cells was upregulated in HF\(^{54,75}\). The receptor upregulation likely explains the amplified effect of muscle interstitial ATP to enhance the muscle mechanoreflex in HF (Fig. 2).

Bradykinin was also suggested to contribute to the enhancement of the muscle mechanoreflex in HF. This auto-oid is increased within skeletal muscle by contraction\(^{76}\), and plays a role in sensitizing group III muscle afferent fibers responding to contraction\(^{17}\). It was also reported that muscle interstitial bradykinin in patients with HF is elevated as compared to that of healthy subjects\(^{77}\). On the basis of these findings, Koba and colleagues\(^{78}\) tested if activation of bradykinin receptors located on muscle afferents during contraction contributes to the exaggerated EPR in HF. In HF rats, the greater RSNA response to intermittent bouts of static muscle contraction than that in healthy controls was reduced by intra-arterial injection into the hindlimb circulation of a B2 receptor antagonist, HOE-140. In healthy controls, on the other hand, HOE-140 had no effect on the EPR-mediated sympathoexcitatory response. These data suggest that bradykinin within exercising skeletal muscle is part of the exaggerated EPR through its enhancing effect of the mechanoreflex in HF (Fig. 2).

Oxidative stress, which is increased in HF, has also been identified as a cause to exaggerate the EPR in this disease. Superoxide reportedly has an enhancing effect on action potential by inhibiting the activity of voltage-gated potassium ion channels in a variety of cells including neural cells\(^{79}\). Koba and colleagues\(^{80}\) tested the hypothesis that muscle oxidative stress in HF plays a role in sensitizing muscle afferents engaged during contraction, thereby contributing to the exaggerated EPR. Electrically induced continuous hindlimb muscle contraction in decerebrate rats with HF evoked larger increases in RSNA and blood pressure as compared to control rats. In the HF rats, the EPR responses were reduced by intra-arterial injection into the hindlimb circulation of Tempol, a superoxide dismutase mimetic. Tempol also attenuated the RSNA response to intermittent bouts of static contraction, which mainly stimulate muscle mechanoreceptors, in the HF rats. In control rats, Tempol had no effect on these responses. These results supported the study hypothesis. Muscle oxidative stress may be mediated by the renin-angiotensin-aldosterone system (RAAS) of which activation is elevated in HF, as discussed in the latter part of this article (Fig. 2).

As discussed, it is considered that muscle metabolite

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Fig. 2  **EPR dysfunction in heart failure and hypertension.** In heart failure, the muscle mechanoreflex is enhanced and the metaboreflex is attenuated. As a result, the EPR becomes exaggerated in heart failure. In hypertension, by contrast, both the muscle mechanoreflexes are enhanced. As a result, the EPR becomes exaggerated in hypertension. Peripheral factors leading to EPR dysfunction are also outlined. RAAS: renin-angiotensin-aldosterone system.
overproduction and/or changes in intramuscular environment, due to alterations of skeletal muscle morphology and metabolism, result in sensitization of mechanically sensitive muscle afferents, thereby exaggerating the EPR.

By contrast, as demonstrated by human studies, the muscle metaboreflex becomes attenuated in HF. Li and colleagues provided rat data demonstrating that the pressor response to injection into the arterial supply of hindlimb of capsaicin, a stimulant of vanilloid receptor subtype 1 (VR1) dominantly located on unmyelinated group IV afferents, was attenuated in rats with HF compared to healthy controls. In order to uncover the mechanisms underlying the attenuated metaboreflex in HF, Smith and colleagues performed sets of experiments. First, the effect of selective withdrawal of group IV afferents on EPR response was examined. Group IV afferent fibers were ablated in neonatal rats by subcutaneous administration of capsaicin. In the neonatal capsaicin-treated adult animals, electrically induced static muscle contraction, as well as passive stretch, recapitulated the exaggerated pressor response to contraction, as seen in rats with HF. Next, the pressor response to hindlimb intra-arterial capsaicin injection was examined in adult capsaicin-treated rats and HF rats. Both adult capsaicin-treated rats and HF rats displayed an attenuated pressor response to capsaicin compared to healthy controls. Moreover, expression of mRNA for the VR1, a marker of group IV fibers, was reduced in HF rats compared to controls, reflecting the death of group IV fibers. Taken together, these observations not only support the concept of attenuated muscle metaboreflex in HF, but also suggest that the EPR dysfunction in HF results, in part, from functional and molecular alterations in group IV muscle afferent fibers (Fig. 2). Of note, this occurs despite an overall exaggeration of the EPR in HF. The group III afferent fibers are considered to overcompensate for the functional abnormalities in group IV afferent fibers in HF.

Another study in which muscle afferent activities in the decerebrate rats were directly recorded has demonstrated that responses of the group IV afferents to either continuous muscle contraction or capsaicin injection into the hindlimb circulation were reduced in HF rats compared to healthy controls.

At present, little research attention has been paid to central mechanisms, which may be involved in the exaggeration of the EPR in HF. In this regard, Wang and colleagues recently focused on the role of the spinal glutamatergic system in HF. The authors tested if the exaggerated EPR in HF is associated with increased glutamatergic activity in the spinal cord. Firstly, microinjection of glutamate into the dorsal horn of the spinal cord during muscle contraction compared to healthy controls. Thirdly, protein expression of both non-NMDA and NMDA glutamate receptors were elevated in the dorsal horn of the spinal cord in HF rats. Finally, HF rats exhibited greater glutamate release into the dorsal horn during muscle contraction compared to healthy controls. These results suggest that the spinal glutamatergic system contributes to the exaggerated EPR in HF.

**Contribution of rat studies to understanding of mechanisms underlying EPR dysfunction in hypertension**

Hypertension is associated with an increased risk of cardiovascular diseases including HF. While antihypertensive treatments include increased physical activity or exercise, we need to note that sympathoexcitatory and pressor responses to a bout of exercise are exaggerated in hypertension. Cardiovascular hyperexcitability is a possible cause of adverse cardiac events such as acute myocardial ischemia, myocardial infarction, left ventricular hypertrophy, or arrhythmia as well as stroke. Human studies have revealed that in hypertension the EPR function becomes abnormal, thereby contributing to the cardiovascular hyperactivity. Mechanisms underlying the EPR dysfunction in hypertension have been investigated in rodent studies.

Smith and colleagues have determined the roles played by the mechanical and chemical components of the EPR in generating this reflex in hypertension. First, Smith et al. showed that electrically induced continuous static muscle contraction reflexly elicited a greater pressor response in spontaneous hypertensive rats (SHRs) than that in normotensive controls, suggesting the exaggeration of the EPR in hypertension (Fig. 2). Then, Leaf et al. showed that pressor responses to either passive muscle stretch or intra-arterial infusion of capsaicin into hindlimb circulation were greater in SHR, suggesting that the exaggerated EPR in hypertension is mediated by both mechanoreflex and metaboreflex overactivity (Fig. 2). Mizuno et al. supported the concept of the enhanced muscle mechanoreflex in hypertension by showing that the blockade of muscle mechanoreceptors with gadolinium attenuated the RSNA and pressor responses to continuous contraction in SHR. Mizuno et al. also supported the notion that the muscle metaboreflex is enhanced in hypertension by demonstrating that treatment with the VR1 receptor antagonist capsazepine in skeletal muscle of SHR reduced the reflex responses to ischemic contraction to a greater extent than in normotensive controls.

Koba and colleagues examined mechanisms underlying the exaggerated EPR in hypertension by focusing on roles for RAAS activity. Angiotensin II (Ang II), an effector molecule of the RAAS, has been known to be elevated in hypertension and activate NADPH oxidases, thereby inducing oxidative stress. Koba et al. found that, in
rats with hypertension induced by 2 weeks subcutaneous infusion of Ang II, the RSNA and pressor responses to continuous contraction became exaggerated, and that Tempol administered within skeletal muscle reduced the EPR responses. Of note, exaggeration of the EPR was mediated, at least in part, by the mechanical component of the EPR, since in the hypertensive rats the RSNA response to intermittent (1- to 4-s stimulation to relaxation) bouts of contraction was also exaggerated. Moreover, the generation of muscle superoxide, and mRNA and protein expressions for gp91phox, a NADPH oxidase subunit, in skeletal muscle tissue, were elevated in the hypertensive rats. These results suggest that increased activity of RAAS in hypertension induces oxidative stress in skeletal muscle, thereby exaggerating the EPR through its enhancing effect of the muscle mechanoreflex (Fig. 2).

Adulthood hypertension can be prenatally programmed by maternal dietary protein deprivation. Recently, in the rat model of prenatal programming of hypertension (PPH), EPR dysfunction was found which may play a role in developing hypertension. Mizuno and colleagues90) demonstrated that the RSNA and pressor responses to contraction were exaggerated in the PPH rats. Moreover, orally-administered treatment with angiotensin converting enzyme inhibitor enalapril in the PPH rats could reduce the exaggerated EPR responses91). Thus, RAAS activity likely contributes to the EPR dysfunction in PPH.

Summary

Animal studies have uncovered mechanisms by which the EPR is evoked. The EPR is mediated by stimulation of mechanically and chemically sensitive muscle afferents due to skeletal muscle contraction. A number of muscle metabolic byproducts during contraction play a role in not only stimulating chemically sensitiveafferent fibers, but also mechanically sensitive afferents. The dorsal horn of the spinal cord is the first synaptic site in the EPR arc. Afferent input from exercising skeletal muscle activates central cardiovascular sites, thereby generating sympathetic outflows to peripheral organs and parasympathetic withdrawal.

Animal studies have also contributed to our understanding of mechanisms underlying EPR dysfunction in diseases. In HF, the muscle metaboreflex is attenuated while the mechanoreflex is enhanced. In hypertension, both muscle metabo- and mechano- reflexes are enhanced. The findings identifying peripheral factors leading to EPR dysfunction (e.g., oxidative stress in muscle) may hold therapeutic potential for suppressing sympathetic hyperactivity in response to a single bout of exercise in HF and hypertension. Future research is necessary to prove the benefits of cardiovascular risk reduction in the pathological conditions associated with physical activity or exercise training by normalizing or altering the EPR dysfunction (Fig. 2).

Conflict of Interests

The author declare that there is no conflict of interests regarding the publication of this article.

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