Sympathetic vasoconstriction in skeletal muscle: modulatory effects of aging, exercise training, and sex¹

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Abstract: The sympathetic nervous system (SNS) is a critically important regulator of the cardiovascular system. The SNS controls cardiac output and its distribution, as well as peripheral vascular resistance and blood pressure at rest and during exercise. Aging is associated with increased blood pressure and decreased skeletal muscle blood flow at rest and in response to exercise. The mechanisms responsible for the blunted skeletal muscle blood flow response to dynamic exercise with aging have not been fully elucidated; however, increased muscle sympathetic nerve activity (MSNA), elevated vascular resistance, and a decline in endothelium-dependent vasodilation are commonly reported in older adults. In contrast to aging, exercise training has been shown to reduce blood pressure and enhance skeletal muscle vascular function. Exercise training has been shown to enhance nitric oxide-dependent vascular function and may improve the vasodilatory capacity of the skeletal muscle vasculature; however, surprisingly little is known about the effect of exercise training on the neural control of circulation. The control of blood pressure and skeletal muscle blood flow also differs between men and women. Blood pressure and MSNA appear to be lower in young women than in men. However, females experience a larger increase in MSNA with aging compared with males. The mechanism(s) underlying the altered SNS control of vascular function in females remains to be determined.

Novelty:

- This review summarizes our current understanding of the effects of aging, exercise training, and sex on sympathetic vasoconstriction at rest and during exercise.
- Areas where additional research is needed are also identified.

Key words: sympatholysis, vascular conductance, blood flow.

Résumé : Le système nerveux sympathique (« SNS ») est un régulateur extrêmement important du système cardiovasculaire. Le SNS contrôle le débit cardiaque et sa distribution ainsi que la résistance vasculaire périphérique et la pression artérielle au repos et pendant l'exercice. Le vieillissement est associé à une augmentation de la pression artérielle et à une diminution du débit sanguin dans les muscles squelettiques au repos et en réponse à l'exercice. Les mécanismes responsables de la réponse éteinte du débit sanguin dans les muscles squelettiques à l'exercice dynamique avec le vieillissement ne sont pas entièrement élucidés; cependant, une augmentation de l'activité des nerfs sympathiques musculaires (« MSNA »), une résistance vasculaire élevée et une diminution de la vasodilatation dépendante de l'endothélium sont fréquemment rapportées chez les personnes âgées. Contrairement au vieillissement, l'entraînement physique réduit, selon des études, la pression artérielle et améliore la fonction vasculaire des muscles squelettiques. Études à l'appui, l'entraînement physique améliore la fonction vasculaire dépendante de l'oxyde nitrique et peut améliorer la capacité vasodilatatrice du système vasculaire des muscles squelettiques; néanmoins, étonnamment, on sait peu de choses sur l'effet de l'entraînement physique sur le contrôle neural de la circulation. Le contrôle de la pression artérielle et du débit sanguin des muscles squelettiques diffère aussi entre les hommes et les femmes. La pression artérielle et la MSNA semblent être plus faibles chez les jeunes femmes que chez les hommes. Toutefois, les femmes présentent par rapport aux hommes une augmentation plus importante de la MSNA avec le vieillissement. Le(s) mécanisme(s) du contrôle altéré du SNS de la fonction vasculaire chez les femmes restent à déterminer. [Traduit par la Rédaction]

Les nouveautés :

- Cette analyse documentaire présente en bref notre compréhension actuelle des effets du vieillissement, de l'entraînement physique et du sexe sur la vasoconstriction sympathique au repos et pendant l'exercice.
- Les domaines où des recherches supplémentaires sont essentielles sont également identifiés.

Mots-clés : sympatholyse, conductance vasculaire, flux sanguin.

Introduction

The sympathetic branch of the autonomic nervous system is a critically important regulator of the cardiovascular (CV) system.

Efferent sympathetic nerve activity, arising from cardiovascular nuclei in the brainstem, contributes to the control of cardiac contractile and pacemaker cell activity and vascular smooth muscle contractile state, thereby regulating cardiac output and

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its distribution, as well as peripheral vascular resistance and blood pressure (Dampney 1994).

The skeletal muscle is a large vascular bed that receives a substantial portion of cardiac output. At rest, approximately 20% of cardiac output is delivered to skeletal muscle (Rowell 1993). During dynamic whole-body exercise, skeletal muscle blood flow increases in concert with metabolic demand, and as much as >90% of cardiac output may be directed to skeletal muscle during maximal intensity exercise (Rowell 1993). Thus, the dynamic regulation of vascular resistance in the skeletal muscle vasculature is of paramount importance for the control of tissue blood flow and the maintenance of blood pressure at rest and during exercise.

Aging is associated with increased blood pressure and decreased skeletal muscle blood flow at rest and in response to exercise (Dinenno et al. 1999, 2001a; 2001b; Moreau et al. 2003, 2007). The age-associated decline in skeletal muscle blood flow has been linked to a reduction in exercise capacity, decreased physical activity, and the pathogenesis of metabolic and CV disease (Lind and Lithell 1993). The mechanisms responsible for the blunted skeletal muscle blood flow response to dynamic exercise in older humans and animals have not been fully elucidated; however, increased muscle sympathetic nerve activity (MSNA), elevated vascular resistance, and a decline in endothelium-dependent vasodilation are commonly reported in older adults (Beere et al. 1999; Hammer and Boegehold 2005; Lawrenson et al. 2003; Poole et al. 2003; Proctor et al. 1998, 2003a).

In contrast to aging, exercise training has been shown to reduce blood pressure and enhance skeletal muscle vascular function at rest and during exercise (Thijssen et al. 2010). Exercise training has been shown to enhance nitric oxide (NO)-dependent vascular function (Jendzjowsky et al. 2014a; Just et al. 2016; Spier et al. 2007), and some studies have reported improved vasodilatory capacity of the skeletal muscle vasculature following exercise training (Jendzjowsky and DeLorey 2012; Lash and Bohlen 1992; Martin et al. 1991; Thijssen et al. 2010); however, surprisingly little is known about the effect of exercise training on the neural control of circulation.

The control of blood pressure and skeletal muscle blood flow also appears to differ between men and women (Keir et al. 2020; Narkiewicz et al. 2005). Blood pressure and MSNA appear to be lower in young women than in men (Narkiewicz et al. 2005). However, females experience a larger increase in MSNA with aging compared with males (Keir et al. 2020; Narkiewicz et al. 2005), and the female vasculature may also become more responsive to sympathetic outflow with aging (Fadel et al. 2004; Narkiewicz et al. 2005). Consistent with these changes in vascular function, women are at an increased risk of developing hypertension and other CV diseases as they age (Burt et al. 1995). The mechanism(s) for the altered sympathetic control of vascular function in females remain to be determined, although circulating estrogen levels have been implicated (Fadel et al. 2003, 2004).

This review summarizes our current understanding of the modulatory effects of aging, exercise training, and sex on the control of sympathetic vasoconstriction in the skeletal muscle vascular bed at rest and during exercise, and identifies areas where additional research is needed. (Note: This review is based on the APNM President's Lecture delivered by the author at the Canadian Society for Exercise Physiology Annual Meeting 2019 and is not intended to be an exhaustive review of the literature in these areas.)

Muscle sympathetic nerve activity

MSNA is generated in the nuclei of the rostral ventrolateral medulla (RVLM) in the brainstem. Inputs from other regions of the brainstem, central nervous system, chemicals (e.g., angiotensin II, NO), and peripheral reflexes (e.g., baroreceptors and chemoreceptors) are integrated with the inherent activity of the RVLM to produce efferent sympathetic nerve activity (Dampney 1994). In humans and animals, MSNA occurs intermittently as bursts of impulses that are coupled to the diastolic phase of the cardiac cycle

(Hagbarth and Vallbo 1968; Johnson and Gilbey 1996; Sundlof and Wallin 1977). MSNA is typically quantified as burst frequency (bursts per unit time) and/or burst incidence (bursts per 100 heartbeats). The amount of activity is highly variable between individuals and changes in response to a variety of acute and chronic stimuli, including exercise. The amount and pattern of neural activity have been associated with the type and quantity of neurotransmitter release (Bradley et al. 2003; Johnson et al. 2001; Pernow et al. 1989). In particular, low discharge frequencies favour adenosine triphosphate (ATP) release followed by norepinephrine (NE), whereas mid-range discharge frequencies produce both ATP and NE release, and high discharge frequencies favour neuropeptide Y (NPY) release (Burnstock 2009; Pernow et al. 1989). NE binds to postsynaptic α_1 - and α_2 -adrenergic receptors, and the non-adrenergic neurotransmitters ATP and NPY contribute to sympathetic vasoconstriction through binding with purinergic (P2X receptors) and NPY receptors on vascular smooth muscle (Buckwalter et al. 2003, 2005; Revington and McCloskey 1988).

Aging

Several studies have reported that resting efferent MSNA increases as a function of age in both men and women (Davy et al. 1998; Dinenno et al. 1999, 2000; Dinenno and Joyner 2006; Moreau et al. 2003; Ng et al. 1993). However, the mechanisms responsible for the increase in MSNA with advancing age have not yet been established. An increase in body and fat mass may contribute to an increase in sympathetic outflow with aging (Jones et al. 1997a, 1997b). Keir et al. (2020) recently reported that relatively modest increases in body mass index with aging contribute to the increase in MSNA with aging in both men and women. Indeed, MSNA has been shown to be markedly higher in obese than in non-obese adults, and loss of fat mass has been shown to decrease MSNA (Grassi et al. 2019; Costa et al. 2019).

Aging is also associated with an increase in sedentary behaviour and a decline in aerobic fitness (Blair et al., 1989; Diaz et al., 2016). Sympatho-excitation in response to activation of the RVLM was elevated in sedentary rats and blunted following exercise training, suggesting that exercise training/fitness may reduce central sympathetic outflow (Mueller 2007, 2010). Somewhat surprisingly, there is limited data on the effect of aerobic fitness on MSNA in older adults, and the available evidence is conflicting. In a study of middle-aged (~45 years of age) men, resting MSNA was not different between fit and sedentary participants (Notarius et al. 2012). In contrast, MSNA (burst frequency and burst incidence) was elevated in older (65+ years of age) endurance-trained male and female athletes compared with age-matched untrained controls (Ng et al. 1994). Interestingly, the differences between athletes and untrained controls were primarily attributable to a marked increase in MSNA in endurance-trained compared with untrained females, raising the possibility that the effect of fitness on MSNA may differ between men and post-menopausal women (Ng et al. 1994).

To date, no direct measurements of sympathetic nerve activity to exercising muscles have been performed in older animals or humans. Thus, our understanding of how aging affects the MSNA response to exercise is based on a limited number of studies and measures of circulating catecholamines and norepinephrine (NE) spillover. Whole-body NE spillover did not differ between young and older men cycling at the same relative exercise intensity (50% of peak oxygen uptake ($\dot{V}O_{2peak}$)) (Mazzeo et al. 1997). In agreement, leg NE spillover was not different between young and older men during cycling exercise at 60% $\dot{V}O_{2peak}$ (Proctor et al. 2003b). Consistent with a similar level of sympathetic outflow, leg blood flow and vascular conductance were not different between young and older men while cycling at the same absolute work rates (20–100 W) and at a matched oxygen uptake (1.1 L/min) (Proctor et al. 2003b). Leg NE spillover was also similar in older and young

endurance-trained men during mild and moderate-intensity cycle exercise, but was greater in older endurance-trained men during very-heavy-intensity cycle exercise (Proctor et al. 1998).

In summary, aging appears to result in a marked increase in resting sympathetic nervous system activity. During exercise, sympathetic activity appears to be similar in young and older adults; however, sympathetic outflow may be increased in older adults during very-heavy-intensity exercise. Further investigation is required to determine the effect of aging on sympathetic outflow during dynamic whole-body exercise and the potential interactions between the effects of age, sex, and fitness on MSNA.

Exercise training

Aerobic exercise training/fitness is associated with a decrease in CV disease risk, and exercise training is viewed as a therapeutic intervention in individuals with established CV disease (Blair et al. 1989). A decline in sympathetic nervous system activity resulting in a decrease in vascular resistance and arterial blood pressure may contribute to a reduction in disease risk in exercise-trained individuals (Joyner and Green 2009).

Exercise training has consistently been shown to reduce renal sympathetic nerve activity (RSNA) in experimental animals (Gao et al. 2007; Liu et al. 2000). Unfortunately, studies that have investigated the effect of exercise training and aerobic fitness on sympathetic nervous system outflow and/or plasma catecholamines in humans have produced conflicting results. Cross-sectional studies comparing untrained young adults with endurance-trained athletes have reported no difference in resting MSNA burst frequency and burst incidence between groups (Seals 1991; Svedenhag et al. 1984) or that aerobically trained adults had elevated levels of resting MSNA compared with age- and weight-matched sedentary adults (Alvarez et al. 2005; Ng et al. 1993).

Four weeks of cycle training at 70% of maximum heart rate did not change resting MSNA in young men (Cooke et al. 2002). Similarly, resting MSNA was unchanged in young men after 8 weeks of cycling at 75% maximal oxygen uptake and 12 weeks of cycle and run training at 75% peak heart rate did not alter MSNA in middle-aged men (Sheldahl et al. 1994; Svedenhag et al. 1984). Several studies have also reported that resting plasma NE concentrations remained unchanged after endurance exercise training (Peronn et al. 1981; Winder et al. 1978, 1979). In contrast, Grassi et al. (1994) reported that 10 weeks of run training (5 d/week) reduced resting MSNA in young men. Recently, Ehlers et al. (2020) reported that 6 weeks of high-intensity interval training on a cycle ergometer reduced resting MSNA in hypertensive and normotensive older men.

The effect of exercise training/aerobic fitness on the MSNA response to acute exercise is also unclear. Experiments that have measured MSNA in an inactive muscle during isolated small muscle mass exercise have provided some insight into the effects of exercise training/fitness on MSNA during exercise. However, given the small muscle mass activated during exercise, it is unclear whether these experiments are representative of whole-body dynamic exercise. Several cross-sectional studies have reported that the increase in MSNA in response to handgrip exercise did not differ between exercise-trained and untrained adults, suggesting that exercise training does not alter the MSNA response to exercise (Ng et al. 1994; Seals 1991; Sheldahl et al. 1994). However, prospective training studies have produced contrasting results. Unilateral forearm exercise training has been shown to attenuate the increase in MSNA and NE spillover in response to both non-fatiguing (25% MVC) rhythmic forearm exercise and isometric handgrip exercise (Sinoway et al. 1996; Somers et al. 1992). In agreement, Ray (1999) reported that the increase in MSNA during single-leg knee extension exercise was attenuated following 6 weeks of 1-legged cycle exercise training.

Collectively, the available evidence, although not conclusive, suggests that exercise training/aerobic fitness does not alter

resting sympathetic outflow in young healthy adults. The effects of exercise training on the MSNA response to exercise are also unclear; however, the available prospective training studies suggest that exercise training may blunt the MSNA response to exercise. Further investigation in this area is required to determine the effect of training duration, intensity, and frequency on resting MSNA and the regulation of MSNA in response to large muscle mass dynamic exercise.

Sex

Compared with men, young women appear to have lower MSNA, lower resting blood pressure, and a reduced risk of CV disease (Baker et al. 2016; Hart and Charkoudian 2014; Maranon and Reckelhoff 2013; Narkiewicz et al. 2005). MSNA appears to rise at approximately age 30 in both sexes, with the increase in MSNA being steeper in women than in men (Keir et al. 2020). Indeed, the increase in MSNA per decade of life has been reported to be $\sim 3\times$ greater in women than in men (Narkiewicz et al. 2005). These findings suggest that the sympathetic nervous system may play a progressively increasing role in the control of skeletal muscle vascular resistance with advancing age in women (Tank 2005). The mechanism(s) responsible for differences in MSNA between young men and women and the larger age-associated increase in MSNA in women compared with men have not been fully elucidated; however, a potential explanation may be differences in reproductive hormones. Estrogen receptors are expressed in multiple central nuclei that are responsible for basal and reflex activation of the sympathetic nervous system, and exposure to estradiol has been shown to blunt efferent sympathetic outflow, indicating that estrogen has an inhibitory effect on sympathetic nervous system activity (Saleh et al. 2000; Saleh and Connell 2007). Estrogen also upregulates the expression of NO synthase (NOS) in the brainstem, and NO has inhibitory effects on MSNA (Ceccatelli 1997; Ceccatelli et al. 1996; Owlya et al. 1997). Thus, estrogen may blunt efferent sympathetic outflow in a receptor-dependent and receptor-independent manner. Consistent with the central sympatho-inhibitory effect of estrogen, estradiol supplementation has been shown to reduce MSNA in postmenopausal women (Vongpatanasin et al. 2001). However, whether an age-related decline in estrogen bioavailability is responsible for the accelerated increase in resting MSNA with aging in women compared with men is less clear. Matsukawa et al. (1998) reported an age-dependent increase in resting MSNA in both men and women and indicated that the increase in resting MSNA in women was accelerated coincident with the onset of menopause. Narkiewicz et al. (2005) also reported a progressive increase in resting MSNA with aging in men and women, but concluded that the age-associated increase in MSNA in women occurred independently of menopausal status. Recently, Keir et al. (2020) reported that MSNA progressively increased in women and men beginning at ~ 30 years of age and argued that the increase in MSNA with advance of the age (~ 50 yrs) at which menopause typically begins, suggested that a decline in estrogen was not the primary mechanism responsible for the progressive increase in MSNA in women.

An attenuated MSNA response to static handgrip exercise has been reported in women compared with men, suggesting that sex may also influence the MSNA response to exercise (Ettinger et al. 1996; Jarvis et al. 2011). The mechanism(s) responsible for sex differences in the MSNA response to exercise have not been identified, but may include differences in muscle mass, fibre types and distribution, and sensitivity of the metabo- and mechano-reflexes between men and women (Ettinger et al. 1996), as well as cyclical changes in reproductive hormones throughout the menstrual cycle in women (Carter et al. 2013; Ettinger et al. 1998; Minson et al. 2000). Indeed, Ettinger et al. (1998) reported that the increase in MSNA during static handgrip exercise at 30% of maximal voluntary contraction (MVC) was smaller during the late than in the early follicular phase of the menstrual cycle, suggesting that high estrogen levels may blunt the

MSNA response to exercise. However, in a subsequent study, a similar increase in MSNA in response to static handgrip exercise at 40% of MVC was observed during the luteal and follicular phases of the menstrual cycle, suggesting that cyclical changes in reproductive hormones may not alter the MSNA response to exercise in premenopausal women (Jarvis et al. 2011).

Overall, the available studies indicate that resting MSNA is lower in young women than in men. Resting MSNA increases as a function of age in both men and women, with the rate of increase in MSNA being substantially greater in women, whereas the MSNA response to exercise appears to be blunted in young women compared with men. Estrogen has been shown to blunt MSNA; however, the mechanism(s) responsible for sex differences in the regulation of efferent MSNA appear to be multifactorial and include differences in reproductive hormones, body and fat mass, and sensitivity of cardiovascular reflexes.

Sympathetic vasoconstriction in resting skeletal muscle

The functional consequence of efferent MSNA in the peripheral vasculature is vasoconstriction. Skeletal muscle is one of the largest vascular beds in the body, and regulation of vascular resistance in the skeletal muscle vascular bed is of paramount importance to the regulation of total peripheral resistance, the distribution of cardiac output and muscle blood flow, and the control of systemic blood pressure at rest and during exercise. It is well established that the sympathetic nervous system produces tonic vasoconstriction in the vasculature of resting skeletal muscles (Rowell 1993). The magnitude of tonic vasoconstriction in resting skeletal muscle is a function of sympathetic innervation, MSNA, and the responsiveness, density, and distribution of postsynaptic sympathetic receptors (Thomas and Segal 2004).

Aging

Whether aging is associated with elevated tonic sympathetic nervous system-mediated vasoconstriction is an unresolved issue. Age-associated increases in the amount and alterations in the pattern of MSNA may predispose older adults to a greater magnitude of adrenergic and non-adrenergic receptor-mediated sympathetic vasoconstriction. In older men compared with young men, non-selective α -adrenergic receptor blockade produced a smaller increase in forearm blood flow, despite evidence of greater plasma NE concentrations in older than in young men, suggesting that tonic α -adrenergic receptor-mediated vasoconstriction was reduced with aging (Dinenno et al. 2002). In contrast, non-selective α -adrenergic blockade resulted in a proportionally larger increase in resting leg blood flow and vascular conductance in older men than in young men, suggesting elevated α -adrenergic vasoconstriction in older men (Dinenno et al. 2001a, 2001b). Furthermore, leg vascular conductance remained approximately 25% lower in older men than in young men in the presence of α -adrenergic blockade, suggesting that non-adrenergic receptor-mediated vasoconstriction may also be elevated with advancing age (Dinenno et al. 2001b). In a canine model of aging, the magnitude of α_1 - and α_2 -adrenergic receptor-mediated restraint of resting skeletal muscle blood flow did not differ between old and young beagles (DeLorey et al. 2010). However, the magnitude of P2X receptor-mediated vasoconstriction was greater in old than in young beagles, whereas the magnitude of NPY-Y1 receptor-mediated restraint of skeletal muscle blood flow was reduced in old beagles at rest, suggesting that the relative contribution of non-adrenergic receptors to overall sympathetic vasoconstriction under basal conditions was altered as a function of advancing age (DeLorey et al. 2010). Overall, the available evidence is conflicting and differences in the limb/vascular bed studied and species differences make it difficult to draw a definitive conclusion on the effect of aging on tonic sympathetic vasoconstriction in the skeletal muscle vascular bed.

The responsiveness of post-synaptic sympathetic receptors may also influence the magnitude of sympathetic vasoconstriction, independent of efferent MSNA. In aged rodents, studies

have reported reduced (Delp et al. 1995; Sullivan and Davison 2001), unchanged (Bearden et al. 2004; Cook et al. 1992; Muller-Delp et al. 2002), or increased (Donato et al. 2007) α -adrenergic receptor responsiveness. Donato et al. (2007) reported increased NE-mediated vasoconstriction in first-order arterioles isolated from the soleus muscle of old rats, whereas vascular responsiveness to NE in vessels isolated from the gastrocnemius muscle was not affected by aging. Infusion of selective α_1 - and α_2 -agonists produced similar decreases in skeletal muscle vascular conductance at rest in old and young beagles, suggesting that α -adrenergic receptor responsiveness was not affected by aging (DeLorey et al. 2012). In humans, tyramine infusion resulted in a smaller decrease in resting forearm vascular conductance in older men than in young men, suggesting that aging blunts α -adrenergic receptor responsiveness in men (Dinenno et al. 2002). Similarly, infusion of tyramine and selective α -adrenergic agonists produced a smaller decrease in resting leg vascular conductance in older men than in young men (Smith et al. 2007), and phenylephrine-induced vasoconstriction was reduced in the resting leg of older men compared with young men (Wray et al. 2009).

The vascular response to sympathetic neurotransmitters and the infusion of selective agonists may also be affected by age-associated changes in receptor protein expression. In beagle gracilis-muscle feed arteries, α_{1D} and α_{2A} adrenergic receptor protein expression was not affected by aging, whereas α_{1B} adrenergic receptor protein expression was elevated in old compared with young beagles (DeLorey et al. 2012). The expression of P2X and NPY-Y1 non-adrenergic receptors did not differ between young and old beagles (DeLorey et al. 2012). Overall, these data suggest that aging differentially affects the expression of post-synaptic sympathetic receptors in a species, vascular bed, and vessel type-dependent manner. Further investigation is required to determine the effect of aging on post-synaptic receptor expression and distribution and how receptor expression interacts with MSNA and receptor responsiveness to regulate skeletal muscle blood flow.

Exercise training

In addition to effects on efferent MSNA, exercise training may modulate the magnitude of sympathetic vasoconstriction through effects on post-synaptic sympathetic receptor responsiveness and expression/distribution of sympathetic receptors. Following a 3-month aerobic exercise training intervention in middle-aged and older adults, non-selective α -adrenergic receptor blockade produced a larger increase in leg vascular conductance, suggesting that exercise training augmented tonic α -adrenergic receptor-mediated vasoconstriction in resting skeletal muscle (Sugawara et al. 2007). Whether elevated vasoconstriction was a function of increased MSNA or augmented α -adrenergic receptor responsiveness after training was not established. However, chronic exercise training has been shown to alter the responsiveness of postsynaptic receptors to sympathetic stimuli (Lash 1998; McAllister and Laughlin 1997; Wiegman et al. 1981). The vasoconstrictor response to NE was enhanced in rat spinotrapezius muscle first-order arterioles following 10 weeks of treadmill training (Lash 1998) and after 7 days of treadmill exercise in the femoral and brachial arteries of miniature swine (McAllister and Laughlin 1997). In contrast, the vasoconstrictor response to NE was decreased in rat cremaster arterioles after 6 weeks of swim training (Wiegman et al. 1981) and unchanged in arterioles from rat gracilis and soleus muscle after 10–12 weeks of heavy-intensity treadmill exercise training, or 4 weeks of mild-intensity treadmill exercise, respectively (Jasperse and Laughlin 1999; Sun et al. 1994). Collectively, the data from studies in isolated blood vessels demonstrate that exercise training may alter postsynaptic sympathetic receptor responsiveness; however, the effects of exercise training appear to be dependent on the muscle and vascular segment investigated and the exercise training stimulus applied. While in vitro data provide important information about the effects of exercise

training on specific blood vessels, these studies may not be reflective of the effects of exercise training on the in vivo integrated regulation of the skeletal muscle resistance vasculature. To address this gap in the literature, my laboratory has used an in vivo anesthetized rat model and chronic exercise training to investigate the integrative control of sympathetic vasoconstriction in resting and contracting skeletal muscles. Jendzjowsky and DeLorey (2012, 2013d) demonstrated that exercise training augmented evoked sympathetic vasoconstriction in resting skeletal muscle in a training intensity-dependent manner. Both α_1 - and α_2 -adrenergic receptor-mediated vasoconstrictor responses were augmented in resting skeletal muscle of exercise-trained rats compared with sedentary rats (Jendzjowsky and DeLorey 2013c; Just and DeLorey 2016). Increased sympathetic vasoconstrictor responsiveness was correlated with an increase in endothelium-dependent vasodilation, suggesting that training adaptations in sympathetic vasoconstriction may occur in an integrative manner with changes in local vasodilation to regulate vascular resistance and muscle blood flow (Just et al. 2016). Consistent with this notion, aerobic exercise training has been shown to produce parallel increases in endothelium-dependent vasodilation and tonic sympathetic vasoconstriction at rest in middle-aged and older adults (Sugawara et al. 2007). In contrast to training-mediated increases in sympathetic vasoconstrictor responsiveness, forearm vasoconstriction in response to lower body negative pressure has been shown to be lower in aerobically fit middle-aged men than in aged-matched sedentary men (Notarius et al. 2012). Lower body negative pressure evoked similar increases in MSNA in sedentary and aerobically fit men, suggesting that aerobic fitness blunts neurovascular coupling and/or postsynaptic sympathetic vasoconstrictor responsiveness (Notarius et al. 2012). The effect of exercise training on non-adrenergic receptor-mediated vasoconstriction has not yet been investigated. The effects of exercise training on the expression of postsynaptic sympathetic receptors are also largely unknown. Mortensen et al. (2014b) reported a small, but statistically significant, increase in skeletal muscle P2X receptor expression following 8 weeks of aerobic exercise training in middle-aged, normotensive men and women, suggesting that postsynaptic receptor expression may be responsive to exercise training. However, further investigation is required to determine the effect of exercise training on the full spectrum of postsynaptic sympathetic receptors and to determine the integrative effects of exercise training on post-synaptic receptor responsiveness, expression, and distribution.

Sex

In addition to the effects on MSNA, sex may also influence the transduction of sympathetic activity into vasoconstriction in the skeletal muscle vascular bed and/or postsynaptic receptor responsiveness. Sympatho-excitation via the cold pressor test and isometric handgrip has been shown to produce similar increases in efferent MSNA, but smaller increases in calf vascular resistance in females than in males (Hogarth et al. 2007), suggesting that α -adrenergic receptor responsiveness may be blunted in females compared with males. In agreement, Hart et al. (2009) observed that resting MSNA and total peripheral resistance (TPR) were positively correlated in young men, but not in women, further suggesting that sympathetic vasoconstrictor responsiveness and/or sympathetic vascular transduction may be blunted in women compared with men. In a subsequent study, MSNA and TPR were correlated in young women in the presence of β -adrenergic receptor blockade (Hart et al. 2011). Infusion of NE also produced a smaller constrictor response in the forearm of women compared with men, and sex differences in constrictor responses were abolished by β -adrenergic receptor blockade (Kneale et al. 2000). Taken together, these findings suggest that β -adrenergic receptor-mediated vasodilation may inhibit α -adrenergic receptor-mediated vasoconstriction in females and contribute to sex differences in neurovascular coupling. However, intra-arterial infusion of selective α_1 - and α_2 -adrenergic receptor agonists in the forearm

produced a similar vasoconstriction in males and females, suggesting that sex does not alter α -adrenergic receptor responsiveness (Limberg et al. 2010). In agreement, evoked vasoconstriction in the resting leg (via neck pressure and isometric handgrip) did not differ between men and women, and β -adrenergic receptor blockade did not alter vasoconstrictor responsiveness in either sex (Pellinger and Halliwill 2007). Cooper et al. (2021) also recently reported that β -adrenergic receptor blockade did not alter sympathetic vasoconstrictor responsiveness in the resting hindlimb of sedentary or exercise-trained female rats. Similar forearm vasodilation to isoproterenol (β -adrenergic receptor agonist) has also been reported in males and females, suggesting that sex may not modulate β -adrenergic receptor responsiveness/function (Limberg et al. 2016). Just and DeLorey (2017) recently reported that non-selective NOS inhibition produced a similar increase in sympathetic vasoconstrictor responsiveness in the resting hindlimb of male and female rats, indicating that sex does not modulate NO-mediated inhibition of sympathetic vasoconstriction in resting skeletal muscle. Finally, selective NPY Y1 receptor blockade increased hindlimb vascular conductance in male rats, but produced no change in female rats, indicating that tonic NPY-mediated vasoconstriction was absent in resting skeletal muscle of female rats, suggesting that sex differences in non-adrenergic receptor-mediated vasoconstriction may contribute to differences in neurovascular transduction between males and females (Jackson et al. 2005).

The effect of sex on sympathetic vasoconstriction may also interact with age. Narkiewicz et al. (2005) reported that the increase in blood pressure per increment in MSNA is markedly greater in older women than in men, suggesting that older females may have an increased vascular responsiveness to sympathetic stimulation. Hart et al. (2011) have shown that β -adrenergic receptor blockade does not alter the relationship between MSNA and total peripheral resistance in postmenopausal women, suggesting that β -adrenergic receptor-mediated opposition to α -adrenergic receptor-mediated vasoconstriction may be lost as women age. Moreover, postmenopausal women who received hormone replacement therapy (HRT) experienced no age-associated decline in basal leg blood flow (Moreau et al. 2003). Notably, HRT did not alter MSNA, suggesting that HRT restored leg blood flow through local vasodilation or greater inhibition of postsynaptic sympathetic receptors (Moreau et al. 2003). In contrast, a smaller decrease in leg vascular conductance in response to sympathetic stimulation (cold-pressor test) has been observed in older women than in men, suggesting a reduced vascular responsiveness to sympathetic stimulation in older women (Parker et al. 2007).

Further studies are necessary to partition the relative contributions of adrenergic and non-adrenergic neurotransmitters and receptors to sympathetic vasoconstriction in males and females to fully elucidate the effect of sex on sympathetic vascular control in the resting skeletal muscle vascular bed. Further investigation of the integrative effects of sex and aging on sympathetic vascular control is also warranted.

Sympathetic vasoconstriction in contracting muscle and sympatholysis

Exercise is characterized by an increase in cardiac output, arterial blood pressure, and skeletal muscle blood flow (Rowell 1993). Vasodilation in the skeletal muscle vascular bed facilitates an increase in muscle blood flow/oxygen delivery, which is closely matched to muscle metabolic demand (Delp 1999). Concomitantly, sympathetic nerve activity to both exercising and non-active tissues (DiCarlo et al. 1996; O'Hagan et al. 1993; Savard et al. 1987) increases to produce vasoconstriction, which opposes robust local vasodilation and maintains arterial blood pressure (Rowell 1993). Indeed, several studies have demonstrated that α -adrenergic and non-adrenergic receptors tonically constrict the vasculature of exercising muscles even during intense and prolonged exercise (Buckwalter et al. 1997, 2005; DeLorey et al. 2006, 2007; O'Leary et al. 1997). However, it is well established that muscular contraction blunts sympathetic

vasoconstriction in the skeletal muscle vascular bed in an exercise intensity-dependent manner, a phenomenon known as sympatholysis (Buckwalter and Clifford 2001; DeLorey et al. 2002; Hansen et al. 2000; Remensnyder et al. 1962). The overarching benefit of sympatholysis is the enhancement of local muscle blood flow/ O_2 delivery while concomitantly maintaining systemic blood pressure during exercise. While the mechanism responsible for sympatholysis has not been definitively established, our present understanding is that a vasoactive molecule released from the endothelium, skeletal muscle, or possibly red blood cells may inhibit the release of sympathetic neurotransmitters or the responsiveness of postsynaptic sympathetic receptors (Just et al. 2016; Thomas and Segal 2004).

Aging

An age-related increase in MSNA may result in elevated tonic vasoconstriction and reduced skeletal muscle blood flow. To test the hypothesis that aging is associated with elevated sympathetic restraint of skeletal muscle blood flow during exercise, DeLorey et al. (2010) injected selective antagonists for α_1 , α_2 , NPY, and P2X receptors into the hindlimb of young and old beagles during treadmill running at 2.5 mph and 4 mph with 2.5% grade. Selective blockade of adrenergic and non-adrenergic receptors produced similar increases in skeletal muscle vascular conductance in young and old beagles during exercise, indicating that the magnitude of tonic adrenergic and non-adrenergic receptor-mediated sympathetic vasoconstriction did not differ between young and old canines during treadmill running at the same absolute exercise intensity (DeLorey et al. 2010). Consistent with a similar magnitude of tonic vasoconstriction, injection of selective α_1 and α_2 -agonists produced similar decreases in skeletal muscle vasoconstriction during moderate- and heavy-intensity treadmill exercise in old and young beagles, suggesting that α -adrenergic receptor responsiveness during exercise was not affected by aging (DeLorey et al. 2012). Similarly, Wray et al. (2009) reported a similar vasoconstrictor response to phenylephrine (α_1 -adrenergic receptor agonist) in the legs of young and older men performing unilateral knee extension exercise at the same absolute exercise intensity. In contrast, Koch et al. (2003) reported a larger decrease in vascular conductance during cycle exercise with cold-pressor-initiated reflex-sympathetic vasoconstriction in older men than in young men, suggesting that vasoconstrictor responsiveness may be increased in aged men. Consistent with this notion, infusion of selective α -adrenergic agonists also produced a larger decrease in vascular conductance in older men than in young men during leg cycling and handgrip exercise (Dinenno et al. 2005; Wray et al. 2009). Similarly, lower body negative pressure produced a larger decrease in vascular conductance during forearm contractions in older women than in young women (Fadel et al. 2004). Collectively, these data suggest that aging may be associated with diminished contraction-mediated inhibition of sympathetic vasoconstriction. While a definitive mechanism has not been identified, there is accumulating evidence that NO is involved in the blunting of sympathetic vasoconstriction (Chavoshan et al. 2002; Jendzjowsky and DeLorey 2013a, 2013b; Jendzjowsky et al. 2014b; Sander et al. 2000; Thomas and Victor 1998). Aging is associated with a decrease in endothelial NO synthase expression and NO bioavailability (Barton et al. 1997; Csiszar et al. 2002; Tanabe et al. 2003), and it has been argued that NO is completely inactivated in humans over 60 (Taddei et al. 2001). However, lifelong physical activity appears to maintain NO bioavailability and functional sympatholysis in older adults (Mortensen et al. 2012; Nyberg et al. 2012).

Aging may also affect the responsiveness of non-adrenergic receptors and contraction-mediated inhibition of non-adrenergic receptor-mediated vasoconstriction. Selective NPY and P2X receptor agonists produced similar vasoconstrictor responses in the hindlimb of young and old beagles during moderate- and heavy-intensity exercise, suggesting that aging does not alter non-adrenergic receptor responsiveness (DeLorey et al. 2012).

Intravascular infusion of exogenous ATP has also been shown to inhibit vasoconstriction (Hearon et al. 2017; Kirby et al. 2008, 2011; Mortensen et al. 2014a; Rosenmeier et al. 2004) and enhance sympatholysis in older men to levels comparable to those observed in young men (Kirby et al. 2011). Moreover, Kirby et al. (2012) have shown that plasma ATP was lower during handgrip exercise in older men than in young men, and that reduced ATP was associated with blunted exercise hyperemia in older men. A decline in intra-vascular ATP bioavailability with advancing age may impair ATP-mediated sympatholysis; however, it is presently unknown whether endogenously produced ATP blunts sympathetic vasoconstriction. Further investigation is necessary to establish the effect of aging on sympathetic vasoconstriction during exercise, particularly in humans, during large muscle mass dynamic exercise.

Exercise training

Exercise training may enhance sympatholysis and improve neural control of vascular resistance, the distribution of blood flow between and within skeletal muscles, and blood pressure during exercise. Indeed, studies in rodents and humans have demonstrated that aerobic exercise training enhances sympatholysis in a training intensity-dependent manner (Jendzjowsky and DeLorey 2013c, 2013d; Jendzjowsky et al. 2014a; Just and DeLorey 2016; Just et al. 2016; Mizuno et al. 2014; Mortensen et al. 2014b).

Selective α_2 -adrenergic receptor blockade reduced sympatholysis following heavy-intensity exercise training (Jendzjowsky and DeLorey 2013c). The decline in sympatholysis in the presence of selective α_2 -adrenergic receptor blockade suggests that the enhanced sympatholysis after heavy-intensity exercise training was partly attributable to an increased ability to inhibit α_2 -adrenergic receptor-mediated vasoconstriction (Jendzjowsky and DeLorey 2013c). However, sympatholysis remained greater in exercise-trained rats than in sedentary rats in the presence of selective α_2 -adrenergic receptor blockade, indicating that exercise training may also augment contraction-mediated inhibition of α_1 -adrenergic or non-adrenergic receptor-mediated vasoconstriction (Jendzjowsky and DeLorey 2013c). In a subsequent study, selective α_1 -adrenergic receptor blockade abolished exercise training-induced improvements in sympatholysis, demonstrating that exercise training augmented contraction-mediated blunting of α_1 -adrenergic receptor-mediated vasoconstriction (Just and DeLorey 2016). Collectively, these data indicate that the relative contributions of α_1 and α_2 -adrenergic receptors to evoked vasoconstrictor responses are altered following exercise training, and that α -adrenergic receptors become more susceptible to inhibition during contraction after aerobic exercise training (Jendzjowsky and DeLorey 2013c; Just and DeLorey 2016).

Exercise training also appears to augment NO-mediated sympatholysis, as evidenced by a marked reduction in sympatholysis in exercise-trained rats following pharmacological blockade of NOS (Jendzjowsky and DeLorey 2013d; Jendzjowsky et al. 2014a; Mizuno et al. 2014). The cellular mechanism of NO-mediated sympatholysis has not been identified; however, NO has been shown to inhibit both α_1 - and α_2 -adrenergic receptor-mediated vasoconstriction in isolated arteries (Ohyanagi et al. 1992). In the presence of selective α_2 -adrenergic receptor blockade, NOS inhibition reduced the magnitude of sympatholysis in heavy-intensity exercise-trained rats, suggesting that exercise training enhanced NO-mediated inhibition of α_1 -adrenergic receptor- or non-adrenergic receptor-mediated vasoconstriction (Jendzjowsky and DeLorey 2013c). Consistent with this interpretation, NOS inhibition in the presence of selective α_1 -adrenergic receptor blockade did not alter sympatholysis in sedentary or exercise-trained rats, suggesting that functional α_1 -adrenergic receptors are required for NO-dependent sympatholysis (Just and DeLorey 2016). Similar findings have been reported in untrained dogs, where NOS inhibition abolished contraction-mediated

inhibition of α_1 -adrenergic receptors but did not change the blunting of α_2 -adrenergic receptor-mediated vasoconstriction during exercise (Buckwalter et al. 2004). Collectively, these data suggest that the primary mechanism responsible for enhanced sympatholysis following exercise training is augmented NO-dependent inhibition of α_1 -adrenergic receptors (Jendzjowsky and DeLorey 2013; Just and DeLorey 2016).

NO derived from both endothelial NOS (eNOS) and neuronal NOS (nNOS) has been shown to inhibit vasoconstriction during exercise in sedentary and exercise-trained rats (Jendzjowsky and DeLorey 2013b; Jendzjowsky et al. 2014a). Exercise training appears to upregulate nNOS-mediated inhibition of vasoconstriction in contracting skeletal muscle (Jendzjowsky et al. 2014a), and selective nNOS blockade has been shown to abolish the enhanced sympatholysis in exercise-trained rats (Just et al. 2016). Consistent with enhanced nNOS-mediated vascular function, skeletal muscle nNOS expression was greater in exercise-trained rats than in sedentary rats (Jendzjowsky et al. 2014a). The training-induced increase in nNOS expression was predominately in muscle with a high proportion of type II, fast-twitch, glycolytic muscle fibres, suggesting that exercise training may enhance NO-mediated sympatholysis in a fibre-type dependent manner (Jendzjowsky et al. 2014a). Further research is required to establish how exercise training may alter sympatholysis in specific skeletal muscle fibre types.

Sex

Sex differences in the regulation of sympathetic vasoconstrictor responsiveness and sympatholysis have received relatively little attention in the scientific literature. Limberg et al. (2010) reported that intra-arterial infusion of selective α_1 - and α_2 -adrenergic receptor agonists produced a similar vasoconstriction in the forearm of men and women during handgrip exercise, suggesting that α -adrenoreceptor responsiveness and contraction-mediated inhibition of vasoconstriction were not different between sexes. In rats, sympathetic vasoconstrictor responsiveness during contraction was lower in females than in males, and sympatholysis was enhanced in female rats (Just and DeLorey 2017). A portion of the enhanced sympatholysis in female rats was NO-dependent, as non-selective NOS inhibition reduced sympatholysis in female rats (Just and DeLorey 2017). However, sympatholysis remained greater in female rats than in male rats in the presence of NOS inhibition, suggesting that other mechanisms also contribute to sex differences in contraction-mediated inhibition of vasoconstriction (Just and DeLorey 2017). Cooper et al. (2021) recently investigated whether β -adrenergic receptor-mediated opposition of sympathetic vasoconstriction may be augmented in female rats compared with male rats and contribute to enhanced sympatholysis in female rats. Consistent with the findings of Just and DeLorey (2017), sympatholysis was greater in females than in male rats; however, β -adrenergic receptor blockade did not augment sympatholysis in male or female rats, indicating that β -adrenergic receptors do not oppose sympathetic vasoconstriction and that β -adrenergic receptor-mediated blunting of sympathetic vasoconstriction does not contribute to enhanced sympatholysis in female rats (Cooper et al. 2021).

A reduction in sympatholysis has been reported in ovariectomized rats and post-menopausal women, and acute estrogen supplementation/therapy restored sympatholysis, suggesting that estrogen may contribute to sex differences in sympatholysis (Fadel et al. 2003, 2004). However, similar blunting of α_1 - and α_2 -adrenergic receptor-mediated vasoconstriction during handgrip exercise in the luteal and follicular phases of the menstrual cycle has also been reported (Limberg et al. 2010). Further research is required to clarify the role of estrogen in the regulation of sympatholysis and to elucidate the mechanism by which females are better able to blunt sympathetic vasoconstriction in the skeletal muscle vascular bed during exercise.

Summary

This review has demonstrated that aging, exercise training, and sex modulate the control of sympathetic vasoconstriction in the skeletal muscle vascular bed at rest and during exercise. The available literature also reveals a fundamental lack of understanding of the mechanisms responsible for the effects of aging, exercise training, and sex on the control of the skeletal muscle vasculature. Exercise training is often viewed as a primary prevention and treatment for age-related vascular dysfunction and is associated with reduced CV morbidity and mortality (Blair et al. 1989). However, our understanding of the adaptive mechanisms of this protection is limited. In addition to a lack of understanding of the basic physiological changes resulting from exercise training, our understanding of the exercise prescription (intensity, frequency, and duration) that will produce the maximum reduction in CV disease risk and maximum improvement in physiological function is limited. Almost no attention has been directed to the examination of the dose-response relationship between exercise training and vascular health, particularly in women.

Unraveling the independent and interdependent effects of aging, sex, and exercise training on neurovascular control is particularly important, as several age-related chronic diseases (e.g., heart failure, hypertension, and metabolic syndrome) are characterized by elevated sympathetic outflow, diminished vascular function, decreased NO bioavailability, and exercise intolerance (Blair et al. 1989; Carter and Ray 2015; Paterson et al. 2004, 2007; Taddei et al. 2001).

Conflict of interest statement

The author has no conflicts to report.

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