HHS Public Access

Author manuscript

Auton Neurosci. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

Auton Neurosci. 2019 December ; 222: 102591. doi:10.1016/j.autneu.2019.102591.

Exaggerated exercise pressor reflex in type 2 diabetes: Potential role of oxidative stress

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Abstract

Type 2 diabetes mellitus (T2DM) leads to exaggerated cardiovascular responses to exercise, in part due to an exaggerated exercise pressor reflex. Accumulating data suggest excessive oxidative stress contributes to an exaggerated exercise pressor reflex in cardiovascular-related diseases. Excessive oxidative stress is also a primary underlying mechanism for the development and progression ofT2DM. However, whether oxidative stress plays a role in mediating the exaggerated exercise pressor reflex in T2DM is not known. Therefore, this review explores the potential role of oxidative stress leading to increased activation of the afferent arm of the exercise pressor reflex. Several lines of evidence support direct and indirect effects of oxidative stress on the exercise pressor reflex. For example, intramuscular ROS may directly and indirectly (by attenuating contracting muscle blood flow) increase group III and IV afferent activity. Oxidative stress is a primary underlying mechanism for the development of neuropathic pain, which in turn is associated with increased group III and IV afferent activity. These are the same type of afferents that evoke muscle pain and the exercise pressor reflex. Furthermore, oxidative stress-induced release of inflammatory mediators may modulate afferent activity. Collectively, these alterations may result in a positive feedback loop that further amplifies the exercise pressor reflex. An exaggerated reflex increases the risk of adverse cardiovascular events. Thus, identifying the contribution of oxidative stress could provide a potential therapeutic target to reduce this risk in T2DM.

Keywords

Exercise pressor reflex; Neural cardiovascular control; Reactive oxygen species; Sympathetic activity; Blood pressure; Neuropathy

1. Introduction

Autonomic adjustments are pivotal in mediating appropriate cardiovascular responses to exercise. By decreasing parasympathetic activity to the heart while increasing sympathetic activity to the heart and peripheral vasculature, blood pressure increases, and blood flow is

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Declaration of Competing Interest

None.

re-distributed away from inactive tissues. At the same time, sympathetically mediated vasoconstriction in the contracting skeletal muscle is blunted by local release of metabolites (i.e., functional sympatholysis) facilitating increases in muscle blood flow (Hansen et al., 2000; Remensnyder et al., 1962). Two primary mechanisms are known to increase sympathetic activity during exercise: Central command, a feed-forward mechanism originating in higher brain centers (Eldridge et al., 1985; Goodwin et al., 1972), and the exercise pressor reflex, a feedback mechanism with the afferent arm originating within the skeletal muscle (Alam and Smirk, 1937; McCloskey and Mitchell, 1972). Furthermore, arterial and cardiopulmonary baroreflexes modulate these adjustments (Fadel and Raven, 2012). The exercise pressor reflex is critical in evoking appropriate cardiovascular responses to exercise; however, an exaggerated reflex increases the risk of adverse cardiovascular events (Kurl et al., 2001; Laukkanen et al., 2001). Although several mechanisms are known to contribute to the autonomic adjustments of the circulation during exercise, this review will focus on the role of the exercise pressor reflex.

The afferent arm of the exercise pressor reflex is comprised of group III and IV afferents, whose peripheral endings are stimulated by mechanical and metabolic stimuli produced during muscle contraction (Adreani et al., 1997; Kaufman et al., 1983). Studies have shown that the exercise pressor reflex is exaggerated in several cardiovascular-related diseases, including hypertension (Leal et al., 2008), peripheral artery disease (PAD) (Baccelli et al., 1999; Stone et al., 2015b; Tsuchimochi et al., 2010), heart failure (Ives et al., 2016; Keller-Ross et al., 2014), and type 1 diabetes (T1DM) (Grotle et al., 2017), as well as kidney disease (Sprick et al., 2019). Furthermore, recent data have indicated that the exaggerated cardiovascular responses to exercise in type 2 diabetes mellitus (T2DM) patients (Holwerda et al., 2016a; Karavelioglu et al., 2013; Scott et al., 2008) are, in part, mediated by the exercise pressor reflex (Grotle et al., 2019a; Kim et al., 2019).

The prevalence of T2DM (US: ~30 million) and pre-diabetes (US: ~84 million) in younger, middle, and older adults are continuing to increase, posing a significant health concern as disease duration increases the risk of diabetic complications (Mayer-Davis et al., 2017; Centers for Disease Control and Prevention 2017, 2018). Individuals with diabetes are at a two to three-fold higher risk for cardiovascular disease (CVD), in which 84% of diabetics over 65 years die from a heart attack or stroke, contributing to a 10-year shorter life expectancy. Moreover, the high prevalence of comorbidities in diabetes, such as hypertension, obesity, and physical inactivity significantly increase mortality from CVD (Einarson et al., 2018). Although an exaggerated blood pressure response to exercise is a predictor for adverse cardiovascular events (Haffner et al., 1998; Mittleman and Siscovick, 1996), exercise training is recommended to combat cardiovascular risk factors in T2DM (Eriksson et al., 2001; Eriksson, 1999). However, in order to prescribe exercise safely and develop effective treatment strategies, it is essential to understand the mechanisms underlying cardiovascular responses to acute exercise.

In recent years, data have implicated oxidative stress as an underlying mechanism in evoking the exaggerated exercise pressor reflex in several cardiovascular-related diseases (Harms et al., 2017; Koba et al., 2009; Koba et al., 2013; Muller et al., 2012; Wang et al., 2009). In T2DM, oxidative stress is a primary mechanism for impaired vascular function, neuropathy,

mitochondrial dysfunction, cardiomyopathies, and autonomic dysfunction (Giacco and Brownlee, 2010). Oxidative stress is a condition of cellular redox imbalance between the production and reduction (i.e., antioxidant defense) of free radicals, including reactive oxygen species (ROS: superoxide, hydrogen peroxide and hydroxyl radical) and reactive nitrogen species (RNS: peroxynitrite). In moderate amounts, free radicals are essential signaling molecules, whereas in higher amounts, they react with and can damage cellular structures such as DNA, lipids, and proteins (Valko et al., 2007). Accumulating evidence suggests that oxidative stress may be an efficacious stimulus, and unifying mechanism, for an exaggerated exercise pressor reflex. However, it is not known whether oxidative stress contributes to the exaggerated cardiovascular responses to exercise in T2DM.

Underlying mechanisms causing an exaggerated exercise pressor reflex in T2DM are incompletely understood. It is likely that these mechanisms involve increased production of metabolites and or changes to the group III and IV muscle afferents. Therefore, the purpose of this review is to discuss potential roles of peripheral oxidative stress in increasing the activity of the afferent arm of the exercise pressor reflex in T2DM.

2. The exercise pressor reflex

The exercise pressor reflex is essential in regulating cardiovascular and ventilatory responses to exercise. Mechanical and metabolic stimuli produced by contracting muscle stimulate receptors and channels on the peripheral endings of group III and IV skeletal muscle afferents (Alam and Smirk, 1937; Kaufman et al., 1983; McCloskey and Mitchell, 1972). Afferent signals from the muscle travel to the dorsal root ganglion (DRG) and then to the dorsal horn of the spinal cord before being transmitted centrally for integration in the rostral ventrolateral medulla (VLM) and nucleus tractus solitarius (NTS) in the medulla oblongata (Craig, 1995; Potts et al., 2002). Studies using electrically induced exercise (excluding central command) and pharmacological attenuation of afferent input from the lower limbs during voluntary exercise, support the importance of the exercise pressor reflex in regulating cardiovascular responses to exercise in humans (Amann et al., 2010; Amann et al., 2011).

The afferent arm of the reflex is comprised of thinly myelinated group III (AS fibers) and unmyelinated group IV (C-fibers) afferents (McCloskey and Mitchell, 1972). Group III afferents respond primarily to mechanical stimuli (i.e., mechanoreflex), such as light stroking or squeezing of the receptive field or stretching the Achilles tendon. These are fast-conducting afferents that discharge vigorously at the onset of muscle contraction in proportion to tension development and tend to decrease their discharge rate as the muscle fatigues (Hayes et al., 2009; Kaufman et al., 1983). In contrast, group IV afferents respond primarily to metabolic stimuli (i.e., metaboreflex), such as metabolites produced during muscle contraction. These are slower conducting afferents that increase their discharge as the muscle fatigues, in proportion to the production of metabolic by-products and with response latencies of 5–30 s (Kaufman et al., 1983; Kaufman et al., 1984). Although group III and IV muscle afferents primarily respond to mechanical or metabolic stimuli, respectively, both types of afferents exhibit polymodal activity in which some group III afferents respond to metabolic stimuli and some group IV afferents respond to mechanical stimuli (Kumazawa and Mizumura, 1977; Rotto and Kaufman, 1988; Rotto et al., 1990).

Metabolic by-products and proteins comprising the metabolically sensitive component (i.e., metaboreflex) of the exercise pressor reflex include lactic acid, bradykinin, arachidonic acid, and its cyclooxygenase (COX) products, including ATP. These metabolites stimulate acid-sensing ion channel 3 (ASIC3), bradykinin B2 (B2) receptors, thromboxane A2 (TXA2) receptors, endoperoxide (EP) receptors, and purinergic 2× (P2X) receptors (Hanna and Kaufman, 2004; Kaufman et al., 1983; Rotto and Kaufman, 1988; Stone et al., 2015b), respectively. However, the exact role of these proteins in healthy and pathological conditions is still unclear (Stone and Kaufman, 2015) and difficult to differentiate due, in part, to redundancy (Stone et al., 2015b).

Less is known about proteins comprising the mechano-sensitive component (i.e., mechanoreflex) of the exercise pressor reflex. This lack of understanding is partially due to the scarcity of antagonists with specificity for mechano-sensitive proteins. Previous studies have used gadolinium, a non-selective antagonist that inhibits multiple classes of mechano-gated channels. Although gadolinium successfully blocks pressor responses to mechanical stimulation such as tendon stretch and muscle contraction (Hayes and Kaufman, 2001; Hayes et al., 2009), it cannot elucidate the contributions of individual channels. Conversely, the recent discovery of Piezo channels (found in two isoforms: Piezo1 and Piezo2) and their selective antagonist *Grammostola spatulata* mechanotoxin 4 (GsMTx-4) (Coste et al., 2010; Gnanasambandam et al., 2017), has led to studies that suggest that Piezo channels may be a significant mediator of the mechanical component of the exercise pressor reflex (Copp et al., 2016a). These studies have shown that injecting GsMTx-4 into the contracting muscle attenuates the exercise pressor reflex and mechanoreflex in healthy rats (Copp et al., 2016a; Sanderson et al., 2019), the exaggerated exercise pressor reflex and mechanoreflex in PAD rats (i.e. ligated femoral artery model) (Copp et al., 2016b) and the mechanoreflex in T1DM rats (Grotle et al., 2019b). Collectively, these findings highlight the importance of identifying signals and proteins involved in evoking the exercise pressor reflex and are crucial to developing effective therapeutic targets in disease.

3. Reflexive cardiovascular responses to exercise in T2DM

3.1. Human studies

Individuals with T2DM have exaggerated blood pressure responses, as well as reduced tolerance, to exercise. Even independently, both of these conditions increase the risk of cardiovascular disease and mortality (Laukkanen et al., 2001; Poitras et al., 2018). Several studies have shown that blood pressure responses to both maximal and moderate intensity dynamic exercise are exaggerated in adolescents (Pinto et al., 2014), middle-aged adults (Regensteiner et al., 2009; Scott et al., 2008), and older adults with T2DM (O'Connor et al., 2015). Although these responses are common, surprisingly few studies have tried to elucidate the underlying mechanisms. A recent study by Holwerda et al. provided some critical insight into the reflexive control of circulation in T2DM (Holwerda et al., 2016a). They found that individuals with T2DM, independent of resting hypertension, had exaggerated pressor and sympathetic responses to isometric handgrip exercise, an effect which remained during post-exercise circulatory occlusion (i.e., metaboreflex), compared to healthy age-matched controls (Fig. 1). Interestingly, these responses were significantly

correlated with disease severity (Holwerda et al., 2016a). Whether T2DM leads to an impaired arterial baroreflex control of sympathetic outflow is unclear (de Moura-Tonello et al., 2016; Holwerda et al., 2016b; Ruiz et al., 2005). However, one study suggested that any impairment in baroreflex control in T2DM may be due to obesity and not diabetes per se (Holwerda et al., 2016b). Thus, further investigation is warranted. Collectively, these findings indicate that the reflexive control of the circulation is altered in T2DM.

3.2. Animal studies

Recently, studies using an unanesthetized, decerebrate rat preparation in which the exercise pressor reflex was isolated by electrically stimulating hindlimb muscle contractions have provided important insight into the effect of T2DM on the exercise pressor reflex. Specifically, these studies have shown that the exercise pressor reflex is exaggerated in two rat models of T2DM. For example, Kim et al. demonstrated that sympathetic and pressor responses to electrically-induced static muscle contraction were exaggerated in a high-fat diet and low-dose streptozotocin-induced T2DM rat model (Kim et al., 2019). However, it was not determined whether these responses changed with severity and progression of the disease. We began investigating whether the progression of T2DM changes the expression of the exercise pressor reflex. Unlike the study by Kim et al., we used the UC Davis-Type 2 Diabetes Mellitus rat model (UCD-T2DM) that develops diabetes naturally (un-treated) over time with similar pathophysiology as that seen in humans (Cummings et al., 2008). This model has allowed us to follow the progression of the disease through the development and progression of T2DM. Indeed, we found that as rats progressed with T2DM, the pressor response to static contraction incrementally increased until it was significantly greater than that in healthy rats (Fig. 2) and only after plasma glucose and HbA1c levels were high and sustained for an extended time (Grotle et al., 2019a). These findings support the association with disease severity found in the study by Holwerda et al. (2016a). Furthermore, these rats exhibited an exaggerated mechanoreflex, which suggests that enhanced mechanical sensitivity of group III and IV afferents may partially mediate the exaggerated pressor reflex in T2DM. Collectively, these studies strongly support the idea that T2DM leads to an exaggerated exercise pressor reflex.

4. Oxidative stress and the exercise pressor reflex

Several studies have demonstrated that free radicals produced during muscle contraction play a role in evoking the exercise pressor reflex. It is well known that muscle contraction generates two to three-fold increases in free radicals, primarily superoxide and nitric oxide (NO). Additionally, superoxide can react with NO to form the highly reactive peroxynitrite (Davies et al., 1982; Powers and Hogan, 2016). Although these free radicals have essential signaling functions in normal conditions, insufficient neutralization in pathological conditions may cause them to accumulate and react with surrounding structures such as sensory afferent endings located in the muscle (Alessio et al., 2000; Davies et al., 1982; Steinberg et al., 2007). Wang et al. were the first to investigate the role of oxidative stress on the exercise pressor reflex and found that infusing a superoxide dismutase (SOD) mimetic inhibitor that increases superoxide production augmented the exercise pressor reflex in healthy rats (Wang et al., 2009). Delliaux et al. were the first to provide electrophysiological

evidence of an effect of ROS on afferent activity when they showed that infusing a ROS donor (H_2O_2) increased impulse activity of group IV afferents (i.e., metaboreceptors) in healthy Sprague Dawley rats. Furthermore, infusing SOD before infusing the ROS donor abolished the responses. More importantly, they showed that infusing SOD before rhythmically contracting the hindlimb muscles significantly attenuated the activity of group IV afferents (Fig. 3) (Delliaux et al., 2009a). Thus, these findings provide compelling evidence that free radicals produced in the contracting muscle can stimulate afferent endings in the muscle and thereby evoke the exercise pressor reflex.

In recent years, studies have demonstrated that reducing intramuscular ROS effectively attenuates the exaggerated exercise pressor reflex in several cardiovascular-related diseases (Harms et al., 2017; Koba et al., 2009; Koba et al., 2013; Muller et al., 2012). For example, locally infusing tiron (superoxide scavenger) into the contracting muscle attenuated the exaggerated exercise pressor reflex in PAD rats (i.e. ligated femoral artery model; Fig. 4) (Harms et al., 2017). Moreover, infusing tempol (SOD mimetic) also reduces the exaggerated pressor reflex in rat models of hypertension (Koba et al., 2013), and heart failure (Koba et al., 2009). Likewise, Muller et al. found that acute intravenous infusion of a non-specific antioxidant (ascorbic acid) attenuated the exaggerated pressor response to low-intensity, one-leg rhythmic plantar flexion in PAD patients (Fig. 5). Electrically contracting the same muscle resulted in similar responses, thus suggesting these responses were independent of central command (Muller et al., 2012). Other studies have demonstrated that local infusion of tempol or tiron during intermittent hindlimb contractions (low metabolite production) attenuated the peak pressor and the synchronization of the renal sympathetic response with tension development (Koba et al., 2009; Koba et al., 2013). These findings are consistent with an augmented mechanoreflex in the same diseases (Copp et al., 2016b; Ives et al., 2016; Leal et al., 2008). Collectively, these data indicate that intramuscular superoxide is an efficacious stimulus for the exercise pressor reflex and may partially mediate its effect by stimulating or sensitizing mechanosensitive afferents.

NADPH oxidase contributes importantly to skeletal muscle superoxide production during exercise (Powers and Hogan, 2016; Sakellariou et al., 2014) and appears to be the primary source for sensitizing the exercise pressor reflex (Harms et al., 2017; Wang et al., 2009). This is probably due to the assembly process of the active complex on the muscle plasma membrane causing the catalytic unit (Nox2) to be oriented in such a way that it can release superoxide into the interstitial space where the group III and IV afferent endings are located (Ferreira and Laitano, 2016; Sakellariou et al., 2014). This role is supported by the finding that inhibiting NADPH assembly (gp91ds-tat) attenuates the pressor response to muscle contraction in rats with ligated femoral artery (i.e. PAD model). Moreover, higher indices of intramuscular NADPH oxidase (Nox2 and p67phox) found in the skeletal muscle of PAD rats compared to healthy controls further supports this role and suggest that pathological conditions increase the activity of NADPH oxidase (Harms et al., 2017). Collectively, these findings provide strong evidence that NADPH oxidase-mediated production of superoxide plays a significant role in evoking an exaggerated exercise pressor reflex in cardiovascular-related diseases.

5. Oxidative stress and T2DM

Oxidative stress is a unifying mechanism underlying diabetic complications, such as vascular dysfunction and neuropathy (Giacco and Brownlee, 2010; Robson et al., 2018; Ziegler et al., 2015). Hyperglycemia and hyperinsulinemia both contribute to oxidative stress in T2DM and may independently have sympathoexcitatory effects (Joyner and Limberg, 2013; Marfella et al., 2000; Marfella et al., 2001; Marfella et al., 1995). Whether glucose and insulin have similar effects during exercise is not known; however, we do know that acute and chronic events of hyperglycemia stimulate superoxide production in a variety of tissues (Greene et al., 1999; Russell et al., 2002; Sedeek et al., 2010). In addition, increased superoxide production stimulates classical pathways such as polyol, hexosamine, protein kinase C (PKC), and formation of advanced glycation end products (AGE), which further increase tissue damage. Endothelial cells and peripheral nerves are especially vulnerable to the deleterious effects of superoxide as their glucose uptake is dependent on external glucose concentration (Giacco and Brownlee, 2010). T2DM impairs insulin-stimulated glucose disposal in skeletal muscle; however, exercise facilitates glucose disposal by an insulin-independent mechanism (Goodpaster et al., 2014; Oguri et al., 2009). Moreover, ROS produced by muscle contraction is thought to play a role in mediating exercise-stimulated glucose uptake (Kellogg 3rd et al., 2017; Sandstrom et al., 2006). Thus, the combination of hyperglycemia and muscle contraction likely exacerbates oxidative stress within the contracting muscle.

The mechanisms by which oxidative stress mediates its effects are complex, multifactorial, and incompletely understood. However, accumulating evidence supports a direct effect of oxidative stress within the contracting muscle in modulating the exercise pressor reflex in diseases associated with excessive oxidative stress (Harms et al., 2017; Koba et al., 2009; Koba et al., 2013; Muller et al., 2012). T2DM also lead to excessive oxidative stress. Thus, it is possible that oxidative stress also modulates the exercise pressor reflex in T2DM by similar mechanisms. Furthermore, oxidative stress may modulate group III and IV afferent activity by other mechanisms. These include acute and chronic vascular impairments affecting contracting muscle blood flow, increased group III and IV afferent activity, and upregulation of inflammatory mediators that can modulate sensory afferent activity (Fig. 6).

5.1. Muscle blood flow

Oxidative stress plays a significant role in causing endothelial dysfunction, which in turn contributes to attenuating blood flow in contracting muscle in T2DM (Frisbee et al., 2018; Kingwell et al., 2003; McVeigh et al., 1992). Moreover, the magnitude of attenuation likely depends on the severity of endothelial dysfunction (Womack et al., 2009). The interaction between the local release of vasoactive substances and sympathetically mediated vasoconstriction allows for precise regulation of muscle blood flow during exercise. However, T2DM leads to exaggerated sympathetic activity (Holwerda et al., 2016a; Kim et al., 2019) and attenuated blood flow responses to exercise (Groen et al., 2019; Kingwell et al., 2003; Lalande et al., 2008), which accelerates muscle ischemia. Muscle ischemia, both acute and chronic, accelerate the onset of muscle fatigue and pain (Frisbee et al., 2019; Senefeld et al., 2019). More importantly, muscle ischemia is a efficacious stimulus for

metabolically sensitive muscle afferents and mediates an augmented reflexive increase in blood pressure (Kuczmarski et al., 2018; Spranger et al., 2015; Tsuchimochi et al., 2010). Thus, accelerated muscle ischemia is consistent with an exaggerated metaboreflex in T2DM (Holwerda et al., 2016a). In healthy, cardiac output is the primary contributor to the metaboreflex-induced increases in blood pressure. However, T2DM leads to an enhanced contribution of peripheral vascular resistance (Roberto et al., 2019). Collectively, these data suggest that oxidative stress indirectly increase the stimulation of metabolically sensitive group III and IV afferents by accelerating muscle ischemia and metabolite accumulation within the contracting muscle.

5.1.1. Vasoconstriction and vasodilation—Studies have shown that oxidative stress increases the production of vasoconstrictors such as endothelin-1 and thromboxane A2, as well as augments reactivity to sympathetic stimulation, which could contribute to reducing muscle blood flow in T2DM (Frisbee et al., 2018; Oguri et al., 2009; Reynolds et al., 2017; Stepp and Frisbee, 2002). For example, oxidative stress and its by-products (8-isoprostane) promote the synthesis of endothelin-1 and thromboxane A2 and can stimulate atherogenesis while inhibiting pro-angiogenic pathways (Kahler et al., 2001; Kahler et al., 2000; Kolluru et al., 2012). Thus, oxidative stress promotes both structural and functional changes to the vasculature. Other lines of evidence suggest that oxidative stress plays an acute role in impairing vasodilation. For example, one study showed that acutely attenuating oxidative stress (tempol) improve blood flow, oxygen uptake, and performance of skeletal muscle in T2DM rats (Frisbee et al., 2018). Moreover, inhibiting NADPH oxidase-mediated production of superoxide (apocynin) was found to restore endothelial function in T2DM rats with NO dysfunction (Fukatsu et al., 2007; Hayashi et al., 2005). In older humans, infusion of ascorbic acid acutely increased blood flow primarily by improving endothelial NO bioavailability (Crecelius et al., 2010). Indeed, decreased signaling of NO appear to be the critical mediator of attenuated blood flow in T2DM (Frisbee et al., 2018); Kingwell et al., 2003). Thus, these data provide strong evidence for a role of oxidative stress in attenuating muscle blood flow in T2DM.

Superoxide can reduce nitric oxide bioavailability by its reaction with NO forming peroxynitrite, a highly efficacious free radical. Peroxynitrite promotes uncoupling of endothelial and neuronal NO synthases (eNOS, nNOS), which synthesizes NO from L-Arginine. This uncoupling, in turn, can lead to further production of superoxide while also reducing endogenous SOD. Ultimately these alterations reduce the antioxidant capacity of the cell and promote cellular damage in the vasculature (Giacco and Brownlee, 2010; Gliemann et al., 2014; Schiffrin, 2008; Zou et al., 2002). In addition to its role in mediating endothelial-dependent vasodilation, NO plays a significant role in attenuating sympathetic vasoconstriction during exercise (i.e., functional sympatholysis). Intraluminal ATP is another mediator of endothelial- dependent vasodilation by stimulating NO production. ATP also attenuates sympathetic vasoconstriction (Mortensen et al., 2009; Rosenmeier et al., 2004). Interestingly, studies have shown that plasma concentrations and signaling of ATP are lower in T2DM and correspond to an attenuated leg blood flow response to ATP infusion and exercise (Groen et al., 2019; Thaning et al., 2010). Thus, these findings suggest that reduced

NO bioavailability and endothelium function impair the ability to vasodilate and override sympathetic vasoconstriction during exercise.

5.1.2. Functional sympatholysis—One study found that oxidative stress can impair functional sympatholysis and promote muscle ischemia during exercise in both rats and humans (Fadel et al., 2012). However, whether T2DM leads to impaired functional sympatholysis capacity is currently unclear. For example, Thaning et al. found preserved functional sympatholysis in T2DM individuals with an intact response to acetylcholine (Thaning et al., 2011). On the other hand, preliminary data from Bock et al., showed attenuated functional sympatholysis in T2DM individuals with a reduced response to acetylcholine (Bock et al., 2019). Thus, these findings suggest that any impairment in functional sympatholysis is dependent on endothelium function. Nonetheless, data do support a significant role of oxidative stress in attenuating blood flow in contracting skeletal muscle. Collectively, these findings provide compelling evidence that oxidative stress indirectly contributes to an exaggerated exercise pressor reflex by reducing blood flow delivery to the working muscles.

5.2. Group III and IV afferent activity

Oxidative stress is a likely mediator of an exaggerated exercise pressor reflex in T2DM due to its ability to increase afferent activity (Delliaux et al., 2009b). A longitudinal study found that superoxide was the strongest predictor for impairments in sensory and autonomic nerves and was associated with increased mortality among T2DM patients (Ziegler et al., 2015). Although, the specific mechanisms by which oxidative stress mediates these effects are still unclear, we do know that oxidative stress plays a significant role in the development and progression of neuropathic pain (Giacco and Brownlee, 2010), which is also mediated by increased group III and IV afferent activity (Janig, 2011; Khan et al., 2002; Orstavik et al., 2006; Pitcher and Henry, 2000). Moreover, group III and IV muscle afferents play a dual role in evoking muscle pain and the exercise pressor reflex (Franz and Mense, 1975; Graven-Nielsen and Mense, 2001; Kaufman et al., 1983). Considering the high prevalence of neuropathic pain (> 50%) in T2DM and that it initially affects distal limb nerves, it is likely that oxidative stress also contributes to an exaggerated exercise pressor reflex by modulating group III and IV afferent activity.

Increased sensitization or damage of group III and group IV afferents results in mechanical allodynia, which is characterized as a painful response to a normally non-painful mechanical stimulus (Janig, 2011; Khan et al., 2002; Orstavik et al., 2006; Pitcher and Henry, 2000; Xu et al., 2015). Indeed, it appears that the sensitivity to mechanical deformation of the muscle is heightened in diabetic rats as they have an exaggerated pressor response to tendon stretch (Grotle et al., 2019a; Grotle et al., 2019b). Studies on mechanical allodynia have suggested that oxidative stress can enhance the activity and increase the expression of mechanically sensitive ion channels leading to neuronal hyperexcitability (Bogeski and Niemeyer, 2014; Hsieh, 2008; Liu and Gutterman, 2002; Lolignier et al., 2015). Moreover, free radicals may lower the activation threshold or prolong the inactivation phase of excitatory ion channels (Hsieh, 2008; Liu and Gutterman, 2002; Schluter and Leffler, 2016). Interestingly, some of the channels associated with mechanical allodynia are also known to play a role in evoking

the exercise pressor reflex. For example, the mechanically activated cation channel Piezo plays a role in evoking the mechanical component of the exercise pressor reflex (i.e., mechanoreflex) and mechanical allodynia in rat models of PAD (i.e. ligated femoral artery model) (Copp et al., 2016b), T1DM (Grotle et al., 2019b), and neuropathy (Eijkelkamp et al., 2013; Park et al., 2008). Similarly, oxidative stress may modulate exci tatory voltage-gated Nav1.7 channels, which play a role in the spinal transmission of the exercise pressor reflex (Stone et al., 2015a) and neuropathic pain (Dib-Hajj et al., 2010; Dib-Hajj et al., 2013). Moreover, other studies have shown that oxidative stress can modulate Nav1.7 channel function by reducing the threshold for activation as well as slowing the inactivation of the channel (Schluter and Leffler, 2016). Although speculative, these findings suggest that oxidative stress may directly modulate ion channels and receptors that play a role in evoking the exercise pressor reflex.

5.3. Inflammatory mediators

Oxidative stress is associated with an increased release of inflammatory mediators that may also play a role in modulating group III and IV afferent activity (Cheng et al., 2009; Franz and Mense, 1975; Mense, 2009). Additionally, oxidative stress contributes to peripheral nerve ischemia, which further disrupts peripheral nerve function resulting in the release of neurotrophic factors (Okamoto et al., 2001). Although neurotrophic factors have regenerative functions, T2DM disrupts their regenerative capacity and promotes chronic inflammation (Mirza et al., 2015; Singh et al., 2016). Likely candidates that contribute to an exaggerated exercise pressor reflex in T2DM include bradykinin (Mense, 1977), arachidonic acid and its cyclooxygenase products (Rotto and Kaufman, 1988; Rotto et al., 1990), ATP (Hanna and Kaufman, 2003; Stone et al., 2014), substance P (Kaufman et al., 1988), nerve growth factor (NGF) (Cheng et al., 2009; Lu et al., 2012), and pro-inflammatory cytokines (Al-Mazidi et al., 2018; Copp, 2015; Miller et al., 2009). Substantial literature suggests bradykinin, which is released from contracting muscle (Stebbins et al., 1990), can stimulate group III and IV muscle afferents (Franz and Mense, 1975; Kaufman et al., 1982; Pan et al., 1993). Moreover, bradykinin is known to play a role in evoking an exaggerated mechanoreflex in PAD rats (i.e. ligated femoral artery model) (Lu et al., 2013), as well as modulating muscle and neuropathic pain (Franz and Mense, 1975). Bradykinin has also been found to cause an 8-fold increase in mechanically activated Piezo2 currents (Dubin et al., 2012). However, whether inflammatory mediators, such as bradykinin, or mechanically gated Piezo channels play a role in evoking the exaggerated exercise pressor reflex in T2DM is not known. Nonetheless, these data indicate that oxidative stress contributes to increasing group III and IV afferent activity either by a direct effect on ion channel activity and/or by stimulating the release of inflammatory mediators that modulate afferent activity.

6. Future directions and conclusion

There are many unanswered questions in terms of the reflexive control of the circulation in T2DM. In this review, we provide supporting evidence for direct and indirect effects of oxidative stress in contributing to an exaggerated exercise pressor reflex. Future studies should focus on determining specific mechanisms behind superoxide and other ROS in evoking the exercise pressor reflex. These mechanisms may act through direct stimulation or

changes in the expression of receptors and channels that mediate the exercise pressor reflex. In order to provide a comprehensive understanding of the role of oxidative stress on the reflexive control of circulation, we believe that these additional studies should be conducted in both animal models and humans.

In conclusion, individuals with T2DM have exaggerated cardiovascular responses to exercise due, in part, to an exaggerated exercise pressor reflex. There is accumulating evidence supporting oxidative stress as a unifying mechanism in contributing to an exaggerated exercise pressor reflex. Specifically, oxidative stress may directly or indirectly increase the activity of group III and IV afferents, evoking neuropathic pain and an exaggerated exercise pressor reflex. Ultimately, the pathological alterations associated with oxidative stress may result in a powerful positive feedback loop that further amplifies the stimulation of group III and IV afferents, and thus, the cardiovascular responses to exercise. Understanding the role of oxidative stress in neurovascular regulation is essential to identifying novel therapies that reduce the risk of adverse cardiovascular events in individuals with T2DM.

Acknowledgments

The authors acknowledge funding support from National Institutes of Health Grant R01-HL144723.

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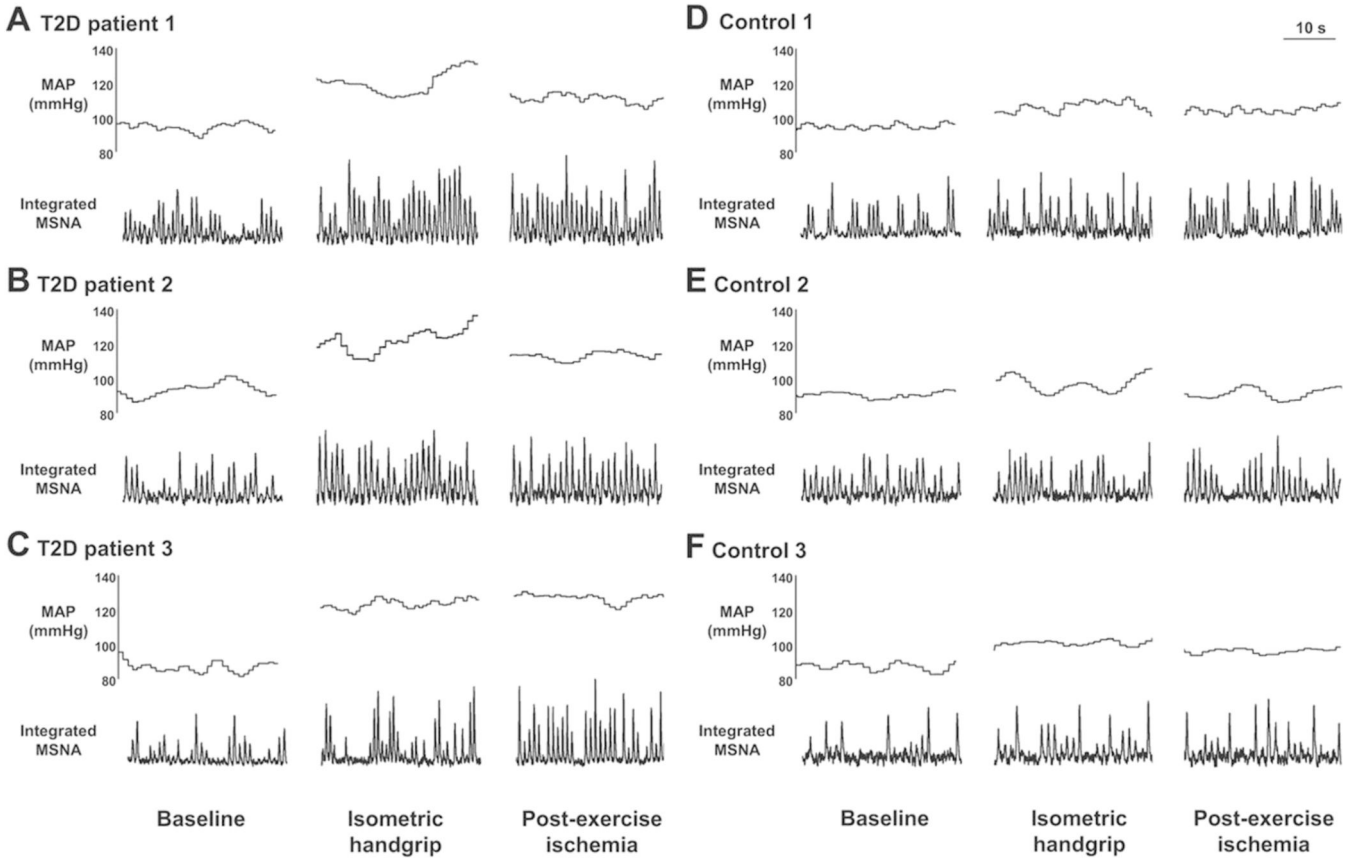

Fig. 1.

Original recordings of muscle sympathetic nerve activity (MSNA) and mean arterial pressure (MAP) in 3 type 2 diabetes patients (T2D; A-C) and 3 control subjects (D-F) at baseline, during 30% maximal voluntary contraction (MVC) isometric handgrip, and during post-exercise ischemia (PEI).

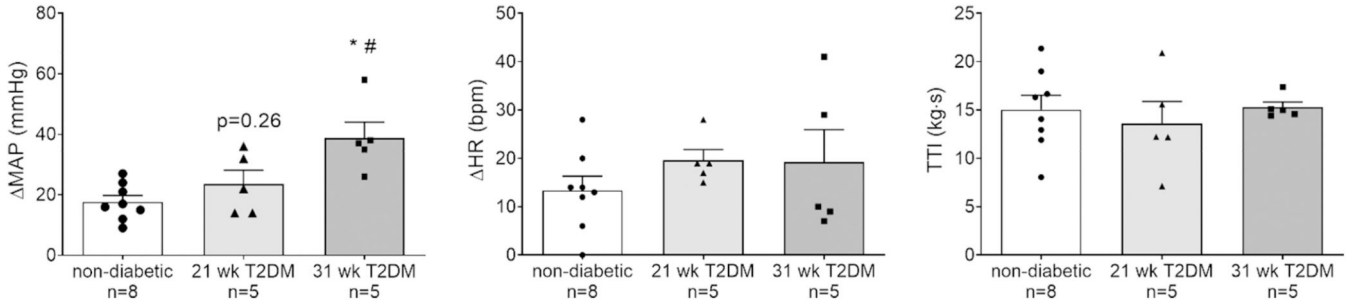

Fig. 2.

Means ± SE and individual data showing that statically contracting the hindlimb muscles evoked an exaggerated peak pressor response in the 31-wk compared with responses in 21-wk T2DM and non-diabetic rats (A). Peak changes in heart rate were not different among the groups (B). Developed tensions (tension-time index (TTI)) were similar among groups (C). $*p < 0.05$ (1-way ANOVA) indicates statistically greater response compared with non-diabetic rats. $\#p < 0.05$ (1-way ANOVA) indicates statistically greater pressor response compared with 21-wk T2DM rats.

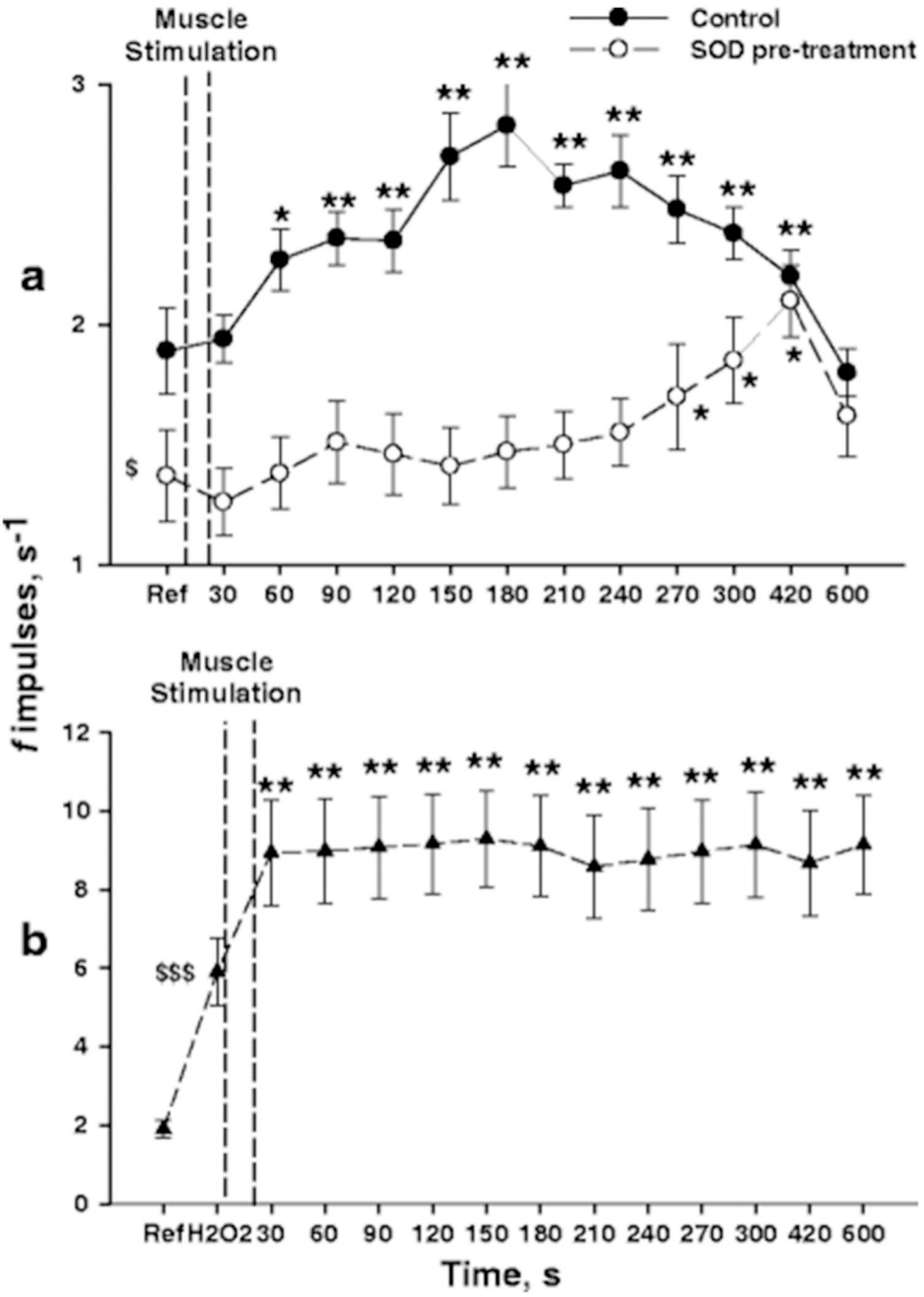

Fig. 3.

Response of group IV afferents to muscle stimulation in healthy Sprague Dawley rats. A) The changes in spontaneous activity of group IV afferents elicited by muscle stimulation are studied in control condition (closed circles: $n = 37$ units) and after intramuscular injection of SOD (open circles: $n = 32$ units). B) H_2O_2 injection before muscle stimulation markedly increased the baseline discharge rate but the response to muscle stimulation was not accentuated compared to control condition ($n = 33$ units). Dashed vertical bars indicate the 1-min muscle stimulation. Asterisk denote significant changes in averaged discharge rate (f

impulses) measured prior to beginning muscle stimulation ($*p < 0.05$; $**p < 0.01$). Symbol $ indicates that the averaged resting discharge rate was significantly lower in rats pre-treated with SOD ($^{\$}p < 0.05$) and markedly higher after H_2O_2 injection ($^{\$\$}p < 0.01$).

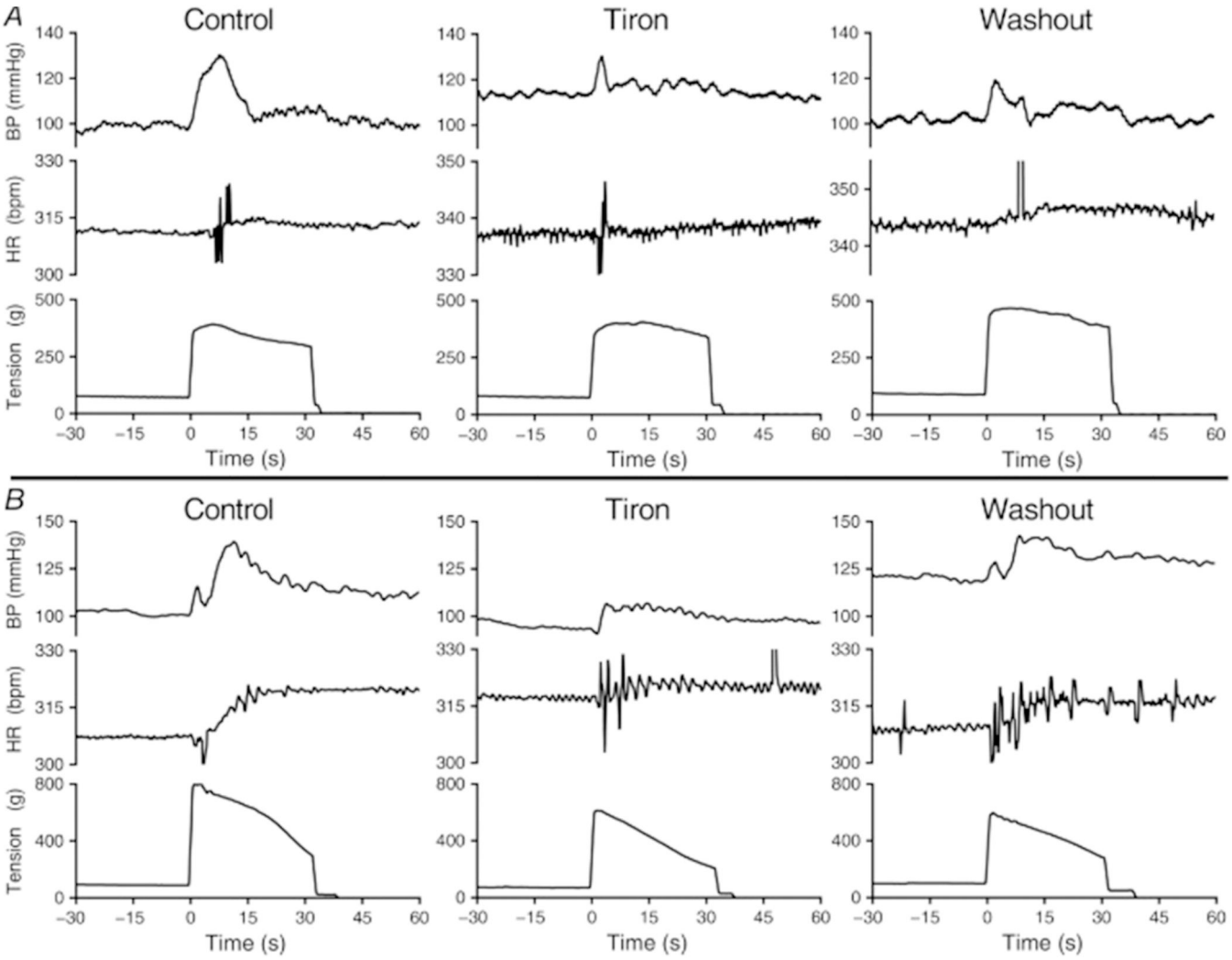

Fig. 4.

Original data traces showing the pressor (BP) and cardioaccelerator (HR) responses to static contraction for two PAD rats (i.e. ligated femoral artery model; A and B) during consecutive infusions of saline (control, left), tiron (center) and saline (washout, right) into the superficial epigastric artery. Tiron reduced the peak pressor and cardioaccelerator responses to contraction, as well as the duration of the pressor responses, compared with responses during saline infusion controls. Reinfusion of saline following tiron contraction (washout) partially restored the pressor and cardioaccelerator responses to contraction.

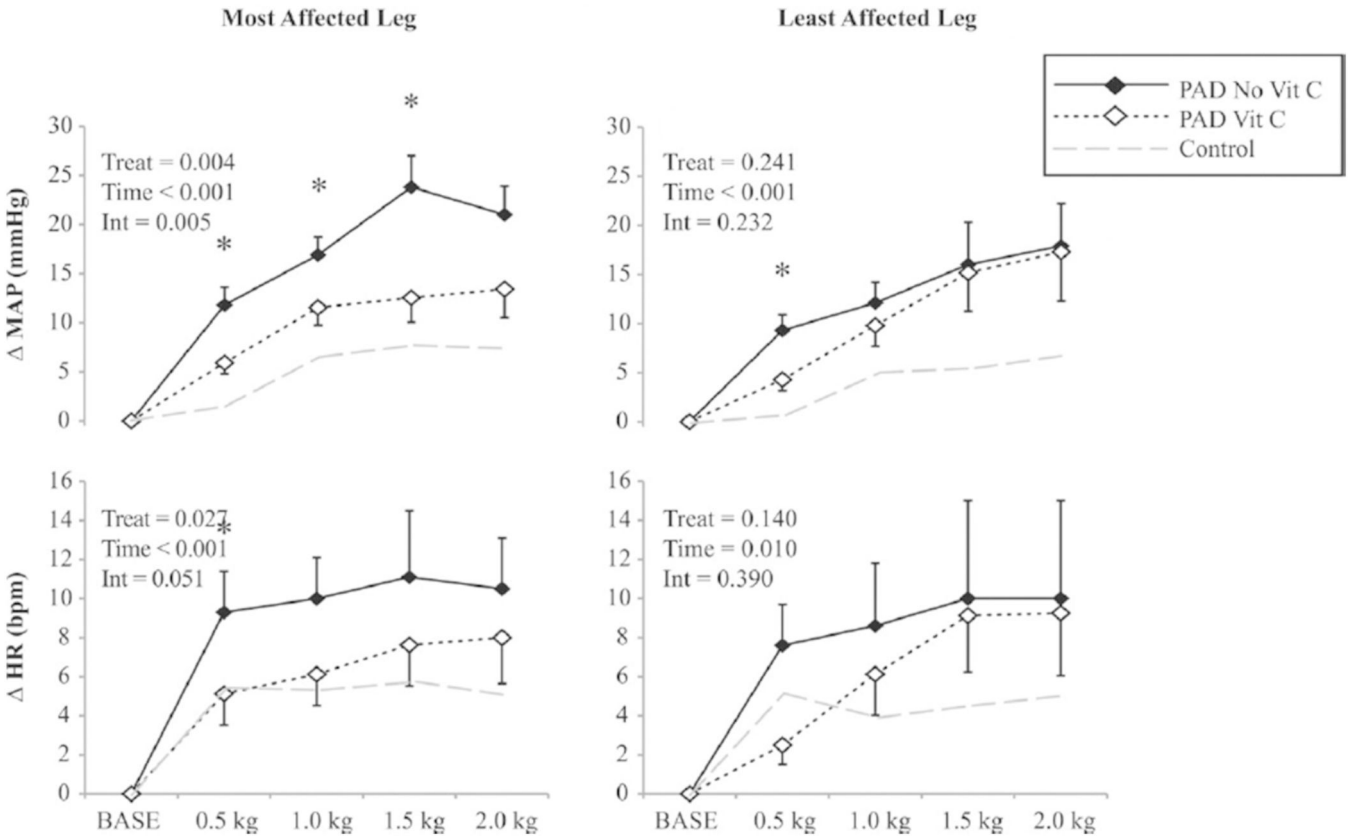

Fig. 5.

Effect of intravenous ascorbic acid (Vit C) on the change in mean arterial pressure (MAP) and heart rate (HR) in patients with peripheral arterial disease (PAD) during bouts of one-leg, low intensity rhythmic plantar flexion exercise. The left panel show responses to contractions in the most affected leg, while the right panel show responses to muscle contraction in the least affected leg. Control data in healthy individuals (grey dashed line) from protocol 1 is included for reference. Mean data from the first 20 s of each exercise stage are presented. Data are mean ± SEM, $n = 8$,*$p < 0.05$ between treatments at a specific time point. INT = interaction.

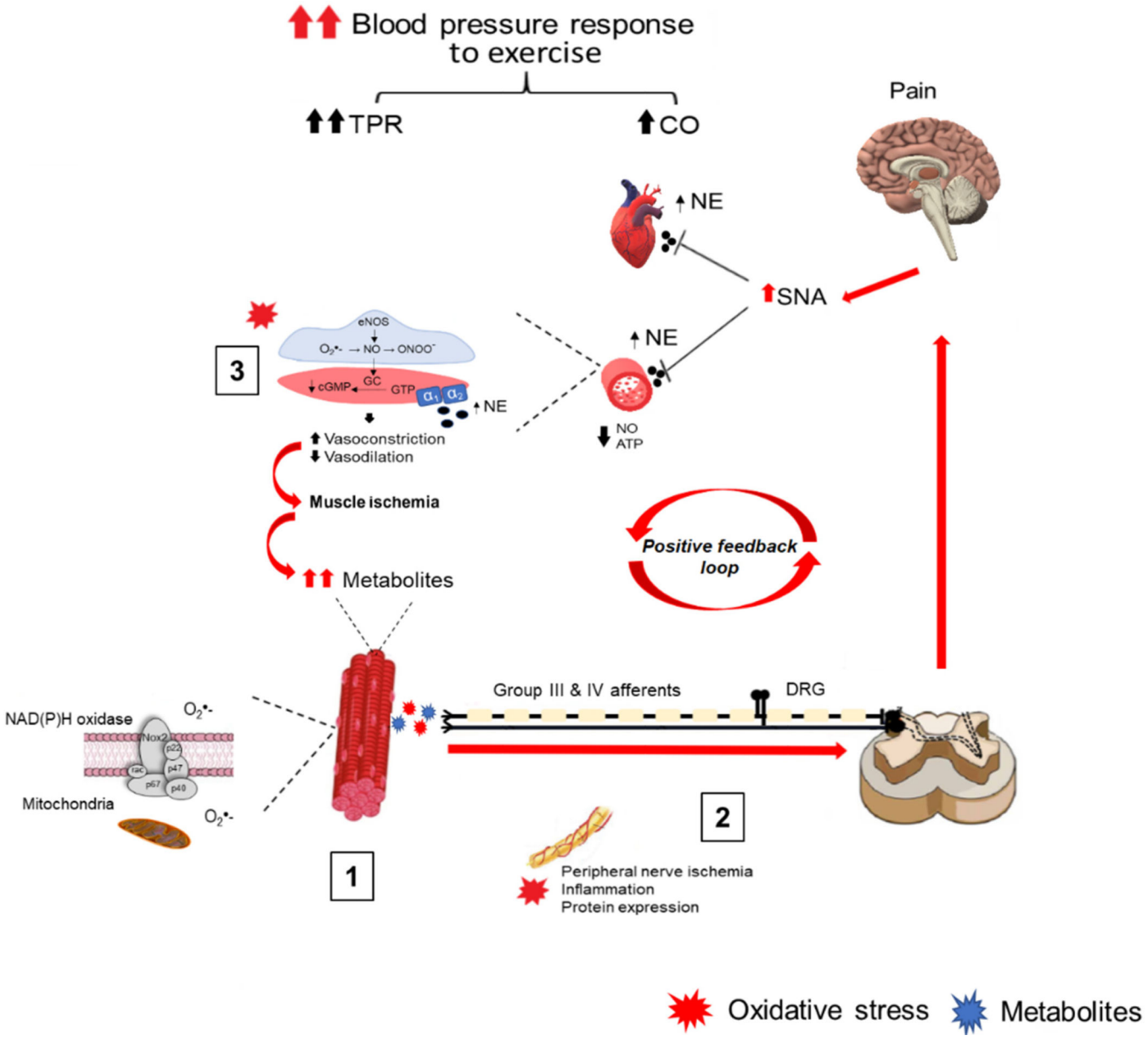

Fig. 6.

Theoretical model depicting the potential direct and indirect roles of peripheral oxidative stress in causing an exaggerated blood pressure response to exercise in type 2 diabetes mellitus (T2DM). In response to muscle contraction, NADPH oxidase release superoxide into the interstitial space, which increases the activity of group III and IV afferents (1). Increased oxidative stress along the afferent nerves and dorsal root ganglion (DRG) may further potentiate the afferent feedback (2). The increased afferent activity is relayed back to the brain stem increasing sympathetic outflow and may also be further relayed to the cerebral cortex causing increased pain sensation. On the vascular side, oxidative stress attenuates contracting muscle blood flow by reducing nitric oxide (NO) bioavailability and impairing functional sympatholysis. The accelerated muscle ischemia leads to accumulation of metabolites and increases the stimulation of group III and IV afferents (3). Collectively,

these impairments result in a powerful positive feedback loop causing an over-stimulation and potentiation of group III and IV afferent activity ultimately causing an exaggerated reflexive increase in blood pressure during exercise.