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Review

Nitric oxide: Is it the cause of muscle soreness?

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ABSTRACT

Skeletal muscle hosts all of the isoforms of nitric oxide synthase (NOS). It is well documented that nitric oxide (NO) regulates force generation and satellite cell activation, and therefore, damage repair of skeletal muscle. NO can also activate nociceptors of C-fibers, thereby causing the sensation of pain. Although delayed-onset of muscle soreness (DOMS) is associated with decreased maximal force generation, pain sensation and sarcomere damage, there is a paucity of research linking NO and DOMS. The present mini-review attempts to elucidate the possible relationship between NO and DOMS, based upon current literature.

Contents

Introduction

Although, delayed-onset of muscle soreness (DOMS) has been extensively studied, the phenomenon is still not completely understood. DOMS peaks about 1–3 days after unaccustomed exercise bouts, the result of lengthening contractions [1,2]. The etiology of DOMS is still vague [3], even after a number of different hypotheses have described the most important symptoms, which are, pain, decreased maximal force generation, and altered permeability of sarcolemma. It was suggested long ago, that DOMS is associated with mechanical damage. In 1977 Abraham [4] measured the ratio of hydroxyproline/creatinine in the urine samples of subjects with and without muscle soreness, and the increased ratio indicated significant damage to connective tissue. From biopsy samples, Friden and co-workers [5,6] reported that DOMS-associated muscle damage included intermyofibrillar sarcoma disturbances, and Z-band streaming, especially in Type 2 fibers [7–10]. This observation was confirmed later using magnetic resonance techniques [10,11]. Edema formation has also been observed in subjects suffering from DOMS [12]. A large increase in creatine kinase (CK) and myoglobin concentrations in the circulation are two of the most often used associated markers of DOMS and indicate increased permeability of the sarcolemma [13–18]. However, it has been reported that the magnitude of DOMS is not always associated with the magnitude of other markers of muscle damage [19].

In normal conditions, tissue damage is associated with inflammation, which, besides the well known beneficial effects, could also result in some of the discomforts of DOMS [20]. Based upon

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this hypothesis, naproxen sodium, which is a potent anti-inflammatory drug, has been used to attenuate the consequences of DOMS. However, significant effects have not been observed on the extent of pain, CK release, or force generation [21]. Among the indirect markers of DOMS, the altered ratio of oxidized to reduced glutathione indicates that, as a result of inflammation or calcium efflux, reactive oxygen species (ROS) are generated [3,22]. The generation of ROS is often observed during aerobic exercise, in which the mitochondrial electron transport chain is one of the main source of ROS [23–25]. However, the fact that eccentric muscle action with high tension and relatively low oxygen demand, such as downhill running, more readily causes DOMS than running with the same intensity on a flat surface [22], suggests that the main source of the generated free radicals is not the mitochondrial electron transport chain, but rather is due to secondary sources such as inflammatory agents [26].

The possible involvement of NO in DOMS was originally suggested by Radak et al. [27]. In that study the subjects developed DOMS after eccentric exercise. NO was measured from skeletal muscle biopsy samples of control subjects and subjects suffering from DOMS. The NO content was evaluated using electron spin resonance methodology, and an approximate 30% increase in NO levels was detected in skeletal muscle of subjects suffering from DOMS. This finding was associated with a significant decrease in maximal force generation. Since that time a number of important studies have been published on the role of NO in skeletal muscle function [28,29], and the findings include down regulation of force production [30,31], sensation of pain, and/or damage repair [32–36]. Although these studies were not always conducted during DOMS, the findings could be readily applicable to DOMS. Therefore, the present review attempts to highlight the role of NO in DOMS, especially in conditions that are associated with factors of DOMS, such as decreased maximal force generation, sensation of pain, and damage repair.

Muscle soreness-induced suppression of maximal force generation and the potential role of nitric oxide

Tiidus and Ianuzzo [37] reported that, in subjects with a high degree of muscle soreness, individuals were unable to lift weights corresponding to 90% max, for even one repetition, 48 h post-exercise. There is general agreement that DOMS results in decreased force generation 1–4 days after DOMS-induced exercise bouts [38,39], although Nosaka et al. [19] reported dissociation between the magnitude of DOMS and loss of muscle strength.

Our group was the first to describe a possible relationship between a DOMS-associated decrease in maximal force generation and NO concentration [27]. We have suggested that the DOMS-induced increase in NO formation that could suppress force generation was, at least in some part, a protective mechanism to prevent further damage induced by maximal contraction. However, at that time it was unclear whether NO was capable of down-regulating skeletal muscle contraction.

NO is produced by nitric oxide synthase (NOS) from L-arginine following an oxygen dependent process. Skeletal muscle hosts the three types of NO isoforms: inducible NO (iNO), endothelial NO (eNO), and neuronal NOS (nNO) [40]. The main NO generating enzyme in skeletal muscle is nNO, which is encoded to dystrophin [29,41]. It is quite clear that NO can regulate muscular function, force generation, and even affect the structure of skeletal muscle [42,43]. This regulatory process includes the NO mediated reversible inhibition of cytochrome oxidase, which affects oxygen uptake [44]. NO can control the IGF-I/p70 S6 kinase signaling pathway during muscle growth [45]. NO has also been implicated in protein S-nitrosylation of skeletal muscle and therefore, could modulate ATP-ase activity [46], as well as an exaggerated exercise-induced fatigue response [47]. It is clear that sarcolemmal nNO is an important regulator of blood flow to active skeletal muscle [29]. It appears that during eccentric exercise the induction of nuclear factor kappa-B, which is one of the main mediators of the inflammatory process [48], modulates the transcription of all of the isoforms of NO [49]. This observation could illustrate an important link between DMOS-inflammation and NO induction. In addition, the exercise induced NO generation appears to be important for the induction of interleukin-6, interleukin-8, hem oxigenase and HSP78 [50]. Indeed, NO, with a relatively long half-life, is an important signaling molecule [44,51,52]. However, because of the gaseous nature of NO, a transmitter would be advantageous to work specifically on targeted sites. Indeed, cyclic guanosine monophosphate (cGMP) is generated by NO, transmits the signal, and readily turns on downstream targets [53].

It is known that both inhibitors and donors of NO can result in decreased force generation [54], which demonstrates that the dose response of NO follows a bell-shaped hormetic curve [55–57]. The hormesis curve is a dose–response phenomenon [58,59] which can be described by low dose caused activation and high dose caused inhibition, a phenomenon which is generally true for other free radicals [58,60,61]. Although, nNO are readily up-regulated by exercise training [53] an increased level of NO or cGMP, can interact via a variety of pathways, to down regulate force production. One of the first studies to report a causative link between NO generation and decreased force generation showed that iNO inhibitions maintained force levels in the diaphragm [62]. Andrade and co-workers [63] have studied the effects of NO donors and cGMP inhibitors on Ca^{++} sensitivity and force generation of single fibers, and concluded that NO can impair Ca^{++} sensitivity, especially on actin filaments. Similarly to these earlier findings, Galler et al. [64] reported that, in skinned fibers, increased levels of NO resulted in decreased force generation through direct interaction of NO with force-generating fibers. It was also revealed that NO, through oxidizing contractile thiol proteins and by the depression of actomyosin ATP-ase, could mediate force development [64]. Moreover, increased levels of NO have been shown, in rabbit skeletal muscle, to result in a decreased number of cross-bridges and hence decreased force generation [65]. NO levels also negatively affect the force generation of cardiomyocytes [66], suggesting that NO and cGMP could have similar affects on contractile function in myocardium as in skeletal muscle. However, there are few studies which report on the effects of NO mediated changes after eccentric exercise and only one in which the investigators studied the possible link between NO and force generation [27]. In another study, in which the effects of eccentric exercise were studied on NO content, it has been shown that eccentric exercise increases nitrate concentration [67], and iNO activity [68–70] but the link between eccentric exercise induced NO and force production requires further study. Nonetheless, DOMS can be induced by eccentric exercise or by an unaccustomed exercise load [21,71,72]. The results of these studies would seem to suggest that enhanced NO production could impair force production in skeletal muscle [57] and the muscle soreness-associated increase could be a protective mechanism for skeletal muscle to prevent the possibility of maximal force generation and extensive damage [27].

Is nitric oxide involved in muscle soreness?

In a critical review, Amstrong [1] suggested that the pain, during DOMS, is due to the activity of macrophages and possibly the by-products of damage-induced exercise that accumulate in the interstitium, activating the endings of group-IV sensory neurons. The activation of macrophages could be a result of inflammation,