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The role of nitric oxide in skeletal muscle regeneration

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Essential processes in the regeneration of an injured muscle include proliferation of satellite cells and vascularization. Myogenesis and angiogenesis are prerequisites for the subsequent morphological and functional healing of the injured muscle, leading to the reconstruction of the damaged myocytes and vessels, restoration of the blood flow and restoration of the oxygen supply to the tissue. Nitric oxide (NO) plays a key role in satellite cells activation. It acts as a signal molecule and vasodilator, promotes expression genes for many growth factors being extracellular signals regulating the functions of the muscular, vascular and nervous systems. NO is produced by three isoenzymes, called nitric oxide synthases (NOS), present in skeletal muscle. The disturbance equilibrium between eNOS and iNOS activities results in pro-apoptotic NO activity and muscle atrophy. A recent study has shown a relationship between NO generation and delayed onset muscle soreness in response to intense resistance exercise. NO generation can be modulated by physical activity, systemic hypoxia (altitude training) or NO precursors such as L-arginine. The present review provides a current overview of NO effects on skeletal muscles and nutritional strategies based on L-arginine intake to aid muscle regeneration.

KEY WORDS: satellite cells, inflammation, DOMS, arginine, hypoxia, physical exercise.

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Introduction

Nitric oxide (NO) is a labile lipid soluble gas synthesized in several cells and tissues, including the adipocytes, brain, endothelial cells, heart, hepatocytes, macrophages and skeletal muscles. The endogenous formation and biological significance of NO were revealed in a series of studies in the 1980s, and for those seminal discoveries three American researchers were subsequently awarded the Nobel Prize in Physiology or Medicine in 1998. Soon after the identification of NO as a signalling molecule in mammals, it was reported that specific nitric oxide synthase (NOS) catalyzes a complex enzymatic reaction leading to the formation of NO from L-arginine and molecular oxygen. Later on, an alternative NOS independent pathway of NO synthesis was discovered, based on a simple reduction of nitrate and nitrite, i.e. the main oxidation products of NO. At that time, the interest in the biological role of NO led to a revolution in pharmacological and physiological research. NO is known to be a mediator in the noradrenergic and non-cholinergic neurotransmission in learning and memory, synaptic plasticity, neuroprotection, and skeletal muscle regeneration. Currently, NO is known to have many signaling functions. Not only can it directly influence the activity of transcription factors, but it can also modulate upstream signalling cascades, mRNA stability and translation, as well as the processing of primary gene products [1, 2, 3].

In 1996, the Nitric Oxide Society was founded to promote the advancement of basic and applied scientific research in all aspects of NO research by publishing meritorious scientific articles in its official journal *Nitric Oxide: Biology and Chemistry*. The journal covers the broad field of NO research and includes basic and clinical topics such as cell biology, molecular biology, biochemistry, immunology, pathology, genetics, physiology, pharmacology and disease processes [http://nitricoxidesociety.org/].

Nitric oxide, due to its multiple roles, has been studied in different areas of biomedical sciences. A simple search in PubMed (15/01/2014) using the term "nitric oxide" and "skeletal muscles" resulted in 2,616 articles, and 1,260 articles have been published in the last decade. These data show the great importance of this molecule in biomedical sciences with various studies aiming at the elucidation of physiological pathways, pathogenesis and treatment strategies based on NO function in skeletal muscles.

Nitric oxide synthesis in skeletal muscles

NO is generated continuously by skeletal muscles through the conversion of L-arginine to L-citrulline by the nitric oxide synthase (NOS) – a production increased by muscular contractions. Skeletal muscle normally expresses the neuronal (type I or nNOS), the inducible (type II or iNOS) and the endothelial (type III or eNOS) isoforms of NOS (Table 1). nNOS is strongly expressed in fast-twitch muscle fibres and localized in the muscle sarcolemma where it is associated with the dystrophin complex. eNOS is localized in the muscle mitochondria. Abnormalities in specific isoforms such as nNOS and eNOS have been reported in muscle diseases with mitochondrial deficiencies, indicating that specific NOS activities and expression may be involved in the pathogenesis of these diseases. Increased nNOS activity and expression were observed in muscle fibbers with mitochondrial proliferation, suggesting that it is related to mitochondrial biogenesis. However, the exact mechanisms involved in these abnormalities are not clear [4]. nNOS content in human skeletal muscle is 60% higher in athletes than non-athletes, while studies investigating eNOS have provided conflicting results [5].

iNOS is only expressed in skeletal muscle during inflammatory responses. Pro-inflammatory mediators such as cytokines IL-1β and TNFα induce iNOS expression in skeletal muscle [7]. Macrophages and T lymphocytes can also produce NO through iNOS mechanism. The excess NO can react with the superoxide anion to produce peroxynitrite by a 1,000,000-fold. Peroxinitrite ($ONOO^-$) is a very aggressive molecule that can induce cellular apoptosis, cellular mitochondrial dysfunction, lipid oxidation, etc. (Fig. 1). Without superoxide, the formation of $ONOO^-$ by way of reaction of NO with oxygen is minimal. NO and superoxide do not even have to be produced within the same cell to form peroxynitrite, because NO can so readily move through membranes and between cells [6, 8].

Table 1. Biochemical properties, regulation and functions of nitric oxide synthase (NOS) in skeletal muscles [2, 4 and 5]

	ISOENZYMES		
	nNOS; type I	iNOS; type II	eNOS; type III
Molecular mass (kDa)	160	130	133
Chromosomal locus	gene *NOS1* chromosome 12q24.22	gene *NOS2* chromosome 17q11.2	gene *NOS3* chromosome 7q36
Intracellular localization	muscle sarcolemma	sarcoplasm	mitochondria
NO production	low output	high output	low output
Regulation by the interaction of Ca^{2+} with calmodulin	yes	yo	yes
Regulation by cytokines	weak	strong	weak
Functions	regulation of α-adrenergic vasoconstriction and blood supply in contracting skeletal muscles, mitochondrial biogenesis	unclear	regulation of mitochondrial respiratory chain
Effect of intense endurance training	yes	yes/no	yes/no

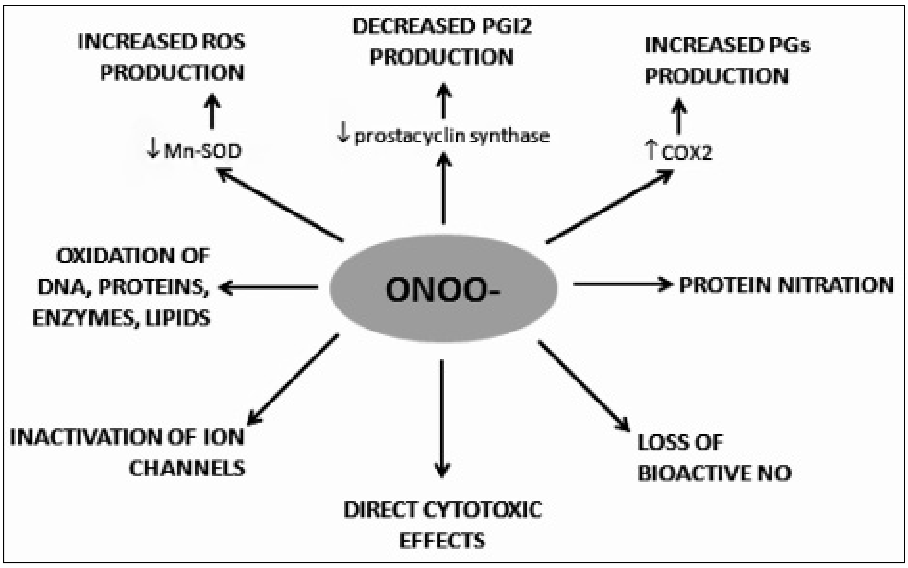

Figure 1. Biological consequences of peroxynitrite (ONOO$^-$) formation. It has two important biological consequences: loss of bioactive nitric oxide (NO) and direct cytotoxic effects. ONOO$^-$ and its conjugate acid can oxidize a variety of molecules with the consequence of protein modification or inactivation of ion channels. ONOO$^-$ inactivates manganese superoxide dismutase (Mn-SOD), thereby increasing the flux of superoxide anion ($O_2^{\cdot-}$) available to react with NO and establishing an autocatalytic spiral of increasing mitochondrial peroxynitrite formation; ROS reactive oxygen species; COX2 cyclooxygenase-2 [6]

A recent study showed that excessive exercise and overtraining led to IL-1β and TNFα generation can inhibit eNOS and activate iNOS. The disturbance equilibrium between eNOS and iNOS activities results in a pro-apoptotic NO activity, decrease in satellite cells number and finally impairment of muscle regeneration [9]. Whereas regular exercise with moderate intensity and duration increases the production of NO *via* eNOS, inhibits the production of pro-inflammatory and pro-apoptotic cytokines, and finally improves muscle function [10, 11]. Athletes demonstrated a significantly higher level of NO generation compared to non-athletes [12].

Nitric oxide and muscles regeneration

Essential processes in the regeneration of an injured muscle are the proliferation of satellite cells and vascularization. Myogenesis and angiogenesis are prerequisites for the subsequent morphological and functional healing of the injured muscle. It leads to rebuilding damaged myocytes and vessels, restoring the blood flow and restoring the oxygen supply to the tissue. NO plays a key role because it can act as a signal molecule and vasodilator, and can promote activation of several growth factors which are extracellular signals regulating the functions of the muscular, vascular and nervous systems (Fig. 2) [3, 13].

One of the first investigations into the role of NO in skeletal muscle damage was reported by Anderson [14] who mechanically crushed muscle of wild, NO knock-out or NO inhibited mice and observed very different repair processes to reveal the importance of NO in damage repair. It followed that NO facilitates the activation of satellite cells, which are located in the basal lamina of skeletal muscle, and this is one of the first steps in the repair process. Moreover, it appears that the beneficial function of NO in damage repair is not just restricted to satellite cell proliferation and differentiation but also to fusion. Hence, NO and the signalling agent of NO, cGMP – the antagonist of myostatin – activate follistatin, which is a negative regulator of myogenesis.

Despite the well described role of NO in the repair of muscle injury, it is possible that the mechanism controlling repair after unaccustomed exercise-induced damage might be different from those after crush injury [11]. Interestingly, treadmill running related overuse of tendons results in increased NO production, which suggests a role in the repair process [15]. The induction of mechanical damage to gastrocnemius muscle has been shown to result in increased NO formation, which is believed to initiate a signalling process for damage

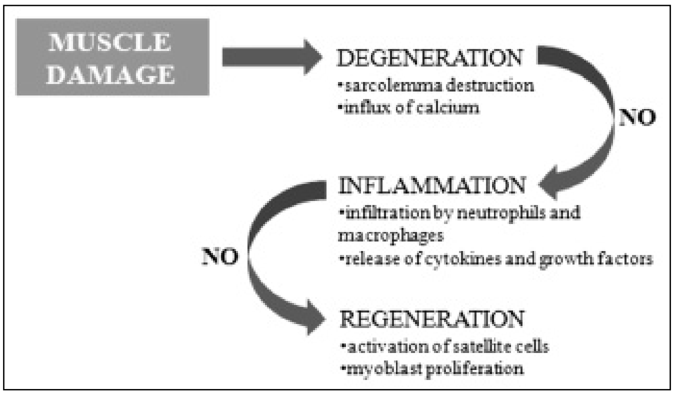

Figure 2. The phases of muscle regeneration [3]

repair [16]. In addition, the importance of NO to muscle function has been demonstrated as NO inhibition resulted in a severe walking speed reduction in rats [17].

NO mediates expression of cytoskeletal proteins in response to mechanical stimuli and is essential for the addition of sarcomeres when the working length is chronically increased. NO, as a cellular mediator in signal transmission, can use several signaling pathways such as activation of guanylyl cyclase, inhibition of cytochrome *c* oxidase in the mitochondrial electron transport chain or S-nitrosylation of transcription factors, including AP-1 (*activator protein-1* controlling about 80 genes), NF-κB (*nuclear factor κB* controlling about 300 genes) and HIF-1 (*hypoxia-inducible factor-1* controlling 100 genes) [18, 19, 20]. HIF-1 targets genes coding for proteins involved in oxygen transport (myoglobin, erythropoietin and vascular endothelial growth factor, VEGF) as well as genes coding for glycolytic enzymes and glucose transporters [21, 22].

Lira et al. [23] suggested that NO has an impact on muscle metabolism and structure by controlling the expression of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α). PGC-1α stimulates transcription of nuclear- and mitochondrial-encoded metabolic genes, as well as mitochondrial DNA replication. PGC-1α is upregulated by contraction and is involved in most of the metabolic adaptations and concomitant health beneficial effects of regular physical activity (Fig. 3). Altogether, NO regulates expression of about 500 genes! [21, 24].

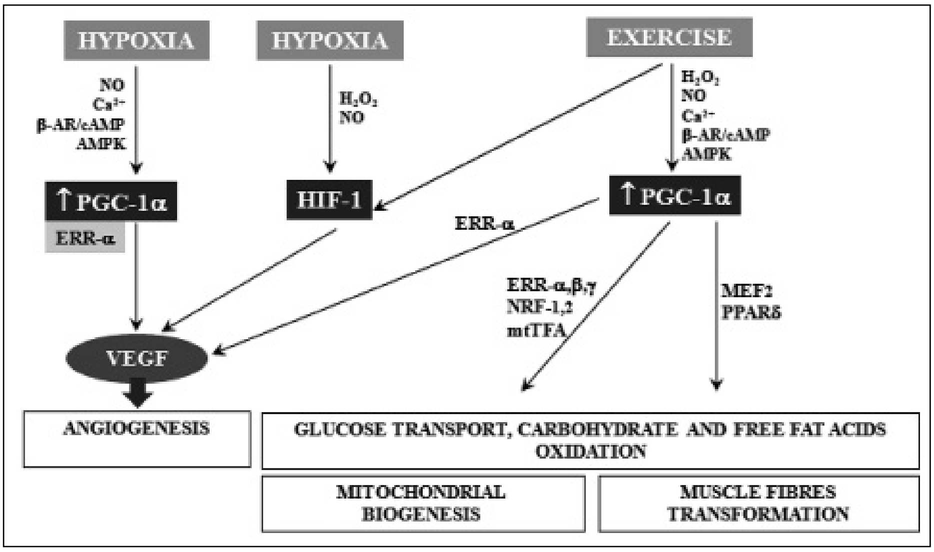

Figure 3. Integration between nitric oxide (NO) and peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) as well as between nitric oxide (NO) and hypoxia-inducible factor 1 (HIF-1) for maintenance of metabolic function in skeletal muscle cells [21, 24]

Nitric oxide and delayed onset muscle soreness

Physical activities that incorporate unaccustomed eccentric contractions are typically associated with high levels of muscle damage, inflammation and delayed onset muscle soreness (DOMS). The possible involvement of NO in DOMS was originally suggested by Radak et al. [25]. The NO content in skeletal muscle biopsy samples was approximately 30% higher in subjects suffering from DOMS. This finding was associated with a significant decrease in maximal force generation. The authors suggested that the DOMS-induced increase in NO formation that could suppress force generation was 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 [11, 25]. We observed that eccentric contractions were necessary to induce NO generation. Long-term exercise with a 15-min eccentric phase (downhill run) induces a significant increase in NO and pro-inflammatory cytokines IL-1β and TNFα concentrations in contrast to an exercise trial without the eccentric phase [26]. Another study, in which the effects of eccentric exercise on NO content were studied, showed that eccentric exercise increased nitrate concentration, and iNOS activity, but the link between eccentric exercise-induced NO and force production requires further reserach [27]. Nonetheless, DOMS can be induced by eccentric exercise or by an unaccustomed exercise load [28]. According to Radak et al. [11, 25] enhanced NO production could impair force production in skeletal muscle, 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.

Arginine – precursor of nitric oxide

In exercise physiology, NO has received much interest, and supplements of NO are thought to be an ergogenic aid. Because L-arginine is the main precursor of NO production, its metabolism and relevance to NO has received much attention over the last decade [1, 29]. L-arginine is considered a conditional essential proteinogenic amino acid that is a natural constituent of dietary proteins. Furthermore, L-arginine could be endogenously synthesized, mainly in the kidneys, where L-arginine is formed from L-citrulline. The liver is also able to synthesize considerable amounts of L-arginine, although this is completely reutilized in the urea cycle [1].

The typical dietary intake of L-arginine is approximately 4-5 g per day. The most common sources of this amino acid are meat, poultry, fish, dairy products and cereals (Table 2). One of the most densely packed L-arginine foods are nuts, whose consumption has been associated with decreased cholesterol and heart disease. Regular intake of another arginine-dense food, e.g. fish, has also been linked to a lower prevalence of heart disease [30]. Wells et al. [30] demonstrated that individuals may be able to lower their risk for cardiovascular disease by consuming more arginine-rich foods such as nuts and fish.

Table 2. Selected foods with a high L-arginine content [30]

FOOD	MEAN ARGININE CONCENTRATION mg/g food
Steak (sirloin)	19.4
Shrimp	15.9
Fish (whiting)	11.8
Peanuts	31.3
Chicken breast (skinless)	17.4
Pumpkin seeds	48.6
Sunflower seeds	24.0
Pecans (dry roasted)	10.3
Pistachios (dry roasted)	17.2
Cashews (dry roasted)	17.9

Dietary intake of L-arginine in humans is directly related to its plasma level. The normal plasma L-arginine concentration depends upon the age of the individual and homeostasis is primarily achieved via its catabolism. The usual mean and standard deviation range of plasma L-arginine in humans has been determined to be between 70 and 115 mmol/L Extracellular L-arginine can be quickly taken up by endothelial and muscle cells. In the presence of molecular oxygen and nicotinamide adenosine dinucleotide phosphate, L-arginine is subsequently oxidized to NO [1].

L-arginine can potentially influence skeletal muscle function and adaptive capacity, increasing the delivery and uptake of fuel substrates *via* NO vasodilating effects. However, there is still no clear evidence that this synthesis of NO results in improvements in exercise performance in healthy individuals [29]. Several studies have found that L-arginine supplementation increases satellite cells proliferation due to increased NO production. They also suggested that arginine bioavailability is a limiting factor for skeletal muscle, development, growth, and regeneration [3, 29]. For example, L-arginine supplementation was found to enable burn patients to maintain muscle mass, although this effect was not found in burn patients that were well fed [31]. Matsumoto et al. [32] showed that in endurance exercise at moderate intensity the oral intake of 2 g of combination of BCAAs and arginine effectively suppresses exercise-induced skeletal muscles proteolysis.

L-arginine also affects the muscle metabolism increasing the secretion of insulin and growth hormone (GH). Both molecules are important anabolic hormones with a remarkable degree of synergy in regulating glucose and fat metabolism. Insulin facilitates glucose entry into cells and an increase in glycogen stores while GH stimulates lipolysis and reduces glucose oxidation to maintain blood glucose levels. Thus the insulin and GH release may enhance exercise performance by increasing fatty acid oxidation and sparing glycogen stores. In addition, GH also causes the release of insulin-like growth factor I (IGF-I) that increases amino acid uptake and protein synthesis. These effects could also improve performance through increased muscle mass and strength [1].

NO generation can be also modulated by systemic hypoxia [33]. Hypoxia may induce mobilization of satellite cells, interstitial cells and mesoangioblasts, which are then recruited to participate in muscle regeneration and hypertrophy [34]. Hypoxia is a very potent stimulator of growth factors secretion which are involved in the regulation of stem cell functions [3, 35]. Kimura and Esumi [36] demonstrated that the effect of NO on VEGF expression is dependent on NO concentration during hypoxia. Small amounts of NO increase VEGF, which acts in a positive feedback to the increase in NO synthesis. Large amounts of NO inhibit VEGF synthesis as a result of the decrease in HIF-1 activity. A similar mechanism was observed in the regulation of BDNF (brain-derived neutrophic factor) which is responsible for proliferation and differentiation of stem cells in the brain and skeletal muscle [37].

Physical training in hypoxia (altitude training) has been used for decades by Olympic and professional athletes to increase endurance, strength and speed, avoid fatigue and improve recovery [38]. Recently, intermittent hypoxic training (IHT) has been introduced into sport practice. IHT is a method by which athletes receive exposure to short bouts of severe hypoxia (9-12% O_2), interspersed with periods of normal air. Studies reported substantial improvements in sea level endurance and anaerobic performance after IHT at rest or during exercise. These enhancements suggest that IHT may be suitable for improving performance in high intensity team sports [39-41]. Even though, we have a huge knowledge about hypoxic training, the effect of intermittent hypoxic training on NO synthesis remains unknown [38, 42].

Conclusions and perspectives

It is well established that unaccustomed exercise induces muscle damage and NO generation. NO could be one of the causes of inflammation and delayed onset muscle soreness. On the other hand, NO appears to be important for the activation of satellite cells required for damage repair. Hence, NO precursors (arginine) or hypoxia (altitude training or intermittent hypoxic training) could promote skeletal muscle regeneration and adaptation.

What this paper adds?

The present article discusses the results of studies on nitric oxide generation and adaptation of skeletal muscle to intense physical exercise. Furthermore, it explores the therapeutic possibility of arginine administration in combination with altitude training to maintain muscle mass and improve adaptation to exercise.

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