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Title:	Nitric oxide : biology and chemistry
Title Abbrev:	Nitric Oxide
Citation:	2023 Feb 1;131:8-17. doi: 10.1016/j.niox.2022.11.006
Article/Chapter:	Nitric oxide regulation of cellular metabolism: Adaptive tuning of cellular energy.
Chapter/Article Author(s):	Pappas G, Wilkinson ML, Gow AJ
NLM Unique ID:	9709307
PubMed UI:	36470373
ISSN/ISBN:	1089-8603 (Print) 1089-8611 (Electronic)
Fill from:	**Any Format**
NLM Call Number:	E-Journal w/ILL access; W1 NI988 (Gen)
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Nitric Oxide 131 (2023) 8–17

Contents lists available at ScienceDirect

Nitric Oxide

journal homepage: www.elsevier.com/locate/yniox

Nitric oxide regulation of cellular metabolism: Adaptive tuning of cellular energy

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ARTICLE INFO

Keywords:
Nitric oxide
Mitochondria
Metabolism
Exercise
Glycolysis
Cellular respiration

ABSTRACT

Nitric oxide can interact with a wide range of proteins including many that are involved in metabolism. In this review we have summarized the effects of NO on glycolysis, fatty acid metabolism, the TCA cycle, and oxidative phosphorylation with reference to skeletal muscle. Low to moderate NO concentrations upregulate glucose and fatty acid oxidation, while higher NO concentrations shift cellular reliance toward a fully glycolytic phenotype. Moderate NO production directly inhibits pyruvate dehydrogenase activity, reducing glucose-derived carbon entry into the TCA cycle and subsequently increasing anaploretic reactions. NO directly inhibits aconitase activity, increasing reliance on glutamine for continued energy production. At higher or prolonged NO exposure, citrate accumulation can inhibit multiple ATP-producing pathways. Reduced TCA flux slows NADH/FADH entry into the ETC. NO can also inhibit the ETC directly, further limiting oxidative phosphorylation. Moderate NO production improves mitochondrial efficiency while improving O_2 utilization increasing whole-body energy production. Long-term bioenergetic capacity may be increased because of NO-derived ROS, which participate in adaptive cellular redox signaling through AMPK, PCG1-α, HIF-1, and NF-κB. However, prolonged exposure or high concentrations of NO can result in membrane depolarization and opening of the MPT. In this way NO may serve as a biochemical rheostat matching energy supply with demand for optimal respiratory function.

1. Introduction

A crucial aspect of metabolic homeostasis is matching adenosine 5′-triphosphate (ATP) production with demand. This process necessitates matching both in terms of total amount but also in terms of rate. Briefly, the most efficient metabolic pathways are also the slowest, so during high-intensity exercise, these pathways are unable to supply ATP at the required rate. Mitochondrial oxidative phosphorylation is required for the efficient conversion of reducing equivalents, such as nicotinamide adenine dinucleotide (NADH), to cellular energy. However, this process is considerably slower than the rates of glycolysis or the hexose monophosphate shunt. The flip side is that such high-rate energy sources are ultimately limited by the buildup of unresolved reduction equivalents that results in acidification. While this may seem like a simple supply and demand problem, it is vital that the rates and routes of ATP production and use are well matched for maximum physiological performance. This represents a complex signaling problem that centers upon the mitochondrion as the key to overall metabolic function and specific rates of oxidative phosphorylation.

Multiple cellular signals serve to regulate metabolic flux broadly. In the cytosol, increased amounts of adenosine monophosphate (AMP), adenosine diphosphate (ADP), and inorganic phosphate (Pi) signify an energy decrement, increasing glycolytic flux and the production of pyruvate and lactate [1–3]. Within the mitochondria, acetyl-CoA (primarily from the breakdown of carbohydrates and fats), calcium ion concentrations, O_2 tension, NADH + H+, flavin adenine dinucleotide (FADH2), ADP, and Pi concentrations influence tricarboxylic acid (TCA) cycle and electron transport chain (ETC) flux respectively [4,5]. A multitude of other signals such as hormones (epinephrine, norepinephrine, insulin, glucagon), blood flow, and body temperature can also regulate metabolic rate. Working together, these pathways act to maintain ATP supply despite rapid increases in ATP demand during muscle contraction. However, an acute regulator of mitochondrial function, whose function can be significantly altered by available O_2 tension is nitric oxide (NO). The role of NO as a fine tuner in mitochondrial function is summarized in Fig. 1.

Nitric oxide is a powerful, short-lasting signaling molecule capable of

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https://doi.org/10.1016/j.niox.2022.11.006
Received 12 July 2022; Received in revised form 24 October 2022; Accepted 29 November 2022
Available online 5 December 2022
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Abbreviations

Adenosine 5′-triphosphate (ATP)
nicotinamide adenine dinucleotide (NADH)
adenosine monophosphate (AMP)
adenosine diphosphate (ADP)
inorganic phosphate (Pi)
flavin adenine dinucleotide (FADH2)
tricarboxylic acid (TCA)
electron transport chain (ETC)
nitric oxide (NO)
nitric oxide synthase (NOS)
xanthine oxidoreductase (XOR)
S-nitrosothiols (SNOs)
reactive oxygen species (ROS)
pyruvate dehydrogenase (PDH)
pyruvate dehydrogenase complex (PDC)
carnitine palmitoyltransferase (CPT-1)
glucose transporter (GLUT)
AMP-activated protein kinase (AMPK)
acetyl-CoA carboxylase (ACC)
S-nitrosoglutathione (GSNO)
O_2 tension (PO_2)
reactive oxygen and nitrogen species (RONS)
mitochondrial permeability transition pore (MPT)
adenine nucleotide translocase (ANT)
uncoupling proteins (UCP)
whole-body O_2 consumption (VO_2)
superoxide (O_2-)
peroxynitrite ($ONOO^-$)
nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)
hypoxia-inducible factor-1 (HIF-1)
nuclear respiratory factor-1 (NRF-1)

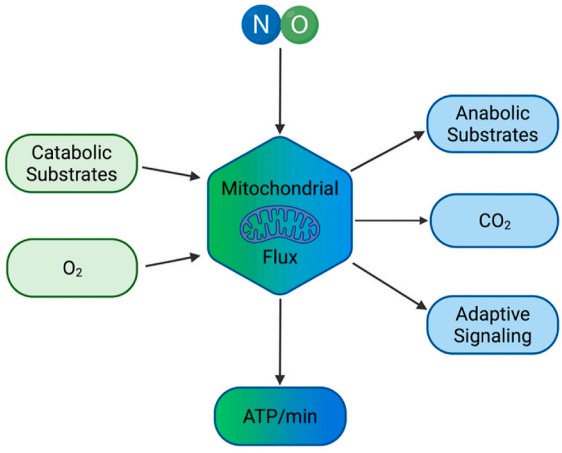

Fig. 1. *Nitric Oxide Operates to Balance Mitochondrial Flux and Optimize Cellular ATP Production.* NO can regulate both catabolic and anabolic substrate flux through the mitochondrion so that O_2 usage can be optimized such that the ATP produced per unit time matches the energy demand of the cell. Ultimately long-term activation of NO signaling can lead to adaptive signaling such that the cell can operate with the highest efficiency.

regulating a wide range of physiological functions, including vascular homeostasis, immune response, cognitive function, and metabolism. Nitric oxide can readily participate in one electron reduction and oxidation reactions leading to the formation of a range of reactive nitrogen species, the production of which is dependent upon the cellular environment [6]. These reactive species can react with lipids and various proteins, including enzymes and transport proteins essential to glucose and fatty acid metabolism, the TCA cycle, and the respiratory chain [7,8]. Endogenously generated by several nitric oxide synthase (NOS) enzymes, NO is present both in the systemic vasculature and within mitochondrial space [9]. It has a short half-life (<2 s) that varies with O_2 concentration within the tissue, and NO exerts its effects in a dose-dependent manner [10]. Recently, the reduction of nitrogen oxides like nitrite and nitrate has been evidenced as an important source of NO chemistry [11]. This review will discuss how NO regulates metabolic flux within the mitochondria by its interactions with specific proteins. In this way, NO modifies cellular utilization of metabolic substrates, the availability of O_2, and the production of extramitochondrial signals to match the energy needs to their supply in the cell, which may be critical for optimal respiration.

2. Production and molecular targets

NO is endogenously generated by several NOS enzymes, which catalyze the oxidation of L-arginine to NO [12]. Regular NO production from the constitutive expression of NOS1 (neuronal; nNOS) and NOS3 (endothelial; eNOS) produces low nanomolar amounts of NO necessary to maintain vascular homeostasis [13–15]. During inflammatory events, NO production is rapidly increased via upregulated NOS2 (inducible; iNOS) expression [12,16]. NOS enzymes are not tissue specific and expression of NOS isoforms have been found within the mitochondria (termed mtNOS) [17]. In addition, it should be remembered, especially within mitochondria, that nitrite can be reduced back to NO by a range of metalloproteins, including xanthine oxidoreductase (XOR) and myoglobin [18]. NO can interact with a wide variety of biological molecules with potential signaling consequences [19–21]. Thus, a critical factor in NO regulation of physiological systems is its flux rate of production and the relative concentrations of target molecules.

NO will bind to metal centers, such as heme-iron or iron-sulfur centers, to produce nitrosyl-metal species or to cysteine thiols (S-nitrosylation) to produce S-nitrosothiols (SNOs) [21,22]. Additionally, nitrosation reactions result in the direct or indirect addition of a nitrosonium ion (NO+), which may also form nitrosothiols [21]. Furthermore, nitration reactions lead to the addition of a nitronium ion (NO_2+), forming a nitro functional group (R–NO_2) [21]. Finally, NO may react with reactive oxygen species (ROS), leading to the production of higher oxides of nitrogen such as peroxynitrite. The topic of NO reactivity has been discussed more thoroughly elsewhere [20,21] and here we will focus on potential targets within metabolic control.

3. TCA cycle flux and the fate of carbon substrates

3.1. Pyruvate dehydrogenase (PDH)

Part of the larger pyruvate dehydrogenase complex (PDC), PDH catalyzes the oxidative decarboxylation of glucose-derived pyruvate into acetyl-COA for entry in the TCA [23–25]. The downregulation of PDH reduces cellular usage of glucose, subsequently increasing the use of fatty acids for energy [26,27].Several mechanisms have been proposed for how NO or NO derivates can directly inhibit PDH activity, including S-nitrosylation of PDC subunit dihydrolipoamide dehydrogenase [28]. PDH inhibition increases with NO production, reducing glucose-derived carbon entry into the TCA and increasing anaploretic pyruvate carboxylation and glutamonolysis [29]. This allows continued production of

TCA intermediates such as α-ketoglutarate, citrate, or itaconate, for continued energy production (glutamine-derived NADH and FADH2 for the ETC) or for the synthesis of lipids [30,31]. While decreased PDH activity may blunt TCA cycle flux and downstream oxidative phosphorylation and ATP output, it also allows for the conservation of valuable metabolic substrates, such as pyruvate and lactate, that can be used for gluconeogenesis or for supporting cellular growth and other anabolic pathways [32–34]. Reduced PDH activity post-exercise may play a role in glycogen resynthesis post-intensive exercise by sparring carbohydrates from cellular oxidation [35,36].

3.2. Aconitase

Mitochondrial aconitase, which catalyzes the isomerization of citrate to isocitrate in the TCA cycle [37], is an iron–sulfur-containing dehydratase, which is a target of oxidation and inhibition by ROS, NO, and NO derivates [37]. Under normal conditions, high TCA cycle turnover and subsequent ETC respiration leads to increased production of ATP and mitochondrial ROS. These ROS can regulate TCA flux, inhibiting aconitase activity, reducing glucose-derived carbon oxidation and sparing glucose for use in other metabolic pathways, and activating alternative pathways for ATP production. NO and NO derivates decrease both mitochondrial and cytosolic aconitase activity in a dose-dependent manner, with a more significant effect on mitochondrial aconitase [38–43]. High levels of NO production lead to complete reduction in aconitase activity, preventing citrate isomerization and subsequent formation of α-ketoglutarate. In turn, this promotes increased glutaminolysis [30].The inhibition of aconitase results in the accumulation of mitochondrial citrate, which has numerous effects on cellular energy production by inhibiting ATP-producing pathways [44]. This includes inhibition of glycolytic enzymes phosphofructokinase, pyruvate kinase, and PDH, as well as decreased carnitine palmitoyltransferase (CPT-1) mediated fatty acid transport [44]. Citrate accumulation upregulates ATP-consuming pathways and supports lipid synthesis [45].

3.3. Glucose and fatty acid metabolism

Physiological levels of NO alter blood glucose homeostasis via upregulation of glucose transporter (GLUT) expression, although the exact mechanism of action varies by cell type [46–53]. In skeletal muscle, insulin-independent GLUT translocation requires activation of the primary energy sensor, AMP-activated protein kinase (AMPK). Increased muscle activity will reduce ATP concentrations, activate AMPK, and stimulate NO production. This signals cGMP-dependent GLUT-4 translocation to the cell membrane [50,54–57]. nNOS-derived NO mediates both insulin-independent (AMPK mediated) and insulin-dependent GLUT transport in skeletal muscle [58]. AMPK itself is directly regulated by NO, creating a mechanism for self-regulation of glucose homeostasis in resting and exercising skeletal muscle [55,59]. In addition to altering glucose transport, both exogenous NO donors and eNOS derived NO reduce gluconeogenesis and glycogenesis in liver cells, i.e., reduce anabolism [60–62]. Not surprisingly, increased glucose uptake coupled with decreased gluconeogenesis, glycogenesis, fatty acid oxidation, and cellular respiration leads to an upregulation of glycolysis as the main source of energy production [63–65].

Both endogenously and exogenously produced NO alter lipolysis, fatty acid uptake, and fatty acid oxidation in a dose-dependent manner. NO inhibits fatty acid synthesis in rat liver while decreasing acetyl-CoA carboxylase (ACC) activity, reducing malonyl-CoA concentration, and leading to upregulation of CPT1 [66]. This is further supported by studies demonstrating that the use of NOS inhibitors decreased fatty acid oxidation via decreased CPT activity [67]. Arginine (a precursor to NO) and low-dose nitrate supplementation increase lipolysis and fatty acid oxidation, with the latter increasing cGMP activity and CPT1 expression in mice [65,68]. Higher nitrate doses also upregulate PGC-1α, resulting in mitochondrial biogenesis and increased fatty acid oxidative capacity [68]. Post-translational modification via S-nitrosylation of acyl-CoA dehydrogenase improves the enzyme's efficiency in mouse liver, which may increase fatty acid metabolism (although this has not been directly tested) [7]. Leptin alters lipolysis via several NO-mediated pathways [69,70]. Acute leptin exposure increases NO production and lipolysis in rat white adipose tissue, an effect that is inhibited with NOS inhibitors [71]. However, prolonged leptin exposure decreases lipolysis via NO-mediated signaling, potentially serving as a self-regulator for energy storage [71]. High flux NO decreases leptin-mediated lypolysis [72]; while iNOS-derived NO in stimulated macrophages decreases lipolysis and β-oxidation via inhibition of the respiratory chain [73]. Finally, NO reduces catecholamine-mediated lipolysis through inhibition of β-adrenergic signaling [74–76].

4. Cellular respiratory chain

4.1. Flow of electrons and the utilization of oxygen

The heme-containing enzymes of the ETC (complexes I-IV) located on the inner mitochondrial membrane are well-studied targets of NO. Electrons are transferred from one complex to the next through a sequence of redox reactions, while complexes I, III, and IV pump protons into the intermembrane space. The resulting proton gradient is used to phosphorylate ADP to ATP via ATP synthase. Oxygen serves as the final electron acceptor binding at complex IV to produce ATP, CO_2, and H_2O. Inhibition at any point in the ETC slows the flow of electrons, altering the rate of O_2 consumption, ATP production, and the generation of ROS. Functionally, a build-up of reducing equivalents NADH and $FADH_2$ will signal energy demands are met and slow upstream TCA cycle flux. Decreased respiratory flux allows O_2 to be diverted toward other, non-ATP producing pathways.

4.2. Complex I and complex III

Detailed mechanisms underlying the inhibition of additional complexes in the ETC have been covered elsewhere [77]. NO can reversibly inhibit the NADH: ubiquinone oxidoreductase (complex I). Unlike at complex IV, inhibition at complex I is likely not due to the direct binding of NO but occurs via the S-nitrosation of specific thiol residues or oxidative stress via interaction with peroxynitrite [78–82]. Similar inhibition has been observed at ubiquinol: cytochrome *c* oxidoreductase (complex III) from mtNOS and NO donor S-nitrosoglutathione (GSNO), leading to increased ROS production [83,84].

4.3. Cytochrome C oxidase

Cytochrome *c* oxidase (complex IV) catalyzes the final step in electron transport, oxidizing cytochrome *c* and reducing O_2 to produce H_2O. The enzyme's O_2 binding site is a binuclear heme iron/copper center, which constantly cycles between oxidized and reduced states [85]. The relative amounts of oxidized to reduced cytochrome *c* oxidase present at any time are dependent on the O_2 levels in the mitochondrial environment, with oxidation increasing with high O_2 tension (PO_2) [86]. NO can bind to cytochrome *c* oxidase in both its reduced (competitive with O_2) and oxidized (non-completive) states. This competitive and non-completive binding allows NO to regulate mitochondrial respiration over the range of normal to hypoxic cellular environments. At high PO_2, NO non-competitively binds the Cu center in fully oxidized cytochrome *c* oxidase, reducing cytochrome *c* oxidase and forming nitrite [87–89]. At low PO_2, NO reversibly binds to reduced cytochrome *c* oxidase, directly competing with O_2. This leads to inhibition of individual mitochondrial respiration, the diversion of O_2 toward other cellular targets, and alters the production of reactive oxygen and nitrogen species (RONS) [90–93].

4.4. Cellular respiration and mitochondrial O_2 gradients

The relative amount of cytochrome *c* oxidase in the reduced state is increased under hypoxic conditions (i.e., contracting skeletal muscle), increasing the affinity for NO. However, in the tissue environment, concentrations of NO and O_2 are not uniform [94]. Cells most proximal to the sources of endogenously produced NO (i.e., the vascular endothelium) will experience greater inhibition of respiration. The sparing of O_2 from consumption in these proximal cells extends the half-life of O_2, allowing O_2 to travel further along its gradient toward deeper, more hypoxic tissue [10,94–96]. Additionally, the half-life of NO increases under hypoxic conditions, allowing for constant diffusion into tissue further from the blood vessel. This establishes a feed-forward mechanism that perpetuates smoothing of the concentration gradient for O_2 [10,94,96]. Finally, because the maximal capacity of mitochondrial respiration exceeds O_2 delivery, sites near the endothelium (or other sources of endogenously produced NO) still retain adequate energy supply, despite modest NO reductions to ETC function. The result is that NO supports increased cellular and/or whole-body energy production through an increased number of respiring mitochondria.

5. Mitochondrial efficiency

5.1. Matching ATP production with O_2 consumption

O_2 consumption is tightly coupled to proton pumping and ATP synthesis during mitochondrial respiration. However, several other pathways exist through which either protons may re-enter the mitochondrial matrix (proton leak) or in which O_2 is consumed. This uncoupling reduces mitochondrial efficiency. Under normal conditions, base levels of proton leak occur unregulated (basal leak), accounting for approximately 5% of total mitochondrial proton leak. NO can alter the electrochemical proton gradient used to synthesize ATP through several mechanisms, including changing inner mitochondrial membrane-bound protein expression or function. High concentrations of NO cause inner membrane depolarization through the formation of ONOO- and the opening of the mitochondrial permeability transition pore (MPT) [97,98]. Low NO flux protects against decreases in membrane potential, potentially via S-nitrosylation of membrane-bound proteins [98–100]. Nitrate supplementation has also been shown to decrease the expression of two mitochondrial membrane proteins, adenine nucleotide translocase (ANT) and uncoupling protein (UCP), which may be important mediators of proton leak [18,101–103]. In a recent study performed by Wynne and colleagues, it was observed that nitrite can stimulate the glycolytic ATP supply without the loss of the oxidative ATP supply in skeletal muscle cells [104]. This indicates that nitrates increase the overall rates of myocellular ATP production [104]. Additionally, nitrates result in an overall shift away from non-mitochondrial respiration [104]. Taken together, this indicates that nitrate supplementation has the potential to lower the oxygen cost of ATP production [104].

5.2. Mitochondrial efficiency and exercise capacity

There is strong evidence that NO can enhance mitochondrial efficiency during exercise by improving the coupling of ATP synthesis with the dissipation of the proton gradient, thus improving the mitochondrial oxidative efficiency [18,105,106]. These effects are likely mediated by NO control over the mitochondrial membrane potential. Several studies have shown that oral nitrate supplementation reduces whole-body O_2 consumption (VO_2) at various submaximal workloads [18,105–109]. Importantly, this observed decrease in VO_2 is not accompanied by any significant changes in heart rate, respiratory exchange ratio, lactate accumulation, or maximal work capacity achieved. This suggests either a reduced O_2 requirement for a given workload or an increased aerobic efficiency at submaximal exercise [105–108]. Additionally, nitrate supplementation during high-intensity exercise has been observed to increase time to task failure without a change in VO_2 max achieved [107,108]. Numerous studies have replicated that nitrate supplementation reduces O_2 demand and increases exercise tolerance across multiple exercise modalities, including cycling, running, and walking [109–117]. This effect is dose dependent, and has sustained benefits, with results persisting up to 15 days [110,112]. Nitrate supplementation has been observed to provide greater benefit at submaximal workloads for low-to-moderate aerobically fit individuals or individuals with reduced exercise capacity due to disease, but not for higher-level athletes. Concurrently, there have been studies that show that nitrite supplementation fails to improve mitochondrial function and efficiency, indicating that improvements seen with nitrate supplementation may occur through a mechanism other than oxygen consumption [118,119]. Additionally, several studies have indicated that nitrate supplementation resulted in no mitochondrial improvements or reduced oxygen cost during exercise, indicating a need for more research in this field to determine the effects of nitrate supplementation and the mechanisms by which they may occur [120,121].

6. Adaptive signaling

6.1. Indirect effects of NO signaling

NO regulates the rate of mitochondrial ROS production, especially superoxide (O_2^-) [11,122,123]. The fate of O_2^- is determined by the relative balance of other oxidants (i.e., NO, $ONOO^-$, NO_2) and antioxidant defense mechanisms [124–126]. Superoxide can form peroxynitrite ($ONOO^-$) by interactions with free NO [127,128], and H_2O_2 and H_2O by mitochondrial superoxide dismutase (mnSOD) [129]. mnSOD is abundantly present in the inner mitochondrial matrix and is essential for the removal of mitochondrially-produced free radicals, which arise during anaerobic metabolism [129–131]. There are several pathways through which mitochondrial ROS cross the mitochondrial membrane and participate in redox signaling within the cell [132]. ROS can act on several downstream bioenergetic mediators, including crucial energy regulators, AMPK and PGC-1α, as well as transcription factors such as NF-κB and HIF-1 [133–136].

AMPK can be activated by various stressors, including low nutrient levels and prolonged exercise [137]. When ATP levels are decreased, AMPK becomes activated [138,139] leading to increased ATP-generation [138,140]. AMPK regulates glucose uptake in muscle and fat cells by increasing GLUT4 trafficking to the cell membrane and regulates the rate-limiting enzymes of lipid metabolism Acetyl-CoA carboxylase and HMG-CoA reductase [138,141–143]. AMPK can also increase mitochondrial biogenesis through activation of signaling pathways such as NRF-1 and PGC-1 [144–147]. AMPK contributes to muscle fiber type remodeling, angiogenesis, and regulates autophagy and mitophagy [3,140,148–150]. AMPK signaling also directly affects NOS signaling. AMPK activation has been shown to inhibit iNOS expression [151,152]. Additionally, AMPK has been observed to phosphorylate eNOS and nNOS, leading to their activation [152–154], while eNOS has been implicated in the induction of AMPK [152,154]. PGC1-α is a transcriptional co-activator that regulates cellular metabolism in muscle tissue [147,155,156]. PGC1-α responds to several stimuli, including ROS, ATP demand, and cellular stress, to initiate transcription of downstream genes [155,157] encoding mitochondrial proteins, leading to mitochondrial biogenesis [155,158–161]. Activation of PGC1-α regulates skeletal muscle fiber type and contraction, lipid uptake, and glucose transport [155,156,162]. Additionally, PCG1-α activation leads to the upregulation of SOD [155,156,163,164]. PCG1-α is directly activated via exercise, low cellular energy [155], and its expression is regulated by NO in skeletal muscle [59]. Short-term exposure to NO in endothelial cells downregulates PGC1-α,however, the opposite effects occur with long-term exposure [165].

HIF-1, a hypoxia sensitive transcription factor, serves to preserve O_2, while maximizing ATP production by stimulating glycolysis,

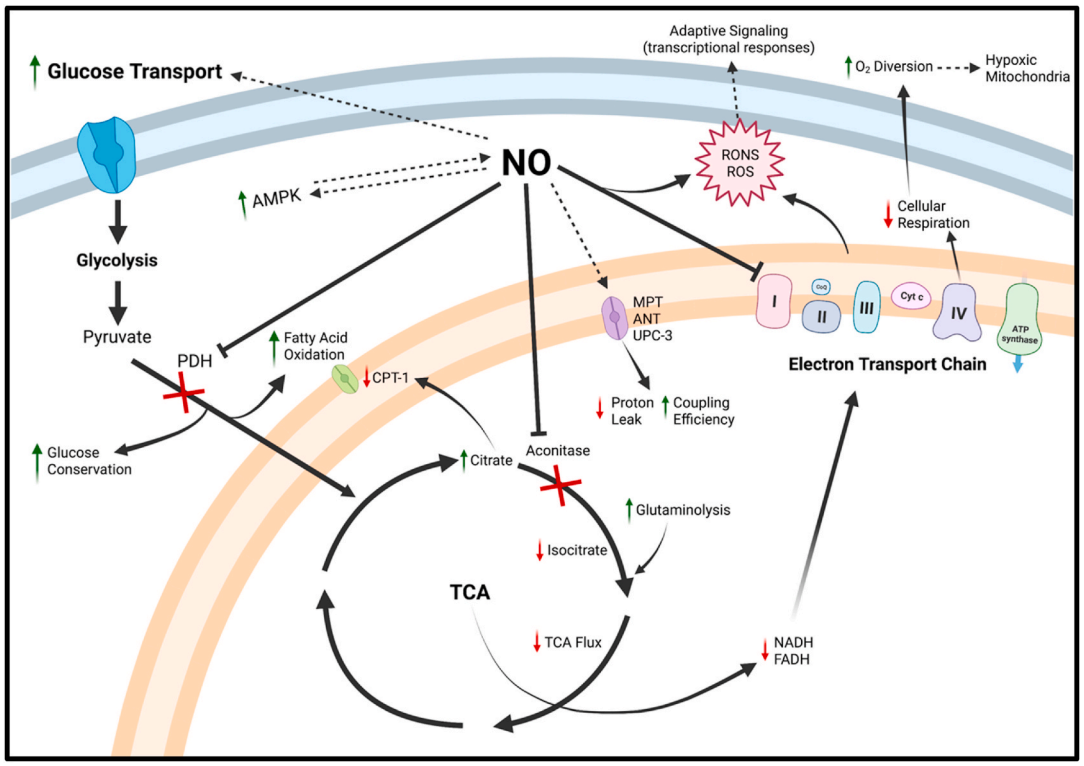

Fig. 2. *NO Regulation of Mitochondrial Metabolism.* Low to moderate NO concentrations upregulate glucose and fatty acid oxidation via multiple pathways, while higher NO concentrations serve to shift cellular reliance away from fatty acid oxidation and cellular respiration toward a fully glycolytic phenotype. NO-induced AMPK activation mediates GLUT4 expression on the cell surface membrane and increased glycolytic flux. AMPK enhances NO production via NOS phosphorylation. Moderate NO production within the cytosol directly inhibits PDH, reducing glucose-derived carbon entry into the TCA, the use of fatty acids for energy while conserving lactate and pyruvate for utilization in other anabolic pathways. Within the mitochondria, NO directly inhibits aconitase, increasing TCA reliance on glutamine for continued energy production. At higher or prolonged NO exposure, subsequent citrate accumulation can inhibit multiple ATP-producing pathways, including CPT-1 and several glycolytic enzymes (not shown). Reduced TCA flux slows NADH/FADH entry into the respiratory chain, which also experiences direct NO inhibition at complex IV. Minor inhibition of the ETC, with increased glucose transport and decreased fatty acid oxidation, serves to increase glycolytic flux during high energy demand (i.e., exercise). Moderate NO production can also improve mitochondrial efficiency via decreased expression of ANT and UPC-3 across the inner membrane while improving O_2 utilization by diverting O_2 toward more hypoxic tissue, increasing whole-body energy production. Long-term bioenergetic capacity may be increased because of NO-derived ROS, which are able to cross the mitochondrial membrane and participate in adaptive cellular redox signaling primarily through AMPK, PCG1-α, HIF-1, and NF-κB. However, prolonged exposure or high concentrations of NO results in membrane depolarization and opening of the MPT, excessive and potentially damaging ROS production, and the shift from oxidative phosphorylation toward total reliance on less efficient glycolysis for energy production.

erythropoiesis and angiogeneis [166,167]. Exercise can generate micro-regions of acute hypoxia, and thus induce HIF-1 signaling [166, 168]. NO and other reactive nitrogen species, can directly and indirectly affect HIF-1 activation [169]. At low NO levels promote HIF-1α degradation, whereas high concentrations promote its function, stabilizing it even in normoxic conditions [169,170]. This upregulation increases transcription of proteins related to mitochondrial function, glycolysis, erythropoiesis, and angiogenesis [171–173]. In addition, the hypoxic conditions that occur in muscle tissue during exercise lead to increased NO production, further contributing to HIF-1 activity and its downstream effects [171].

6.2. *Direct NO signaling and metabolic adaptations*

Low levels of NO, that do not significantly inhibit cellular respiration, decrease superoxide production [174]. Similarly, inhibition of mitochondrial respiration during hypoxic conditions (i.e., contracting skeletal muscle) temporarily decreases mitochondrial-derived ROS production via NO reduction of ETC flux [175,176]. However, mitochondria are the primary source for ROS following exercise, which may be important in adaptation to training [177–180]. Conversely, moderate and high levels of NO, result in inhibition of complex I & IV, decreasing O_2 consumption and inducing a dose dependent increase in ROS and a buildup of reducing equivalents [80,181].

7. Conclusions

Although often overlooked in models of metabolic regulation, NO plays a vital role in fine-tuning the catabolic and anabolic pathways of the cell. The potential interactions of NO in metabolic regulation of working tissue, such as contracting muscle, are summarized in Fig. 2. The overall effect of NO on metabolic output is driven by NO concentration, rate of production, and the localization of NO within the cell or tissue environment [10,98]. The mobilization and subsequent oxidation of glucose and fatty acids is upregulated by low, potentially eNOS-derived, NO production. During times of increased energy demands, such as in contracting skeletal muscle, NO activates AMPK-mediated pathways for energy procurement [49,54,140]. Physical activity directly increases NO flux, as increased blood flow and sheer stress stimulate vascular eNOS expression and NO production [182–184]. Minor inhibition at the respiratory chain coupled with increased glucose transport, decreased fatty acid oxidation, and an increased need for ATP serve to increase glycolytic flux during intensive exercise. At submaximal intensities, moderate NO production improves the utilization of O_2 for ATP production via decreased uncoupling across the inner membrane and increased recruitment of respiring mitochondria [105]. Post-physical activity

recovery or long-term bioenergetic capacity may be increased because of NO-derived ROS, AMPK, PCG1-α, HIF-1, and NF-κB signaling [3,175,177,185,186]. Increased mitochondrial biogenesis and transcription of mitochondrial proteins increase the overall oxidative capacity of the cell, leading to long-term training adaptions and improvements.

NO is known for its diverse roles in multiple biological processes ranging from vascular health to cognition and metabolic function. NO is capable of inhibiting or enhancing metabolic function, dependent on its own production rate and localization within the cell. Metabolic output is tightly controlled to balance ATP producing and ATP consuming processes. While there are many regulators of metabolic flux, there is clear evidence that NO is central to cellular energy control, serving as both a sensor and director of metabolic output. In this way, it appears that NO operates like a metabolic rheostat fine tuning energy production to match demand. For this function it is necessary that the right amount of NO be produced at the right time for efficient regulation, not that more is always better.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: The study received support from National Institute of Environmental Health Sciences (NIEHSP30ES005022, T32-ES007148) and National Heart Lung and Blood Institute (NIH-HL086621).

Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

No data was used for the research described in the article.

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