

# Nitric oxide stimulating dietary supplements: where is the evidence?

## Nitric oxide supplements

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**ABSTRACT:** *Dietary supplements purported to increase nitric oxide production have gained enormous popularity within the athletic (e.g., bodybuilding) community in recent years. Although anecdotal reports suggest a potential benefit from using such products, the scientific evidence is sparse. To the knowledge of this author, only one ingredient consumed in oral form by human subjects has been reported within the scientific literature to promote an increase in blood nitric oxide. This ingredient is a unique form of L-carnitine called glycine propionyl-L-carnitine (GPLC). This article discusses the scientific evidence for nutritional supplements to increase nitric oxide production, as well as the physiological rationale as to why nitric oxide may be important related to athletic performance. Directions for future scientific work in this area of sport supplementation are presented.*

### INTRODUCTION: WHAT IS NITRIC OXIDE?

Nitric oxide (NO<sup>•</sup>), first referred to as endothelium-derived relaxing factor (1), is biosynthesized from the amino acid L-arginine, oxygen, and a variety of cofactors, by nitric oxide synthase enzymes (2), including endothelial nitric oxide synthase (eNOS), inducible nitric oxide synthase (iNOS), and neuronal nitric oxide synthase (nNOS). Nitric oxide is a gaseous chemical compound that acts as an important signaling molecule within the human body, known to facilitate a variety of critical functions as previously described in detail (for recent reviews please see (3, 4). In this regard, high concentrations of NO<sup>•</sup> favours cell cycle arrest and apoptosis, while brief production at low (nanomolar) concentrations favour a wide array of beneficial physiological functions including enhanced blood flow and immune defence, decreased platelet and leukocyte adhesion, decreased smooth muscle cell proliferation, regulation of neurotransmission and muscle atrophy/hypertrophy, and the stimulation of satellite cells—which may be related to muscle tissue hypertrophy (3-6). These effects appear mediated via both a cyclic guanosine monophosphate (cGMP) dependent and independent signalling cascade (3). In relation to sport supplementation, NO<sup>•</sup> is of great interest primarily related to the ability of this molecule to facilitate vasodilatation, by acting on vascular smooth muscle cells (3). This major discovery, initially by Furchgott and Zawadzki (1), has led countless other scientists from around the world to devote their research agendas to work related to NO<sup>•</sup>. In fact, NO<sup>•</sup> was recognized as “molecule of the year” by Science magazine in 1992, and the Nobel Prize in Physiology or Medicine was awarded in 1998 to Robert Furchgott, Louis Ignarro, and Ferid Murad for their work related to NO<sup>•</sup> as a gaseous signalling molecule within the cardiovascular system. Over the past 5 years in particular, NO<sup>•</sup> has received significant attention from the athletic community (primarily bodybuilders), fuelled largely by the aggressive marketing campaigns of sport supplement companies who manufacture products touted to “stimulate nitric oxide production”. In this regard, the primary desired effect is the potential increase in blood flow to active skeletal muscle, mediated by the claimed increase in blood concentrations of NO<sup>•</sup>.

It is hypothesized that this proposed increase in blood flow would then lead to an increase in oxygen and nutrient delivery (e.g., amino acids and glucose) to skeletal muscle in order to aid exercise performance and to help facilitate recovery.

### EXERCISE AND NITRIC OXIDE

Before considering the impact of a dietary supplement on NO<sup>•</sup> production, it is important to understand the role of exercise itself in facilitating increased NO<sup>•</sup>. This is most often determined by the combined measurement of nitrate (NO<sub>3</sub><sup>-</sup>) and nitrite (NO<sub>2</sub><sup>-</sup>) in blood or urine, which are considered stable products of the rapidly degraded NO<sup>•</sup> (half life equal to 3-4 seconds).

Previous reports indicate that acute exercise results in increased blood NO<sup>•</sup> (7-9), a finding evident for both dynamic (10) and isometric (11) exercise. Moreover, studies involving chronic exercise training performed 3-4 days per week have also noted an increase in resting levels of NO<sup>•</sup> (12-14), outside of the context of an acute exercise session. Based on these findings, it may be hypothesized that exercise trained individuals would experience a greater magnitude of NO<sup>•</sup> increase either during or following an acute exercise bout. While anecdotal accounts of enhanced blood flow (suggested to be due to increased NO<sup>•</sup>) during an acute exercise bout appear greater for trained compared to untrained individuals, this author is not aware of controlled studies that have specifically measured this response in trained and untrained subjects, either during or following the performance of acute exercise. Regardless, the findings of increased resting NO<sup>•</sup> may help to explain some of the positive health (e.g., reduced blood pressure, reduced angina) and performance outcomes (e.g., enhanced walk time) apparent in exercise trained individuals compared to their sedentary counterparts (typically older, deconditioned adults). Hence, what may be perhaps the most important initial recommendation is the performance of regular, structured exercise by all individuals interested in reaping the potential benefits of increased circulating NO<sup>•</sup>. While NO<sup>•</sup> is indeed thought to play a role in enhanced blood flow during an acute bout of exercise (again, the chief marketing point of most

sport supplement companies selling such products), other mechanisms are indeed involved (e.g., flow mediated dilation, muscle contraction-induced distortion of resistance vessels) as previously described (15). In fact, these other mechanisms are believed to be primarily responsible for allowing for optimal blood flow redistribution and hyperaemia with acute exercise, with NO<sup>•</sup> playing only a minor role (16). Therefore, even if such nutritional supplements did result in a significant and measurable increase in NO<sup>•</sup>, the question becomes, would this have any physiological relevance in the context of an acute exercise bout? Clearly, no data presently exist to address this question.

#### PHARMACEUTICALS, DIETARY SUPPLEMENTS AND NITRIC OXIDE

Aside from exercise, pharmaceutical agents have been used with success to either induce NO<sup>•</sup> biosynthesis or to enhance/maintain the actions of NO<sup>•</sup>, with the primary end goal of promoting vasodilatation (17). These include nitrates (transdermal long acting, sublingual rapid acting), propionyl-L-carnitine (intravenous), and L-arginine (intravenous), as well as agents used for the treatment of erectile dysfunction (e.g., Viagra<sup>®</sup>, Cialis<sup>®</sup>). In most cases, the above drugs are used to treat ailments involving impairments in blood flow including various forms of cardiovascular disease, such as angina arising from myocardial ischemia, as well as peripheral arterial disease. In some studies, treatment with high dose L-arginine, the NO<sup>•</sup> precursor amino acid, has been associated with enhanced vasodilatation (18, 19). However, it should be noted that the route of administration in such studies has been intravenous injection and not oral intake. In fact, a review of studies involving oral intake of L-arginine at dosages ranging from 10-20 grams indicates no benefit of this amino acid with regards to either increased circulating NO<sup>•</sup> or enhanced blood flow (20-22). In addition, an oral dosage of only 10 grams per day has been noted to have an unpleasant taste and in some cases result in gastric distress (22). It is evident that sport supplement companies are simply basing their "research" related to their products on investigations involving intravenous injection of L-arginine. Obviously, the route of administration is important in this regard. For example, work involving direct comparisons between intravenous and oral intake of L-arginine indicates no effect of oral L-arginine intake on vasodilatation, partly due the fact that oral L-arginine bioavailability is only ~68 percent and varies across subjects (23). Moreover, while the dosage of L-arginine used in intravenous studies has often ranged from 6-30 grams given in a bolus dose, most of the dietary supplements sold on the market today include only 3 grams of arginine per serving (For details on such products, readers are referred to [www.bodybuilding.com](http://www.bodybuilding.com)). At this low dosage, it is highly unlikely that oral intake of such supplements will have any impact on NO<sup>•</sup> or on the desired changes fostered by the proposed increase in this molecule.

Equally important, although L-arginine is the precursor to NO<sup>•</sup> biosynthesis, it has been suggested that this amino acid is not the rate limiting component (24). Rather, nitric oxide synthase enzymes may be most important to NO<sup>•</sup> biosynthesis.

In fact, a recent report indicates that 3 grams per day of L-arginine results in no increase in NO<sup>•</sup> availability and actually reduces exercise time to fatigue (25).

Any anecdotal effect that individuals claim to experience when using many of the marketed products may be more dependent on the sugar contained within the product, rather than the L-arginine. This is because sugar intake results in an insulin spike, and insulin itself has been shown to yield a vasodilation effect (19, 26). In fact, intravenous L-arginine itself at a dosage of 30 grams over 30 minutes has been shown to increase insulin release (19) and promote vasodilatation. It is possible that some "cocktail" products which contain several ingredients aside from sugar and L-arginine may promote an effect on NO<sup>•</sup> and subsequent vasodilatation. However, only well designed, controlled scientific studies will determine whether or not such products can substantiate the radical claims currently being made for such products.

Despite the lack of scientific data, it is evident that dietary products marketed to increase NO<sup>•</sup> production are rampant within

the supplement industry. In fact, a quick scan of many of the popular bodybuilding magazines indicates that in any given month there are 30 or more entire pages of advertisements devoted solely to this class of dietary supplement. Indeed, this is an area of interest within the athletic community.

#### GLYCINE PROPIONYL-L-CARNITINE AND NITRIC OXIDE

One novel ingredient that has emerged as a potential candidate to result in a measurable increase in NO<sup>•</sup> production is glycine propionyl-L-carnitine (GPLC). GPLC is a molecular bonded form of propionyl-L-carnitine and the amino acid glycine. We have recently reported in previously sedentary men and

women (27) and in resistance trained men (28) that oral intake of GPLC at a dosage of 4.5 grams per day results in increased plasma NO<sup>•</sup>, as measured by NO<sub>3</sub><sup>-</sup> + NO<sub>3</sub><sup>-</sup>. Our findings agree with other recent work using PLC exclusively (29) which demonstrated an increase in blood NO<sup>•</sup> in response to 6 grams per day of PLC given via intravenous infusion. The mechanisms of action for this effect appear mediated by a decrease in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation (30), which subsequently leads to superoxide radical generation (31) and decreased NO<sup>•</sup> bioavailability. It has also been reported that PLC augments endothelial nitric oxide synthase (eNOS) (32), leading to increased NO<sup>•</sup> production. Additional work to investigate the mechanisms associated with the increase in plasma NO<sup>•</sup> with GPLC treatment is needed.

## CONCLUSION

With the exception of two recently published studies reporting an increase in plasma NO<sup>•</sup> with oral intake of GPLC (27, 28), there are no other published reports to indicate that the currently available dietary supplements which are marketed as "nitric oxide stimulators" have any proven efficacy. Several interesting research questions remain to be answered with regard to this entire class of dietary supplement. For example, can such products 1) Stimulate an increase in NO<sup>•</sup> production? 2) Stimulate an increase in blood flow? 3) Stimulate an increase in oxygen and nutrient delivery to target tissue? 4) Enhance aerobic and anaerobic exercise performance? 5) Enhance exercise recovery? and/or 6) Enhance muscle mass? Only continued funding by committed supplement companies and government agencies will provide the opportunity for these and other questions to be addressed. Without such work, and subsequent evidence showing measurable improvements in these variables, this field will remain much more hype than effect. Current marketing campaigns by many of the top sport supplement companies are presented as though these questions have already been answered in the affirmative. Clearly, this is not the case.

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### Real or perceived conflict of interest

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