Getting the “NAC” of antioxidant supplementation

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It is almost impossible to go through an entire day without being told by some advertisement that you must supplement your diet with some form of antioxidant, whether this be a breakfast cereal that has been fortified, a new fruit juice that has more antioxidants per glass than a traditional fruit juice, or even shampoo that has been enriched with antioxidants. We all seem to accept this premise without paying too much attention to exactly what antioxidants are and what they do – especially with respect to exercise. This article will review the current data regarding antioxidant supplementation in the sporting environment and produce general guidelines as to its optimal application.

What is an antioxidant?

Oxygen poses us a problem. On the one hand it is essential for life, on the other, it is a toxic mutagenic gas, resulting in the formation of potentially harmful reactive oxygen species (ROS). Historically, the first living organisms on earth survived under an atmosphere containing little oxygen and essentially were anaerobic. Rising atmospheric oxygen concentration, due to the evolution of photosynthetic organisms, resulted in many of these anaerobes becoming extinct. The few remaining anaerobes have adapted to the current oxygen concentration of 21%, by restricting themselves to environments where oxygen could not penetrate. Obviously, not all animals did this and a second line of defence was developed – this being the evolution of an antioxidant system to protect them against the toxicity of atmospheric oxygen.

An antioxidant is any compound that prevents oxidation by molecular oxygen. Put simply, antioxidants neutralise ROS. Antioxidants can be divided into two classes: exogenous and endogenous.21 Exogenous antioxidants such as Vitamin C (VC) and E (VE), are obtained through the diet, whereas endogenous antioxidants are naturally produced by the body. Notable endogenous antioxidants include glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX).19

Does antioxidant supplementation improve performance?

It is without doubt that uncontrolled ROS production can severely damage cellular lipids, proteins and DNA and are even associated with certain cancers.19 Intense contractile activity accelerates ROS production to the extent that the cells antioxidant defences are transiently overwhelmed. The term “oxidative stress” is commonly used to describe this condition where there is a change in the “redox balance” (Figure 1). However, it must be stressed that the true definition of oxidative stress involves the imbalance in oxidant/antioxidant ratio resulting in...
damage. Recently, there is overwhelming evidence to suggest that a modest change in the redox balance results in oxidative signalling. This results in positive adaptations and thus, the generic use of the term oxidative stress may in fact be misleading (this will be discussed in more detail later in the article).

The implication of ROS in the development of several pathologies, including ageing and muscular fatigue, has resulted in the traditional view that ROS are only involved in negative physiological processes. Against this backdrop, a series of early studies focused on the role of medium-term, (4-8 weeks), VE and/or VC consumption, in reducing ROS production and enhancing exercise performance. With few exceptions, this body of research revealed that antioxidant supplementation variably reduced markers of ROS production and consistently failed to enhance performance. Several assays exist to measure ROS production, however, none are without limitation. A major problem in the measurement of ROS is the fact that they have a very short half life, and are thus extremely difficult to detect. For example, the hydroxyl radical is reported to have a half life of 10-12 seconds!

Indeed, inconsistent results with respect to an antioxidant modulated decrease in ROS production are likely attributable to differences in assays between studies and the lack of a gold-standard assay. In any event, ROS have rarely enhanced performance, hence the prescription of antioxidants for this purpose cannot be recommended.

Does antioxidant supplementation improve recovery from exercise induced muscle damage?

Eccentric exercise is known to induce muscle damage and/or delayed onset of muscle soreness (DOMS), a condition defined by muscular pain and impaired muscle function. Interestingly, ROS are produced as part of the immune response to DOMS. This enhanced period of ROS production occurs around 72-96 hours post exercise and in some situations results in a further decrement in muscle function. It follows that antioxidant supplementation may improve muscle function post-exercise, via suppressing the secondary spike in ROS production. The associated literature suggests that VC treatment can modestly attenuate exercise-induced pain, but does not enhance performance on isokinetic dynamometry tests.

Interestingly, there is some evidence to suggest that VC supplementation may delay recovery, since this secondary spike in ROS production seems to be required for exercise-induced adaptation. Indeed, in recent times, the literature has focused on the role of antioxidants and ROS in regulating training adaptations.

Have cells signalled the end of antioxidant supplementation?

It has recently been discovered that ROS are vital signalling molecules that promote the expression of endogenous antioxidant and mitochondrial proteins. Antioxidant supplementation appears to abolish these favourable adaptations. For instance, Gomez-Cabrera and colleagues revealed that expression of PGC-1α, an important transcription co-activator that regulates mitochondrial biogenesis, is significantly reduced following eight weeks of aerobic training when supplemented with VC (1g·d⁻¹) in human subjects. Moreover, this impairment in PGC-1α attenuated improvements in VO₂max (Figure 2). Expression of the endogenous antioxidant enzymes SOD and GPX was also attenuated by VC supplementation. Similar results have been reported by others. Perhaps the ultimate realisation of this research is that moderate exercise is an antioxidant, acting to trigger beneficial adaptations to endogenous antioxidants. The question must therefore be asked why are we so keen to stop these adaptations by administering antioxidants during training without fully understanding the precise role of ROS in skeletal muscle?

Training-induced increases in endogenous antioxidant enzymes represent a rapid training adaptation that occurs in individuals naive to exercise. It is revealing that studies indicating a negative effect of antioxidants on cell signalling processes have utilised sedentary subjects and measured adaptations over a relatively short period (~6-8 weeks). Interestingly, it may be that no impairment occurs in individuals already engaged in exercise training. In support of this, researchers from our laboratory have recently demonstrated that VC (1g·d⁻¹) supplementation does not impair performance.

Figure 1. Effects of oxidant/antioxidant balance on oxidative/reductive stress. When there is a balance of oxidants and antioxidants homeostasis is achieved, this being known as ‘redox balance’. However, when the number of oxidants is greater than antioxidant defences the cell is under ‘oxidative stress’, and conversely when the number of antioxidants is greater than the oxidants the cell is under ‘reductive stress’.
Importantly, these studies used a randomised approach to ensure fairness in the comparison. However, with the lack of evidence of training adaptations in untrained but not trained individuals, the effectiveness of antioxidant supplementation has been shown to significantly improve fatigue resistance across several modes of exercise. Importantly, NAC supplementation has been shown to significantly improve fatigability resistance across several modes of study (see Figure 3). These findings indicate that ROS production may play a direct role in the process of muscular fatigue.

N-acetylcysteine (NAC)

From the discussion so far, antioxidant supplementation does not enhance or impair performance. The majority of the current literature has focused on VC and VE. Interestingly, re-synthesis of many endogenous antioxidants, notably glutathione peroxidise (GPX) and glutathione, is limited by cysteine availability. The intracellular cysteine pool can be enhanced through NAC supplementation. It follows that this enhancement could preserve the viability of endogenous antioxidant defence mechanisms during exercise through increasing their resynthesis. Importantly, NAC supplementation has been shown to significantly improve fatigue resistance across several modes of study (see Figure 3). These findings indicate that ROS production may play a direct role in the process of muscular fatigue.

In endurance-trained humans, NAC treatment (125mg·kg⁻¹·h⁻¹) pre-exercise and (15mg·kg⁻¹·h⁻¹) during exercise, prolongs time-to-exhaustion by around 20-25%. Importantly, these studies used a randomised controlled cross-over design which enhances the robustness of their findings, since the subjects effectively acted as their own controls. One major issue with the studies that have investigated acute NAC treatment is that NAC was administered intravenously both before and during exercise. Suffice to say, this treatment strategy is invasive and impractical. These findings would be strengthened if they persisted after oral NAC supplementation; unfortunately, no study to date has been published demonstrating improved performance using oral NAC, and thus this hypothesis remains untested. Of equal importance, the long term effects of NAC treatment on performance are also unknown. It is, however, unlikely that chronic supplementation would benefit the athlete since the dramatic attenuation of ROS production observed following acute NAC treatment would likely hinder beneficial ROS signalling and thus impair training adaptation. We stress that this hypothesis has not been tested experimentally to date.

Future directions

It is becoming clear that VC and VE are unable to improve muscle performance and/or recovery and may even impair training adaptations. NAC is the only antioxidant that has consistently been shown to enhance short-term athletic performance. Future studies should try to tease out the role of acute oral supplementation in enhancing performance. NAC may inhibit training adaptation over a longer period. However, sport presents some unique situations in which the realisation of training adaptations is largely inconsequential. For instance, in the current football world cup, the enhancement of muscle recovery will take precedence over training adaptations, since the athletes will (hopefully) already be in optimal condition and the recovery time between exercise bouts is limited. It could be that NAC is able to increase recovery time between games in these situations. A similar example could be seen when considering a tennis competition, where games are often played every second day. To this end, we are currently investigating the effects of acute NAC supplementation on performance during a simulated soccer tournament. In addition, future studies should be undertaken to determine the effects of antioxidants supplementation in resistance trained athletes as our knowledge of this area is limited.

Practical recommendations

The answer to this question depends on the desired outcome of the supplementation, training status of the individual, time-course (acute or chronic) and the actual treatment used (VC, VE or NAC). In an attempt to properly address this question we have composed the following recommendations:

1. Ensure athletes eat a well balanced diet rich in fruit and vegetables to provide sufficient exogenous antioxidants from good food sources. This should provide sufficient exogenous antioxidants even for athletes engaged in intense training. Athletes with a limited area is limited.

![Figure 2: The effects of vitamin C supplementation on VO2max following 8 weeks of moderate endurance training in humans (personal communication, MC Gomez).](image)

![Figure 3: Positive effects of NAC on fatigue resistance across research models. The black bar indicates the minimum improvement whereas the grey indicates the maximum. References: in vitro; in situ; electrical stimulation; small-muscle mass [e.g. single joint exercise]; large muscle mass [e.g. endurance running]. Taken from Ferreira and Reid.](image)
poor diet lacking in fruits and vegetables should initially try to eat more fruit and vegetables and if after consultation with a dietician or sports nutrition professional they are still concerned, then they may wish to consider a multi vitamin containing 100% RDA of the vitamins and minerals.

2. The untrained individuals engaging in exercise training should not supplement with any antioxidant. This may hinder the adaptations to the training.

3. Trained individuals should not supplement daily with antioxidants during periods of training, as this may compromise adaptation.

4. Mega dose VE and VC tablets should not be taken long-term for performance enhancement, irrespective of training status.

5. Short term (prior to exercise) NAC supplementation may be a useful strategy to enhance acute endurance performance in trained-individuals.

6. Theoretically, antioxidant supplement may help in tournament situations where recovery is more important than adaptations, but this possibility remains untested.

References


