

# Performance-enhancing effects of dietary nucleotides: do mitochondria play a role?

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## ABSTRACT

*Nucleotides are group of natural biomonomeric molecules and novel dietary supplements with performance-enhancing attributes. However, their mechanisms of action and target biological structures are poorly understood and identified. This short paper overviews the possible role of mitochondria during the utilization of nucleotides for exercise performance. Mitochondria-related effects of nucleotides have been identified, along with obstacles for dietary nucleotides delivery to the organelle.*

**Key words:** Nucleotides, Mitochondria, Exercise performance, Bioenergetics, DNA repair.

## Introduction

Nucleotides are complex organic biomolecules composed of a nitrogen-containing base, ribose or deoxyribose, and one or more phosphate groups. They build the structure of nucleic acids (such as DNA and RNA) and energy-rich molecules (e.g. adenosine triphosphate, ATP), and act as signaling molecules and/or metabolic co-factors in human metabolism. Utilization of these essential compounds seems to be tissue-dependent, and cells with higher energy requirements (e.g. skeletal muscle, brain) and/or vigorous DNA replication (e.g. immune cells, enterocytes) process more nucleotides (Van Buren et al., 1994). In addition, heavy exercise may increase the person's need for nucleotides due to elevated turnover during work and recovery (Bangsbo et al., 1993). Although nucleotides can be synthesized or salvaged in the human body, increased requirements during stress-related conditions (such as exercise, inflammation or malnutrition) should be secured through the diet, with extra nucleotides might provide additional physiological advantage. Several studies reported beneficial effects of dietary nucleotides in athletic environment. McNaughton and co-workers (2007) reported that a chronically ingested nucleotide supplement blunts the response of the hormones associated with physiological stress in 30 moderately trained male subjects. Same group (McNaughton et al., 2006) found that dietary nucleotides offset post-exercise cortisol response associated with demanding endurance exercise, suggesting possible stress-relief effects of the formulation. Ostojic and co-workers (2012) found that 50 mg/day of sublingual nucleotides positively affected several immunity indicators (e.g. serum immunoglobulin A, natural killer cells count, cytotoxic activity, salivary lactoferrin) in young active males when administered for 14 days. Time to exhaustion was significantly improved in healthy males supplemented with nucleotides for two weeks ( $315.4 \pm 20.8$  s vs.  $330.5 \pm 18.6$  s,  $P = 0.04$ ) (Ostojic et al., 2013). In addition, specific nucleotide formulation (480 mg/day during 30 days) improved post-exercise recovery, and counteract the impairment of immune function after heavy exercise (Riera et al., 2013). Although the previous studies were small pilot studies and showed some

design flaws, it seems that dietary nucleotides might positively affect exercise performance. However, the exact mechanism of nucleotides' action remains subject to debate, and no target tissue and/or cellular compartment has been identified so far. Since mitochondrion plays an essential role in energy conversion and metabolic signaling during exercise (Willis et al., 1994), the organelle might be a specific spot for possible action of dietary nucleotides. Here we discuss obstacles and opportunities for dietary nucleotides delivery to mitochondria.

## Does dietary nucleotides affect mitochondria?

Mitochondrion is a place of turbulent utilization of nucleotides. Several metabolic reactions may affect nucleotides promotion and degradation, such as oxidative phosphorylation through ATP production, cellular proliferation regulation, and mitochondrial genome replication (Kaasik et al., 2001). In normal conditions, the recycling of nucleotides inside the organelle is likely balanced between endogenous synthesis (from amino acids, glucose, or DNA and RNA salvaged remains) and nucleotides breakdown to nucleosides and uric acid (Carver et al., 1995). However, in energy-demanding situations (such as heavy exercise), mitochondrial nucleotides pool might be depleted, with additional nucleotides needed to complement a deficit. In this case, externally supplied nucleotides (or its building blocks) should be transported via mitochondrial biomembranes, and delivered to the specific location inside the organelle. Several mitochondria-related effects of exogenous nucleotides have been identified, with a possible relevance for exercise performance improvement. Orally administered nucleotides decrease acetoacetate:beta-hydroxybutyrate ratio, an indicator of mitochondrial redox state, suggesting less oxidative stress and restored mitochondrial function after cellular injury (Perez et al., 2004). In addition, the concentrations of ATP (along with adenosine diphosphate and monophosphate) and adenine nucleotides, which are the carriers of electrons and the final acceptors of the energy generated during the mitochondrial energy coupling process, were superior after nucleotides administration.

Therefore, the utilization of dietary nucleotides might enhance the efficacy of oxidative phosphorylation, electron transport, and the turnover between oxidized and reduced forms of nicotinamide adenine dinucleotide, which would stimulate the production and storage of energy in the cell (Perez et al. 2004). Furthermore, dietary nucleotides normalized activities of mitochondrial enzymes (e.g. ATPase, citrate synthase, malate dehydrogenase) in isolated mitochondria after chronic stress (Arnaud et al., 2003), suggesting earlier recovery of altered mitochondrial function after nucleotides intake. Finally, exogenous nucleotides might enhance reparation of damaged mitochondrial DNA that can appear as a consequence of heavy exercise (Jafari et al., 2005). However, no animal or human interventional studies so far monitored mitochondria-related effects of oral nucleotides during or after exercise. In addition, several issues can limit nucleotides delivery to the organelle. Theoretically, nucleotides are transported through facilitated diffusion or specific sodium-dependent carrier mediated mechanisms (Gutierrez-Castrellon et al., 2007; Klingenberg, 2008). However, it remains unclear does dietary nucleotides reach mitochondria due to several barriers and/or obstacles recognized

(e.g. low bioavailability after oral administration, poor resistance of nucleotides to acidic environment, high negative charge of molecules that might impact transport through bilayer membranes, additional ATP needed for facilitated transport) (Bacha et al., 2013). Although nucleotides positively affect mitochondrial function in vitro, more studies are needed to assess mitochondria-related ergogenic effects of these compounds in the clinical environment.

## Conclusion

Dietary nucleotides are semi-essential nutrients that provide metabolic, immunological, and physiological benefits during and after heavy exercise. Mitochondria could be a target subunit for exogenous nucleotides, with these compounds might positively effect energy production, oxidative stress regulation and DNA repair in the organelle. However, more studies are needed to evaluate nucleotides delivery and uptake by mitochondria after oral administration in vivo.

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