

SELECTED SUBSTANCES SUCH AS POTENTIAL OR PROVEN ERGOGENIC AID

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Abstract

Selected substances that are not mentioned on the World Anti-Doping Agency (WADA) Prohibited List may improve exercise capacity. An example is creatine, which is indirect precursor of ATP, via phosphocreatine and ADP transformations. The ergogenic activity of creatine has been confirmed by numerous sports organizations, i.e. the International Olympic Committee (IOC), the International Society of Sports Nutrition (ISSN) or the Australian Institute of Sport (AIS) and approved health claims by European Food Safety Authority (EFSA) in European Union (EU). It has been shown that other substances involved in the regulation of energy generation processes can affect as support of physical performance. An example of such as compound is guanidinoacetic acid (GAA/glycocyamine), however is not approved by EFSA as an ingredient of food or dietary supplements. Another example is cordycepin – the active ingredient of mushrooms *Cordyceps* spp. Cordycepin interacts with adenosine receptors, AMPK signaling pathway and demonstrated significant anti-inflammatory potential, thus may decrease inflammation process in response to physical activity. In the case of ATP supplementation, it was found that there is insufficient scientific evidence to confirm an effect on improving muscle function or exercise capacity.

Key words: ergogenic aid, creatine precursors, ATP precursors, glycocyamine, cordycepin, ATP

Introduction

The term „ergogenic” means improvement or strengthening psychomotor skills. In scientific work published by Karpovich (1941), numerous biologically active agents about proven ergogenic activity were characterized, such as: oxygen, benzedrine, coramine or caffeine. Some of the substances described at the time were dietary interventions, e.g. fruit of juices or vitamins [1]. In the publication of Fowler Jr (1969) ergogenic agents are divided into the following categories: pharmacological, physical and nutritional agents [2].

Ergogenic support is interest not only to the sports community – elite athletes or non-elite athletes. Also, military personnel use ergogenic substances to improve the psychomotor performance in difficult environmental conditions. In group of US Army Special Forces and Ranger, 64% of personnel declared the use of dietary supplements or sports nutrition. High percentage of soldiers supplemented “Pro-Performance Mixture” of proteins, carbohydrates, fats, vitamins and bioelements, Creatine as physical performance aid, it's used by 18% of soldiers [3].

The use of various forms of dietary ergogenic support in military service has been described in a systematic review and meta-analysis performed by Knapik et al. (2014). The study demonstrated that elite military personnel significantly more often use dietary supplements and sports drinks (a broad spectrum of category products, including various products, such as isotonic, re-hydrates or electrolytes drinks and

others) like ergogenic support than other military service. Taking into account the division into sex, women in the military used dietary supplements more often than males [4].

In Germany, 80% of young (11–14 years old) elite athletes declared that use dietary supplements. Vitamins, bioelements, sport drinks and energy drinks were used most often by participants. Due to the age of the volunteers, the frequency of use ergogenic supplements, such as caffeine, creatine, estimated at 24% [5].

Current recommendations for ingredients with scientifically proven ergogenic activity are presented by sports and scientific organizations such as: the International Olympic Committee (IOC), the International Society of Sports Nutrition (ISSN) or the Australian Institute of Sport (AIS). All these organizations agree that, for example, creatine is an ergogenic agent improving exercise capacity and building muscle [6–8].

Ergogenic intervention may be considered as doping in sport, if violates the principles established by the World Anti-Doping Agency (WADA), which include basic regulations, such as the World Anti-Doping Code and the Prohibited List [9].

Some studies conducted with volunteers indicate that creatine precursors or indirect ATP precursors, as well as the ATP “alone”, may improve exercise capacity. Creatine and ATP are available for general sale, as single-ingredient products of dietary supplement, but in many cases, they are a one of component in multi-ingredient products such as pre-workout supplements.

Currently, guanidinoacetic acid (GAA/glycocyamine) in dietary supplements is a marginal issue. Cordycepin as indirect precursor of ATP is derived from mushroom *Cordyceps* spp [10, 11].

Guanidinoacetic acid

Guanidinoacetic acid (GAA) also known as glycocyamine, it's N-amidino derivative of glycine. GAA (Fig. 1.) acts as precursor of creatine in human body. GAA is formed in the kidneys and pancreas. GAA is biosynthesized from the amino acids L-arginine and L-glycine. This reaction is catalyzed by the enzyme arginine: glycine amidinotransferase (AGAT). In the next step, the methyl group from S-adenosylmethionine (SAM) is transferred to GAA, and the enzyme involved in the reaction is guanidinoacetate N-methyltransferase (GAMT) [12].

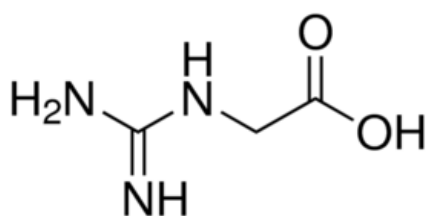


Figure 1. Chemical structure of guanidinoacetic acid

In the group of healthy young volunteers, it was confirmed that 6-weeks supplementation of GAA in the amount of 2.4 g/day significantly increases the concentration of creatine (Fig. 2) and its metabolite (creatinine), both in the blood and in the excreted urine.

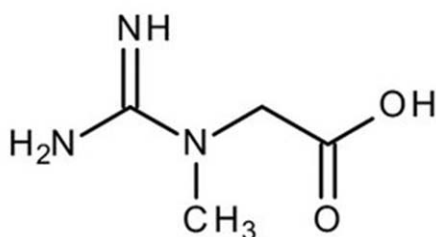


Figure 2. Chemical structure of creatine

The study indicated an increased level of homocysteine which predisposes to the development of cardiovascular diseases (CVD). The increase homocysteine concentration results from the biotransformation of GAA as an acceptor of methyl groups as well as the interaction with S-adenosylmethionine (SAM) metabolism. Increasing the concentration of homocysteine and potential development of CVD is one of the limitations of GAA use by humans [13]. Hypothetically, consumption of substances acting as a methyl group donor in biochemical reactions, such as betaine, choline, folate, vitamin B₆ and B₁₂ or serine, should antagonize the undesirable effect of GAA influence on the increase of homocysteine concentration. Methyl group donor have the ability to decrease homocysteine level. EFSA has approved health

claim for betaine, choline, folate, vitamin B₆ and B₁₂ that contributes to normal metabolism of homocysteine. Serine was not mentioned in Commission Regulation (EU) No 432/2012 [14].

GAA is commonly co-administered with betaine. Health claim for betaine in terms of normal metabolism of homocysteine, may be used only for food which contains at least 500 mg of betaine per portion. The beneficial effect is obtained with a daily intake of 1.5 g of betaine. However, it should be noted that EFSA also inform that daily intake in excess of 4 g of betaine may significantly increase blood cholesterol levels [14].

In double-blind, placebo-controlled trials a group of young, healthy volunteers of both sexes, it was found that 6-week supplementation of GAA improves muscle endurance, even at a low dose of 1.2 g/day. However, it should be taken into account that this study was conducted on a small number of subject (n = 48) [15]. In another study, on the group of healthy participants, it has been proved that physical exercise contributed to decrease level of GAA in blood. It was confirmed that endurance running resulted in a decrease serum GAA concentration by 20.1%, while in resistance training as free-weight exercise (bench press) resulted in a reduction of GAA concentration in blood by 11.7%. This indicate that two different modes of exhaustive exercise, correlates with the depletion of GAA resources in the human body [16].

Finally, sport organizations IOC, ISSN and AIS did not include GAA in their recommendations, what is presented in Table 1. So far, the long-term safety of GAA has not been established in human subject. GAA is approved by EFSA only as an ingredient in animal feed [17, 18].

Cordycepin

Cordycepin (Fig.3.) demonstrated some chemical structure similarities to ATP, however not contains phosphate groups. Cordycepin has been shown an animal experiment to act as indirect precursor of ATP, as result can improves exercise capacity. Cordycepin is a bioactive substance isolated from mushrooms *Cordyceps* spp. [19].

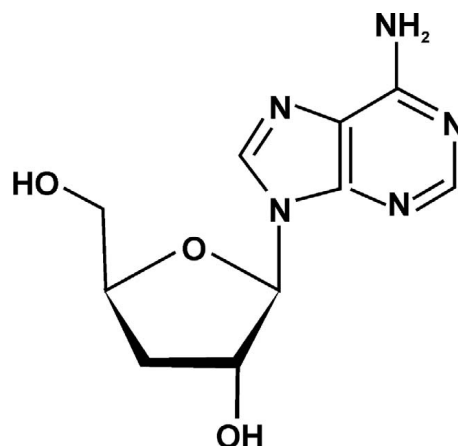


Figure 3. Chemical structure of cordycepin

In experiments on rodents, it was found that cordycepin stimulate the production of ATP and increases the concentration of phosphocreatine [20].

In older individuals, 12-week consumption of *Cordyceps sinensis* has been shown to improve of exercise parameters. The active components of CordyMax™ Cs-4 was adenosine (0.14%), mannitol (5.0%) and polysaccharides (0.5%). Cordycepin is not specified in protocol of the study [21].

Some research have demonstrated that 5-week supplementation of *Cordyceps sinensis* (as CordyMax™ Cs-4) does not improve aerobic capacity or exercise performance in trained male cyclists [22].

In animal model, cordycepin influenced on increase testosterone production [23]. However, studies with volunteers have not been able to achieve similar results to animal experiments. It was confirmed that 8-week supplementation of *Cordyceps sinensis* containing adenosine (5.92 µmol/g), cordycepin (1.23 µmol/g) does not improved of training and physical performance in young adults males. Supplementation of *Cordyceps sinensis* was no interference with the endocrine system – without effect on testosterone concentration [24].

Positive results in terms of improving physical effort refers to mushroom blend contain combination of six adaptogenic mushrooms (*Cordyceps militaris*, *Ganoderma lucidum*, *Pleurotus eryngii*, *Lentinula edodes*, *Hericium erinaceus*, *Trametes versicolor*). It was confirmed that the use of a mixture of adaptogenic mushrooms (including *Cordyceps militaris*) may have a positive effect on exercise capacity in healthy individuals [25].

However, sports organizations, so far has not confirmed the ergogenic activity of *Cordyceps* spp. [Table 1]. Also in European Union, EFSA has not approved health claims for *Cordyceps sinensis* [26].

Adenosine-5'-triphosphate

Adenosine-5'-triphosphate (ATP) is a molecule that is a source of energy for each living cells in the human body.

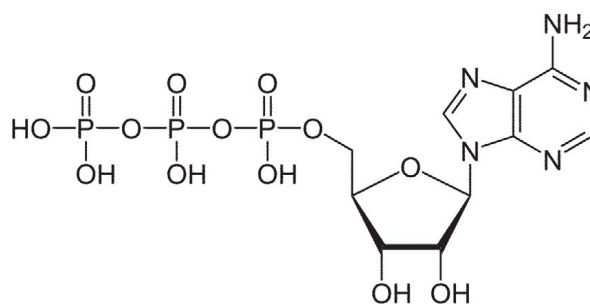


Figure 4. Chemical structure of adenosine-5'-triphosphate

ATP (Fig. 4) presents of multidirectional profile of biological activity. ATP is involved in regulating the transmission of signals between cells such as neuromuscular transmission. ATP affects purinergic receptors and plays the role as a neurotransmitter. ATP interferes with the transport of chloride and calcium ions. It has been confirmed that ATP affect the cardiovascular system, including platelet function, heart function, and vasodilation [27].

ATP demonstrated lability at acidic pH of the stomach. This contributes to the problem of bioavailability ATP after oral application and indicated ineffectiveness of oral ATP supplementation in human body [28]. Also, some scientific works prove the lack of ergogenic effect of ATP with oral supplementation [29, 30].

However, other studies proved that both short-term (15 days) and long-term (12 weeks) supplementation of ATP in dose 400 mg/day is capable to support exercise performance in males [31, 32].

It has been confirmed that single consumption of 400 mg of ATP in a group of 11 males (recreational physical activity) correlates with an increase total weight lifted in lower body part resistance exercises, as well as with an improvement in oxygen consumption [33].

According to the recommendations of ISSN from 2018, ATP was placed in the II category of dietary supplements or ingredients for which there is insufficient scientific evidence confirming the effectiveness. IOC and AIS did not introduce ATP in any group of dietary supplements or ingredients, that can support or enhance sports performance (Table. 1).

Table 1. The active ingredient according to recommendations/regulations of sports organizations or EFSA [6-8]

Organization Substances	IOC	ISSN	AIS	EFSA
Creatine	+	+	+	+
GAA	–	–	–	+ (as feed additive for animals)
Cordycepin	–	– (only as <i>Cordyceps sinensis</i>)	–	– (only as <i>Cordyceps sinensis</i>)
ATP	–	+	–	+

+ Included in recommendations or regulations

– Not included in recommendations or regulations

EFSA regarding to health claim of ATP supplementation in dose 60 mg to 90 mg per day, relating to maintenance of normal muscle function (including: improves effectively muscular tonus, helps muscle recovery or supports muscle fatigue recovery, contributes to the reduction of muscle soreness and contracture, reduction of muscular tension) concludes that a cause and effect relationship has not been established between the consumption of (ATP) and maintenance normal muscle function [34].

Conclusion

GAA is an unauthorized ingredient in dietary supplements or foods, but has been approved by EFSA as feed additive for poultry. So far in the EU, only one substance – creatine has an approved health claim by EFSA for increases physical performance. For GAA, cordycepin and ATP described in these work, there is still little scientific evidence confirming their ergogenic activity.

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