The Biological Role of Carnosine and Its Possible Applications in Medicine

Rola biologiczna karnozyny i możliwości jej zastosowania w medycynie

Abstract
The article reviews current literature on the biological role of carnosine, its properties and use as a supplement in periods of intense physical activity. Studies carried out on laboratory animals and humans have shown that carnosine can have a beneficial influence on the organism. Carnosine is found naturally mainly in the skeletal muscles, central nervous system, olfactory neurons and in the lens of the eye in some vertebrates, including humans. Due to its antioxidant, protective, chelating, anti-glycation activity, this dipeptide can be used to prevent and treat diseases such as diabetes, neurodegenerative diseases, diseases of the sense organs and cancers. It may also cure or alleviate many other disorders thanks to its wide spectrum of activity. Carnosine is already used by athletes to achieve better results, due to its buffering feature, which contributes to the maintenance of the acid-base balance in the muscles. Future studies on the influence of carnosine on the human organism may lead to the therapeutic use of this dipeptide for many diseases, in addition to improving both amateur and professional athletes’ results (Adv Clin Exp Med 2013, 22, 5, 739–744).

Key words: carnosine, antioxidant effect, dementia, somatic diseases, dietary supplementation.

Carnosine is an endogenous dipeptide, composed of β-alanine and L-histidine. This dipeptide occurs naturally in some species of vertebrates, including humans. The biggest concentration is observed in skeletal muscle tissue, the stomach, the kidney, cardiac muscle, the brain and olfactory bulb [1–3]. Studies performed on the gastrocnemius muscle show that carnosine content in the human body is dependent on gender (the level is higher in males), age (there is a decrease in

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carnosine concentration with age) and diet (organisms on a vegetarian diet have a lower concentration of carnosine in the skeletal muscles) [4, 5]. In addition, researchers suggest that synthesis of carnosine in muscles is dependent on the availability of the amino acid alanine in the body [3, 6]. Carnosine contributes as much as 0.2–0.5% to the net weight of some muscles [7]. In animals, such factors as trauma, shock, starvation or injection negatively affect the level of carnosine in muscle tissue. Infection and trauma may be associated with cellular calcium dysregulation and myocardial depression. Carnosine administration may also have a role in the contractility of cardiac cells and the regulation of intracellular calcium [2]. Despite the fact that carnosine was isolated from biological material by v. Gulevich as early as 1900, its full potential has not yet been discovered [7].

**Antioxidant Activity**

When provided to humans as a supplement, carnosine has antioxidant properties, acting against free radicals, which are factors contributing to the aging of the human system. Carnosine scavenges both reactive oxygen and nitrogen, which contain unpaired electrons, and also creates complex chemical compounds with zinc and copper ions [8, 9]. Carnosine dipeptide may inhibit lipid oxidation through a combination of free radical scavenging and metal chelation. It also provides cells with an antioxidant system that functions in the cytosolic environment, where water soluble oxidation mediators are often present in high concentrations [2]. It has been proved that oral use of carnosine for a period of three months improved the overall appearance of the skin and reduced the wrinkles that appear with age [10]. In mice that underwent laboratory-accelerated aging, carnosine administration prolonged life expectancy and improved characteristics of their physical appearance and behavior [11].

**Neuroprotective Activity**

Kozan et al. found that in rats that had undergone anaphylactic shock after intracortical penicillin injections, intraperitoneal administration of 500 mg/kg of carnosine before and after the penicillin injection reduced the incidence of involuntary muscle contractions. In the future carnosine may be considered as a support treatment for epilepsy and for protecting the nervous system from the effects of neurotoxins [12]. Carnosine may help prevent neurodegenerative diseases like Parkinson’s disease, moderating its neurological symptoms and providing antioxidants and an anti-inflammatory effect on the striatum of the brain [9, 13, 14]. In rats it shows protective activity against malondialdehyde, higher concentrations of which are observed in cases of neurodegenerative diseases [1, 15]. In mice, carnosine supplementation, especially a D-carnosine, reduces damage in cases of spinal cord injury [16].

Moreover, Stvolinsky and Dobrota showed that carnosine has a protective effect on heart cells and also improves the contractility of the human heart, which can counteract ischemia [17]. The data suggest that carnosine may be used in medical therapy following a stroke, due to its protective effects on the nervous system and reduction of the extent of infarction and neuronal damage, protecting against the harmful effects of ischemia [9, 18].

**Antitoxic Activity**

It has been demonstrated that carnosine administered to experimental animals protects against toxic substances such as cyclophosphamide and Adriamycin, which are used as cytostatic drugs in the treatment of cancers and connective tissue disease and can cause many side effects [19, 20]. Carnosine’s ability to react with deleterious aldehydes such as hydroxynonenal, malondialdehyde, acetaldehyde and methylglyoxal may also contribute to its protective functions [9]. Carnosine can prevent the increase of liver transaminase levels in the serum and inhibit the activity of lipid peroxides under the influence of ethanol, as shown in rats [21]. The consumption of alcohol leads to a fatty liver, which is a consequence of cirrhosis; the antioxidant and anti-inflammatory action of carnosine may be helpful in the treatment of chronic alcoholic liver damage, while also preventing the development of a fatty liver [1, 21, 22].

People suffering from lung cancer and receiving radiation therapy as part of their treatment often experience side effects of this type of therapy. Carnosine supplementation in combination with x-ray radiation in these individuals moderates the unwanted effects of this therapy [8].

**Effects on the Sense Organs**

**Vision**

Oral administration of carnosine to rats that had remained hyperglycemic for six months reduces the blood vessels of the retina by protecting retinal capillary cells [23, 24]. Studies carried out
The Biological Role of Carnosine

on a population of 50,500 people show that the use of eyedrops containing N-acetylcarnosine contributed to preventing the development of eye diseases. The application of this kind of eyedrops prevented cataracts and lens turbidity, which lead to blurred vision and even blindness in the elderly. These drops can also be applied in cases of glaucoma, a disease that causes progressive and irreversible damage to the optic nerve and retinal ganglion cells, and in diseases related to macular degeneration and eye ailments associated with age [24]. In Russia, eyedrops of 5% carnosine have been developed and permitted for medical use [2].

Hearing

Zhuravskii et al. demonstrated carnosine’s ability to act in a protective manner on the hearing system. In rats, intraperitoneal injections of carnosine at a dose of 200 mg/kg body weight reduced the severity of degenerative-atrophic changes in the nuclei of cells in the cochlea after strong acoustic trauma [25].

Olfaction

It is probable that carnosine may play a neuromediator role in the sense of smell in mammals [26].

Therapeutic Action

Diabetes

Swedish studies have shown that in mice with type 2 diabetes, intraperitoneal and topical administration of carnosine in quantities of 100 mg/kg body weight improves the healing of wounds, increases the expression of growth factors and the production of cytokines [27]. In vitro studies with human fibroblasts from derma and vascular endothelial cells showed that carnosine increases cell viability in the presence of high glucose levels [27]. The administration of carnosine protects humans against diabetic nephropathy [1, 28]. Studies conducted on rats by a team of Japanese scientists showed the possibility of using L-carnosine to lower blood glucose levels by regulating the activities of autonomic nerves [29]. Carnosine has an anti-glycation effect and inhibits secondary complications associated with diabetes [9].

Cancer

In rats, L-carnosine probably inhibits splenic sympathetic nerve activity and proliferation, and the multiplication and growth of cancer cells, by increasing so-called natural killer cells (NK cells), which are responsible for the natural cytotoxicity of the organism [30]. It has been shown that in humans carnosine may inhibit the growth of glioblastoma multiforme (GBM), a primary malignant tumor of the brain usually located in the frontal and temporal lobes. These results may open the door to important therapeutic opportunities due to the very good tolerance of carnosine, which occurs naturally in the human body [31].

The Metabolic Syndrome

Italian studies carried out on obese rats treated with L-carnosine and D-carnosine at a dosage of 30 mg/kg in drinking water for 24 weeks suggest that both L-carnosine and D-carnosine reduce hypertension, cholesterol and triglycerides fractions in the serum, and also decrease kidney damage caused by elevated levels of glucose in the blood [32].

Other Medical Applications

Human consumption of natural products with a high carnosine content, such as chicken soup or dishes with chicken breast, can inhibit the formation and growth of influenza virus infections and colds, and also help to prevent those infections [33].

Physical Activity

Carnosine has a buffering effect and regulates the pH of muscles, allowing them to continue working at an appropriate level and improves excitation-contraction coupling [5, 6]. Regular oral supplementation of β-alanine increases carnosine levels in the skeletal muscles, which results in an increase in physical activity during intense aerobic and short-term exertion; and in some series of exercises lasting more than 60 seconds, it delays the onset of fatigue in the neuromuscular system and also raises the anaerobic threshold [6]. Professional sprinters have a high content of carnosine in their muscles, due to a genetic predisposition or the adaptation of the organism to this discipline [5]. Other studies suggest that sprint training combined with a vegetarian diet or mixed diet does not affect carnosine content in the muscles [34]. In addition, β-alanine supplementation has no effect on isometric strength levels or the time course of isometric strength for a distance of 400 m [35].

Hill et al. found that oral intake of β-alanine by males for four weeks and 10 weeks led to an increase of carnosine levels of 58.8% and 80.1% respectively [3]. The same researchers also observed an increase in carnosine in both type I and IIA muscle fibers, and significant increases in the total work done (13% for the group receiving the supplement for four weeks and 16.5% for the group receiving it for 10 weeks). In the control group receiving a placebo there was no increase in carnosine content or in the total work done [3]. However, research carried out by Suzuki et al. using
a cycloergometer showed that there is a significant correlation between carnosine content and muscle fiber type: Type IIX fibers contain higher levels of carnosine, and it has also been revealed that there is a significant correlation between the average power per kilogram of body weight and the content of carnosine in muscles during efforts lasting up to 30 seconds [36]. Goto et al. examined the effects of supplementation with chicken breast meat extract (CBEX) containing carnosine and anserine on hormonal responses to resistance exercise” [37].

Group of males took carnosine and anserine orally in liquid form twice daily for 30 days at a dose of 2 g without physical training. Goto et al. wrote: “Before and after the supplementation period, the subjects completed 5 sets of bilateral knee extension exercises (with a 90-s rest between sets)”. The results were compared with the placebo group. It was shown that the level of free testosterone did not change in either group after 30 days of supplementation. As Goto et al. stated, “The blood lactate response to exercise was attenuated after supplementation in both groups […] In the CBEX group, the plasma epinephrine and norepinephrine concentrations after exercise were significantly lower after supplementation […] The serum growth hormone response to exercise was also reduced in the CBEX group after supplementation. […] No significant differences in exercise-induced strength reduction (fatigue index) were observed in the 2 groups after supplementation. in exercise-induced strength reduction (fatigue index) observed in the two groups after supplementation” [37].

Kendrick et al. studied the influence of 10 weeks of resistance training on carnosine concentrations in the skeletal muscles and the effect of a β-alanine dose of 6.4 g/day to increase the work done during resistance training [38]. Participants in the control group (physically active and taking a placebo) and those in the research group (taking the daily β-alanine dose) were assessed regarding whole body strength, muscular endurance, muscle mass, fat content and isokinetic force production. Only the research group showed an increase in carnosine levels, but there were no significant differences in the parameters studied [38]. However, it has been observed that a 12-week course of β-alanine supplementation in a dose of 3.2 g daily improves exercise capacity in healthy older people, based on time of exhaustion in a constant-load submaximal test and in an incremental test, and that it increases carnosine levels in the gastrocnemius muscle [39]. Jagim et al. conducted a study on the effects of β-alanine supplementation (an oral dose of 4 g in the first week and of 6 g in the next four weeks) on a group of wrestlers, rugby players and people who do resistance training recreationally [40]. The study measured lactate levels in the blood before and after supramaximal treadmill exercise, but there were no significant differences between the placebo group and the research group [40].

Conclusions

Due to its broad spectrum of activity, carnosine may be regarded as a therapeutic factor in the treatment of many disorders and may also be used by athletes who want to improve their performance. This dipeptide shows antioxidant activity (protection from free radicals), has buffering effects (helping to maintain the acid-base balance), chelating effects (reducing the toxicity of metals), anti-glycation effects, and protects against some neurotoxic substances. To establish appropriate daily doses and the duration of carnosine supplementation, it is necessary to identify any side effects and the mechanisms of its action, which requires long-term research carried out on each age group, including participants who lead physically active lives as well as those with a sedentary lifestyle.

References

The Biological Role of Carnosine


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