



## On the use of carnosine and antioxidants: A letter from Russia

Sir,

Carnosine, an endogenously synthesized dipeptide found in muscular and other tissues, was reported to possess antioxidant properties. Favorable actions of carnosine were explained by its effects against reactive oxygen species (ROS), against peroxynitrite damage and different types of viral injury [1-6]. Moreover, one of the mechanisms of detoxification from aldehydes, accumulating in inflammation, ischemia, and other pathological conditions was reported to be conjugation with carnosine [7-10]. Among other potential applications, carnosine-containing eye drops have been recommended for the treatment, dissolution and prevention of cataracts, in particular, senile cataracts [5,11]. From the viewpoint of biochemistry, it is difficult to envisage how carnosine can contribute to the dissolution of cataracts, regarded to be the end stage of metabolic and structural transformations including conformational changes and aggregation of proteins [12]. To decide whether a local or general supplementation of a substance is indicated, the question should be answered whether there is a local or general deficiency. Such deficiency is *prima facie* improbable for substances that are supplied with food and can be synthesized in different cells and tissues of the body. Tissue carnosine concentrations are influenced by the diet being lower in vegetarians [1,4,13]. If the presence of carnosine in body fluids is important for the preservation of the lens transparency [5,11] or some physiological functions [4,14], the incidence of cataracts or other pathological conditions among vegetarians/vegans would be higher than in the general population. On the contrary, vegetarians have been reported to have a lower risk of cataract than meat eaters: There was a strong relation between the cataract risk and a diet group, with a progressive decrease in risk of cataracts in high meat eaters to low meat eaters, fish eaters, vegetarians, and vegans [15]. Admittedly, the topic is not without controversy [16], probably confounded by geographical (exposure to sunlight) and other factors. Furthermore, it has been suggested that carnosine is an anti-aging substance with a beneficial effect on the cardiovascular system [3,17,18]. There is, however, evidence that vegetarians have lower rates of coronary heart disease, hypertension, etc. Overall, their cancer rates appear to be moderately lower than in other people living in the same communities, and life expectancy appears to be greater [19]. A very low meat intake was reported to be associated with greater longevity [20]. However, benefits from the vegetarian versus carnivorous diet [9] are beyond the scope of this letter.

Carnosine has been used in sports nutrition to increase performance and was reported to have benefits in obesity

and diabetes mellitus [2,21]. The latter is understandable as peptides are non-carbohydrate nutrients favorable for diabetics. Nutritive value of carnosine can explain for higher performance in sports. Dietary supplementation of carnosine has been shown to suppress stress in animals, to improve cognition and well-being in humans [22], which can be also explained by the nutritive value. Modulation of glycolysis and inhibition of the glycolysis-induced protein dysfunction have been attributed to carnosine [3]; however, modulation or “inhibition of dysfunction” is a regulatory function that cannot be ascribed to a simple substance as it presupposes a feedback mechanism. The following logical fallacy can be encountered in some papers on substances participating in metabolism such as carnosine. First, the important biochemical role of the substance is stressed, which is natural for a metabolite. After that, benefits from supplementation are discussed, even though it remains unproven, whether a deficiency of the substance occurs, and if it does, whether it can be compensated by a diet or some natural products. Purified preparations might be both expensive and unnecessary. Diet modification, e.g., consumption of more meat as a source of carnosine may suffice if supplementation is indeed indicated.

As for antioxidants affecting ROS, their increased levels may produce unpredictable outcomes since ROS can have both harmful and beneficial effects [23]. The same is true particularly for carnosine [24]. Generation of ROS is usually considered to be a side effect of aerobic metabolism [23], which is a ubiquitous process in living organisms. The redox status is maintained in dynamic equilibrium of oxidative and reductive processes under the impact of numerous factors [25-27]. Some experts suggest that boosting of antioxidant status has no benefits [25]. Certain reviews on antioxidants discuss vitamins and other substances with complex action mechanisms [28,29]. In general, antioxidants are regarded to be far from any scientifically founded clinical application [23]. It has largely remained unclear whether, when, and how much antioxidants should be taken in [23,30,31], the more so as antioxidants at higher doses may act as pro-oxidants [25].

Some generalizations regarding the oxidants/antioxidants balance, attempting to present it as universal biological concept, seem to be oversimplifications. The problem consists of several partly interrelated topics: Antioxidants and cancer [23], wine, ethanol and cardiovascular risk [28,32], radiation protection [33], lens transparency and cataract [5,11], flavonoids, healthy aging, menopause, atherosclerosis prevention [34], antioxidants, carnosine and diseases of the nervous system [22,35-37], etc. Indications to the use of particular substances are questionable.

Several large randomized clinical trials found that antioxidant supplementation does not reduce the risk of cardiovascular, mental disease and cancer, or the evidence was found to be not relevant to clinicians or consumers [23,30,35]. For example, numerous reports on inverse relationship between regular intake of low to moderate amounts of alcoholic beverages and cardiovascular risk have inspired some people to drink more alcohol in spite of possible psychosocial and other complications. While the association between alcohol consumption and decreased cardiovascular risks is regarded to be proven, it remains uncertain whether this implies causation. Although a number of points do suggest that the association between moderate alcohol consumption and decreased cardiovascular risk may indeed represent a cause-effect relationship, it is unclear to what extent it is related to antioxidants in wine and to ethanol per se [32]. The question can be clarified by large-scale experiments with different diets and supplements. However, human studies and animal experiments may be planned only in the presence of integrity, adequate equipment and ability to objectively evaluate scientific data.

The topic of antioxidants, in particular, is complicated by conflicts of interests. Some antioxidants seem to be propagated as inexpensive substitutes for evidence-based medications, i.e., in support for placebo marketing. There are many examples of marketed substances without scientifically demonstrated effectiveness [38-41]. Publications of questionable reliability are sometimes indirectly used in Russia for advertising of drugs and food supplements, for their official registration and obtaining permissions for practical use. As a result, substances with unproven effects can be offered to the elderly and other patients misinformed not only by advertising but also by some publications supposed to be scientific. The carnosine eye drops sold in Russia are relatively expensive; they are prescribed to aged patients. Theoretically, at least for patients with low income, carnosine preparations could be replaced by a meat-rich diet and/or by isotonic defatted meat broth or extract applied locally to eyes. It can be reasonably assumed that useful properties, e.g., chicken broth [6,42] are related not specifically to carnosine but to the whole mixture of peptides and other substances. A similar suggestion was made, e.g., in regard to glycosaminoglycan-containing chondroprotective agents versus natural glycosaminoglycans for osteoarthritis [41]. To support the placebo effect, the patients may be advised that the natural products can be sources of carnosine similarly to pharmaceuticals, although an effect is guaranteed neither from the drugs nor from meat products. However, considering uncertainties about antioxidant effects discussed above, we would rather abstain from such recommendations. Even more precarious, because of complication risks [43], are recommendations of peribulbar injections of carbinine (the analog of carnosine) as an antioxidant for prophylactic purposes [44]. Until recently, peribulbar injections of amino acid taurine were used in the former Soviet Union for the treatment of eye conditions associated with atherosclerosis and aging [45] or inflammatory conditions [46], against payment in elderly patients, while hematomas were observed as complications. Analogously to carnosine, taurine is widely distributed in tissues, synthesized within the body and supplied with animal-derived

food products [47]. In conclusion, practical recommendations should be based on research of high quality shielded from conflicts of interest. Only such research should be included into reviews and meta-analyses.

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**Received:** March 17, 2016

**Accepted:** April 09, 2016

**Published:** April 21, 2016

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**Source of Support: Nil, Conflict of Interest: None declared.**