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Carnosine Effect on Advanced Lipoxidation End-Products: a Brief Review on Tissues

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Abstract

Purpose of review Advanced lipoxidation end-products (ALEs) are defined as adducts and cross-links that are made by the reaction of produced reactive carbonyl species in peroxidation with DNA, proteins, and aminophospholipids in a nonenzymatic process. Carnosine is synthesized by carnosine synthase and is found in the brain and muscular tissues that acts as an antioxidant compound. Regarding the increased prevalence of chronic diseases and the direct effect of oxidative stress, we considered the possibility of the effect of carnosine on advanced lipoxidation end-products in various problems.

Recent findings Data for this review were obtained electronically from PubMed, Scopus, and Google scholar. English articles were analyzed and the publication year of conducted studies was considered from 2005. Twenty related articles were retrieved on carnosine effects on ALEs. These studies were divided into eight categories of tissue problems. All articles indicated that carnosine could diminish the ALE level in tissues.

Summary The results of this study showed that carnosine has the potential ability to reduce the plasma and tissue levels of the ALEs and oxidative stress, and can be effective in oxidative-related diseases.

Keywords Carnosine · Advanced lipoxidation end-products · Lipoxidation · Oxidative stress · Malondialdehyde

Introduction

Advanced lipoxidation end-products (ALEs) are defined as adducts and cross-links that are made by the reaction of produced reactive carbonyl species (RCS) in peroxidation with DNA, proteins, and aminophospholipids in a nonenzymatic process [1]. Malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), 4-hydroxyhexanal (4-HHE), and acrolein (ACR) are the well-known ALEs. ALE formations demolish biological molecules and processes including proteins, loss of enzymatic activity, and DNA damage and mutagenesis [1, 2] that induce many chronic diseases, such as diabetes, rheumatoid arthritis, and neurodegenerative, cardiovascular, and kidney diseases [3, 4].

Carnosine (βalanyl-Lhistidine) that was discovered by a Russian scientist as a constituent of brain and muscular tissues is synthesized by carnosine synthase [5]. Acting as an antioxidant, regulating immune response, tissue pH buffering, chelating heavy metals, and rejuvenating senescence are some of the potential properties of carnosine [6, 7], and in humans positive results of carnosine have been investigated in heart failure and psychology and psychiatry [8, 9].

Regarding the increased prevalence of chronic diseases and the direct effect of oxidative stress, the review of the antioxidant properties of carnosine can be useful for the use of this dipeptide for therapeutic purposes. In our previous studies, the effect of carnosine on the advanced glycation end-products in animals and cells was determined [10, 11]. We will now consider the possibility of the effect of carnosine on advanced lipoxidation end-products in various problems.

Methods

Data for this review were attained electronically from PubMed, Scopus, and Google scholar. The publication year of conducted studies was considered from 2005 and only English articles were analyzed. The keywords used for the search were “carnosine and advanced lipoxidation end

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products," "carnosine and ALE," "carnosine and malondialdehyde," and "carnosine and MDA."

Results

Twenty related articles were retrieved on carnosine effects on and ALEs. These studies were divided into eight categories of diabetes, liver, aging, muscle, brain, renal, heart, and other problems. These studies were assembled in Table 1.

Kumral et al. [29] after supplementation of 250 mg/kg carnosine found that carnosine alone or with vitamin E decreased thiobarbituric acid reactive substances (TBARS), diene conjugate (DC), and protein carbonyl (PC) in the heart, liver, and kidney. Their results indicated that carnosine alone or with vitamin E protects against toxicity in tissues and could be a useful supplement to the prevention of toxic complications of doxorubicin in chemotherapy.

In a study in 2016, 10 mg/kg carnosine supplementation on 28 rats for 8 weeks showed that carnosine treatment increased the contents of total antioxidant capacity in the intervention group and decreased MDA. Carnosine also prevented the decrease in albumin and the level of total protein and stimulated hepatic enzymes. They concluded that carnosine could prevent acetate-induced hepatotoxicity by enhancing antioxidant capacity and inhibition of lipid peroxidation [12].

Zhang et al. [21] after supplementation of carnosine to 54 experimental subarachnoid hemorrhage rats found that the level of MDA, 3-nitrotyrosine (3-NT), and 8-hydroxydeoxyguanosine (8-OHDG) were significantly reduced in brain cortex at 48 h. Also, in the similar study, Xie et al. [20] found that carnosine treatment significantly diminished the increased level of ROS, MDA, 3-NT, and 8-OHDG induced by intracerebral hemorrhage. These two findings indicated that carnosine supplementation after brain injury may provide neuroprotection.

Yapislar and Taskin [23] after supplementation of 50 mg/kg carnosine in nephrectomized rats for 15 days found that this treatment augmented the level of nitric oxide (NO), reduced the level of MDA, and improved RBC deformability and can have beneficial effects on chronic kidney diseases.

In the study by Dursun et al. [26] on 40 adriamycin-induced cardiomyopathic rats for 2 weeks after supplementation of 10 mg/kg/day carnosine, the level of MDA, glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), creatine kinase, and catalase (CAT) was attenuated. Evran et al. [25] found that carnosine supplementation on isoproterenol-induced myocardial-infarcted rats decreased plasma lactate dehydrogenase and aspartate transferase activities, cardiac MDA, and PC and increased the antioxidant enzymes activities. But, the plasma and erythrocyte MDA and PC levels did not change.

Doğru-Abbasoğlu et al. [27] after treatment of rats by carnosine found that carnosine supplementation did not change hypertriglyceridemia, insulin resistance, or liver's antioxidant system, but it declined lipid peroxidation in the of high fructose diet rats. However, carnosine combined with tocopherol attenuated inflammation, insulin resistance, and lipid peroxidation.

In the other study on 72 recipient pigs of 0, 25, 50, or 100 mg/kg carnosine supplement for 8 weeks, supplementation with 25 mg/kg carnosine did not affect Ca-ATPase activity, MDA, and PC in skeletal muscle. In the 100 mg/kg carnosine group, the MDA concentrations were lower than that of the 0 or 25 mg/kg but there were no changes in muscle MDA between the recipient of 50 and 100 mg/kg carnosine at 24 h and 48 h postmortem [19].

In the other study on 32 testis ischemic rats, Abbasoğlu et al. [30] found that, however, carnosine supplementation in a dose of 250 mg/kg carnosine did not change TBARS, SOD, and GPx, but it decreased the elevated level of DC and PC and regulated spermatogenesis in these rats.

Possible Mechanism

Anti-oxidative activity of carnosine is more than both β-alanine and L-histidine. Thus, the efficient antioxidant ability of carnosine is principally dependent on the linkage of β-alanyl and L-histidine [31].

Radical Scavenging

The powerful antioxidant activity of carnosine can be shown by its action as an electron donor to singlet oxygen, superoxide, and hydroxyl radicals [32, 33]. Imidazole rings are recognized to counter with singlet oxygen but carnosine as a compound consisting of imidazole ring was stated to react more than twofold faster than other L-histidine components [34]. Also, carnosine might increase the activity of antioxidant proteins and enzymes like glutathione, GSH-Px, and SOD and play a significant role in reducing products of lipid peroxides [35, 36]. On the other hand, carnosine or related peptides chelate iron or copper (metal ions such as iron are the common producers of free radicals) hence blocking free radical production [37, 38].

Reaction with Aldehydes

Lipid peroxidation produces a lot of aldehyde products. Carnosine reacts with these kinds of toxic compounds, forms protein-carbonyl-carnosine adducts, and thereby quashes their toxicities [39, 40]. Aldini et al. [41] confirmed the suppressive ability of this dipeptide on PC in obese rats. These findings were consistent with the study of Hipkiss et al. [42] which used "carnosinylated" protein term for the protein-carbonyl-

Table 1 Studies of carnosine effects on advanced lipoxidation end-products

Reference	Number and type of subjects	Carnosine dose and length of study	Oxidative causer compound	Main conclusion
Liver problems				
Hasanein et al. [12]	Rat $N = 28$	10 mg/kg 8 weeks	Acetate	Treatment with carnosine decreased MDA in liver and inhibit hepatotoxicity.
Aydın et al. [13]	Rat $N = 31$	2 g /L 3 months	Thioacetamide	Carnosine reduced the level of MDA in liver of cirrhotic rat.
Fouad et al. [14]	Rat $N = 30$	250 mg/kg –	Ischemia/reperfusion in liver	Carnosine decreased MDA in liver.
Aging problems				
Aydın et al. [15]	Rat $N = 48$	250 mg/kg 5 days/week for 2 months	D-galactose	Carnosine reduced brain acetylcholinesterase activity and MDA level in brain of aged rats.
Kalaz et al. [16]	Rat $N = 48$	250 mg/kg 5 days/week for 2 months	D-galactose	Carnosine reduced MDA in liver of aging rats.
Aydın et al. [17]	Rat $N = 38$	250 mg/kg 1 month	–	Carnosine supplementation decreased the high level of MDA in liver of aged rats.
Muscle problems				
Yang et al. [18]	Pig $N = 24$	- -	–	The level of MDA decreased by accumulation of carnosine content of longissimus dorsi muscle.
Ma et al. [19]	Pig $N = 72$	0, 25, 50, 100 mg/kg 8 weeks	–	MDA and carbonyl protein complexes in skeletal muscle lessened by carnosine.
Brain problems				
Xie et al. [20]	Rat $N = 48$	1000 mg/Kg –	Collagenase audatum	Carnosine decreased level of ROS, MDA, 3-NT, 8-OHDG and increased GSH-Px and SOD activity in brain of intracerebral hemorrhage rats.
Zhang et al. [21]	Rat $N = 54$	1000 mg/kg –	Experimental brain injury	Carnosine treatment reduced the elevated MDA, 3-NT, 8-OHDG, IL-1β, IL-6, and TNF-α.
Tsai et al. [22]	Mice $N = 40$	0.5, 1, and 2 g/L 4 weeks	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine	Carnosine pretreatments significantly reserved levels of carnosine and total antioxidant and decreased the generation of MDA and ROS in neurotoxic mice.
Renal problems				
Yapislar, Taskin [23]	Rat $N = 24$	50 mg/kg 15 days	Nephrectomy	Carnosine treatment reduced MDA levels, improved deformability of RBCs but increased levels of NO.
Noori, Mahboob [24]	Rat $N = 24$	10 mg/kg 10 days	Cisplatin	Carnosine decreased plasma and tissue MDA and 4-HNE in renal of rats.
Heart problems				
Evran et al. [25]	Rat $N = 32$	250 mg/kg 12 days	Isoproterenol	Carnosine pretreatment diminished cardiac MDA level, but increased GSH levels and SOD and GSH-Px activities.
Dursun et al. [26]	Rat $N = 40$	10 mg/kg 2 weeks	Adriamycin	An increase in lipid peroxidation (MDA) and incapacity of SOD and GSH-Px were prohibited by carnosine in cardiomyopathy.
Diabetes				
	Rat	2 g/L	Fructose	

Table 1 (continued)

Reference	Number and type of subjects	Carnosine dose and length of study	Oxidative causer compound	Main conclusion
Doğru-Abbasoğlu et al. [27]	$N = 30$	8 weeks		Carnosine alone and with vit E reduced insulin resistance, inflammation, and MDA in insulin-resistant rats.
Lee et al. [28]	Mice $N = 75$	0.5, 1 g/l 4 weeks	Streptozotocin	Carnosine administration enhanced catalase activity and decreased lipid peroxidation in kidney and liver of diabetic mice.
Other problems				
Kumral et al. [29]	Rat $N = 24$	250 mg/kg 12 days	Doxorubicin	CAR alone or with vit E, decreased TBARS in heart, liver, and kidney in toxic rats.
Xie et al. [20]	Rat $N = 16$	150 mg/kg 28 days	Mycobacterium butyricum	Carnosine prohibited high concentration of 4-HNE and MDA in brain and plasma of arthritis rats.
Abbasoğlu et al. [30]	Rat $N = 32$	250 mg/kg –	Experimental testis ischemia	Carnosine did not alter TBARS in testis but decreased the elevated level of DC and PC.

ROS, reactive oxygen species; *MDA*, malondialdehyde; *3-NT*, 3-nitrotyrosine; *8-OHDG*, 8-hydroxydeoxyguanosine; *GSH-Px*, glutathione peroxidase; *SOD*, superoxide dismutase; *IL-1β*, interleukin 1 beta; *IL-6*, interleukin 6; *TNF-α*, tumor necrosis factor alpha; *RBC*, red blood cell; *NO*, nitric oxide; *TBARS*, thiobarbituric acid reactive substances; *4-HNE*, 4-hydroxynonenal; *DC*, diene conjugate; *PC*, protein carbonyls

carnosine adducts. Carnosine-HNE adducts were found in both animals and humans [43]. It is suggested that carnosine facilitate the proteolytic elimination of modified protein on proteasomes [44].

Conclusion

The results of this study showed that carnosine has the potential to reduce the plasma and tissue levels of the ALEs and oxidative stress, and can be effective in oxidative-related problems such as cerebral, cardiac, and renal disease, although there is a limitation in human study.

Compliance with Ethical Standards

Conflict of Interest The authors reported no conflict of interest.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Pamplona R. Advanced lipoxidation end-products. Chem Biol Interact. 2011;192(1–2):14–20.
2. Naudí A, Cabré R, Jové M, Ayala V, Gonzalo H, Portero-Otín M et al. Lipidomics of human brain aging and Alzheimer's disease pathology. International review of neurobiology. Elsevier; 2015. p. 133–89.
3. Semchyshyn HM, Lushchak V. Oxidative stress–molecular mechanisms and biological effects. 2012.
4. Bengmark S. Amplifiers of systemic inflammation-the role advanced glycation and and lipoxidation end products in foods. Kuwait Med J. 2008;40(1):3.
5. Gulewitsch W, Amiradžibi S. Ueber das carnosin, eine neue organische base des fleischextractes. Ber Dtsch Chem Ges. 1900;33(2):1902–3.
6. Hipkiss AR, Cartwright SP, Bromley C, Gross SR, Bill RM. Carnosine: can understanding its actions on energy metabolism and protein homeostasis inform its therapeutic potential? Chem Cent J. 2013;7(1):38.
7. Artioli GG, Sale C, Jones RL. Carnosine in health and disease. Eur J Sport Sci. 2018:1–10.
8. Lombardi C, Carubelli V, Lazzarini V, Vizzardi E, Bordonali T, Ciccarese C, et al. Effects of oral administration of orodispersible levo-carnosine on quality of life and exercise performance in patients with chronic heart failure. Nutrition. 2015;31(1):72–8.
9. Ghajar A, Khoaie-Ardakani M-R, Shahmoradi Z, Alavi A-R, Afarideh M, Shalbafan M-R, et al. L-carnosine as an add-on to risperidone for treatment of negative symptoms in patients with stable schizophrenia: a double-blind, randomized placebo-controlled trial. Psychiatry Res. 2018;262:94–101.
10. Ghodsi R, Kheirouri S. Carnosine and advanced glycation end products: a systematic review. Amino Acids. 2018:1–10.
11. Ghodsi R, Kheirouri S, Nosrati R. Carnosine supplementation does not affect serum concentrations of advanced glycation and

precursors of lipoxidation end products in autism: a randomized controlled clinical trial. Ann Clin Biochem. 2018: 0004563218796860.
12. Hasanein P, Kazemian-Mahtaj A, Khodadadi I. Bioactive peptide carnosin protects against lead acetate-induced hepatotoxicity by abrogation of oxidative stress in rats. Pharm Biol. 2016;54(8): 1458–64.
13. Aydın AF, Küskü-Kiraz Z, Doğru-Abbasoğlu S, Güllüoğlu M, Uysal M, Koçak-Toker N. Effect of carnosine against thioacetamide-induced liver cirrhosis in rat. Peptides. 2010;31(1): 67–71.
14. Fouad AA, El-Rehany MA-A, Maghraby HK. The hepatoprotective effect of carnosine against ischemia/reperfusion liver injury in rats. Eur J Pharmacol. 2007;572(1):61–8.
15. Aydın AF, Çoban J, Doğan-Ekici I, Betül-Kalaz E, Doğru-Abbasoğlu S, Uysal M. Carnosine and taurine treatments diminished brain oxidative stress and apoptosis in D-galactose aging model. Metab Brain Dis. 2016;31(2):337–45.
16. Kalaz EB, Çoban J, Aydın AF, Doğan-Ekici I, Doğru-Abbasoğlu S, Öztezcan S, et al. Carnosine and taurine treatments decreased oxidative stress and tissue damage induced by D-galactose in rat liver. J Physiol Biochem. 2014;70(1):15–25.
17. Aydın A, Küçükgergin C, Özdemirler-Erata G, Koçak-Toker N, Uysal M. The effect of carnosine treatment on prooxidant–antioxidant balance in liver, heart and brain tissues of male aged rats. Biogerontology. 2010;11(1):103–9.
18. Yang P, Hao Y, Feng J, Lin H, Feng Y, Wu X, et al. The expression of carnosine and its effect on the antioxidant capacity of longissimus dorsi muscle in finishing pigs exposed to constant heat stress. Asian-Australas J Anim Sci. 2014;27(12):1763–72.
19. Ma X, Jiang Z, Lin Y, Zheng C, Zhou G. Dietary supplementation with carnosine improves antioxidant capacity and meat quality of finishing pigs. J Anim Physiol Anim Nutr. 2010;94(6):e286–e95.
20. Xie R-x, Li D-w, Liu X-c, Yang M-f, Fang J, Sun B-l, et al. Carnosine attenuates brain oxidative stress and apoptosis after intracerebral hemorrhage in rats. Neurochem Res. 2017;42(2):541–51.
21. Zhang Z-y, Sun B-l, Yang M-f, Li D-w, Fang J, Zhang S. Carnosine attenuates early brain injury through its antioxidative and anti-apoptotic effects in a rat experimental subarachnoid hemorrhage model. Cell Mol Neurobiol. 2015;35(2):147–57.
22. Tsai S-J, Kuo W-W, Liu W-H, Yin M-C. Antioxidative and anti-inflammatory protection from carnosine in the striatum of MPTP-treated mice. J Agric Food Chem. 2010;58(21):11510–6.
23. Yapislar H, Taskin E. L-carnosine alters some hemorheologic and lipid peroxidation parameters in nephrectomized rats. Med Sci Monit. 2014;20:399.
24. Noori S, Mahboob T. Antioxidant effect of carnosine pretreatment on cisplatin-induced renal oxidative stress in rats. Indian J Clin Biochem. 2010;25(1):86–91.
25. Evran B, Karpuzoğlu H, Develi S, Kalaz EB, Soluk-Tekkeşin M, Olgaç V, et al. Effects of carnosine on prooxidant–antioxidant status in heart tissue, plasma and erythrocytes of rats with isoproterenol-induced myocardial infarction. Pharmacol Rep. 2014;66(1):81–6.
26. Dursun N, Taşkın E, Öztürk F. Protection against adriamycin-induced cardiomyopathy by carnosine in rats: role of endogenous antioxidants. Biol Trace Elem Res. 2011;143(1):412–24.
27. Doğru-Abbasoğlu S, Kumral A, Olgaç V, Koçak-Toker N, Uysal M. Effect of carnosine alone or combined with α-tocopherol on hepatic steatosis and oxidative stress in fructose-induced insulin-resistant rats. J Physiol Biochem. 2014;70(2):385–95.
28. Lee Y-t, Hsu C-c, Lin M-h, Liu K-s, Yin M-c. Histidine and carnosine delay diabetic deterioration in mice and protect human low density lipoprotein against oxidation and glycation. Eur J Pharmacol. 2005;513(1–2):145–50.
29. Kumral A, Giriş M, Soluk-Tekkeşin M, Olgac V, Doğru-Abbasoğlu S, Türkoğlu Ü, et al. Beneficial effects of carnosine and carnosine plus vitamin E treatments on doxorubicin-induced oxidative stress and cardiac, hepatic, and renal toxicity in rats. Hum Exp Toxicol. 2016;35(6):635–43.
30. Abbasoğlu L, Kalaz EB, Soluk-Tekkeşin M, Olgaç V, Doğru-Abbasoğlu S, Uysal M. Beneficial effects of taurine and carnosine in experimental ischemia/reperfusion injury in testis. Pediatr Surg Int. 2012;28(11):1125–31.
31. Chan WK, Decker EA, Lee JB, Butterfield DA. EPR spin-trapping studies of the hydroxyl radical scavenging activity of carnosine and related dipeptides. J Agric Food Chem. 1994;42(7):1407–10.
32. Boldyrev AA, Aldini G, Derave W. Physiology and pathophysiology of carnosine. Physiol Rev. 2013;93(4):1803–45.
33. Wu H-C, Shiau C-Y, Chen H-M, Chiou T-K. Antioxidant activities of carnosine, anserine, some free amino acids and their combination. J Food Drug Anal. 2003;11(2):148–53.
34. Hartman PE, Hartman Z, Ault KT. Scavenging of singlet molecular oxygen by imidazole compounds: high and sustained activities of carboxy terminal histidine dipeptides and exceptional activity of imidazole-4-acetic acid. PcPb. 1990;51(1):59–66.
35. Ito M, Shii D, Segami T, Kojima R, Suzuki Y. Preventive actions of N-(3-aminopropionyl)-L-histidinato zinc (Z-103) through increases in the activities of oxygen-derived free radical scavenging enzymes in the gastric mucosa on ethanol-induced gastric mucosal damage in rats. Jap J Pharmacol. 1992;59(3):267–74.
36. Choi HS, Lim J-Y, Chun HJ, Lee M, Kim ES, Keum B, et al. The effect of polaprezinc on gastric mucosal protection in rats with ethanol-induced gastric mucosal damage: comparison study with rebamipide. Life Sci. 2013;93(2–3):69–77.
37. Canabady-Rochelle LL, Selmeczi K, Collin S, Pasc A, Muhr L, Boschi-Muller S. SPR screening of metal chelating peptides in a hydrolysate for their antioxidant properties. Food Chem. 2018;239: 478–85.
38. Abdelkader H, Longman M, Alany RG, Pierscionek B. On the anticataractogenic effects of L-carnosine: is it best described as an antioxidant, metal-chelating agent or glycation inhibitor. Oxidative Med Cell Longev. 2016;2016:1–11.
39. Aldini G, Facino RM, Beretta G, Carini M. Carnosine and related dipeptides as quenchers of reactive carbonyl species: from structural studies to therapeutic perspectives. BioFactors. 2005;24(1–4): 77–87.
40. Hipkiss A. Carnosine and protein carbonyl groups: a possible relationship. Biochemistry (Mosc). 2000;65(7):771–8.
41. Aldini G, Orioli M, Rossoni G, Savi F, Braidotti P, Vistoli G, et al. The carbonyl scavenger carnosine ameliorates dyslipidaemia and renal function in Zucker obese rats. J Cell Mol Med. 2011;15(6): 1339–54.
42. Hipkiss AR, Brownson C, Carrier MJ. Carnosine, the anti-ageing, anti-oxidant dipeptide, may react with protein carbonyl groups. Mech Ageing Dev. 2001;122(13):1431–45.
43. Baba SP, Hoetker JD, Merchant M, Klein JB, Cai J, Barski OA et al. Role of aldose reductase in the metabolism and detoxification of carnosine-acrolein conjugates. J Biol Chem. 2013:jbc. M113. 504753.
44. Hipkiss AR, Brownson C, Bertani MF, Ruiz E, Ferro A. Reaction of carnosine with aged proteins. Ann N Y Acad Sci. 2002;959(1):285–94.