Review Article

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Is carnosine effective to alleviate lung injury: a systematic review

Karnozin akciğer hasarını hafifletmede etkili midir: Sistematik bir derleme

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Abstract

Objectives: Lung injury is one of the most important risk factor for morbidity and mortality, especially in older people. There are several reasons causing acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) such as pneumonia, sepsis, viruses, oxidants, and trauma. Evidence has shown that carnosine has many properties, such as suppressing hydroxyl, superoxide, and peroxy radicals, inhibiting peroxidation, membrane protection and wound healing. We aimed to analyze the effects of carnosine on lung injury in this systematic review.

Content: A systematic research was performed in Pubmed, Web of Science, and Scopus databases for following

keywords; “carnosine” AND “lungd” until October 31st, 2020. Bias analysis was done with RevMan 5.3 software.

Summary: We screened totally 51 publications and only nine articles were used for the final analysis. Eight animal studies and one in vitro study were included in this study. All studies indicated that carnosine has beneficial effects on improving lung injury.

Outlook: The study demonstrates that carnosine may be a promising new therapeutic agent and help to improve lung injury by reducing oxidative stress, proinflammatory cytokines, and apoptosis. Further investigations are needed to elucidate which mechanism is more effective to cure lung damage, especially in humans.

Keywords: carnosine; lung; lung injury; respiratory diseases; systematic review.

Öz

Amaç: Akciğer hasarı, özellikle yaşlılarda morbidite ve mortalite için en önemli risk faktörlerinden birisidir. Akut akciğer hasarına (ALI) ve akut solunum sıkıntısı sendromuna (ARDS) neden olan pnömoni, sepsis, virüsler, oksidanlar ve travma gibi çeşitli nedenler vardır. Kanıtlar, karnozinin hidroksil, süperoksit ve peroksil radikallerini baskılamak, peroksidasyonu inhibe etmek, membran koruması ve yara iyileşmesi gibi birçok özelliğe sahip olduğunu göstermiştir. Bu bilgiler ışığında, bu sistematik derlemede karnozinin akciğer hasarı üzerindeki etkilerini analiz etmeyi amaçladık.

İçerik: Pubmed, Web of Science ve Scopus veri tabanlarında “karnozin” ve “akciğer” anahtar kelimeleri ile 31 Ekim 2020 tarihine kadar sistematik bir araştırma yapılmıştır. Yanıtlık analizi RevMan 5.3 yazılımı ile yapılmıştır.

Özet: Toplam 51 yayın tarandı ve son analiz için sadece 9 makale kullanılmıştır. Bu çalışmaya sekiz hayvan çalışması ve bir in vitro çalışma dahil edilmiştir. Tüm

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çalışmalar, karnozinin akciğer hasarını iyileştirmede faydalı etkileri olduğunu göstermiştir.

Görünüm: Çalışma, karnozinin oksidatif stresi, proinflatuar sitokinleri ve apoptozu azaltarak akciğer hasarını iyileştirmeye yardımcı olabilecek yeni potansiyel tedavi aracı olabileceğini göstermektedir. Özellikle insanlarda akciğer hasarını tedavi etmek için hangi mekanizmanın daha etkili olduğunu aydınlatmak amacıyla daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: karnozin; akciğer; akciğer hasarı; solunum hastalıkları; sistematik derleme.

Introduction

Carnosine, discovered at the beginning of 20th century by V.S. Gulewitsch, is a natural dipeptide that consisting of β -alanine and L-histidine [1]. Carnosine, which is mainly found in muscles, has different characteristics. Many studies

have shown that carnosine has antioxidant effects by scavenging reactive oxygen and nitrogen species and chelating metals [2–4]. Carnosine also exhibits pH-buffering activity via suppressing lipid peroxidation [2, 4]. Studies have also shown that carnosine can provide membrane protection by inhibiting lipid peroxidation and lowering malondialdehyde (MDA) levels [2].

There are many studies that observing the effects of carnosine on wound healing. Roberts et al., who investigated the effects of carnosine on wound healing, demonstrated that carnosine improved wound healing when given as a part of an enteral formula [5]. In another study examining the effects of carnosine on lung injury was indicated that carnosine can accelerate lung injury induced by irradiation [6].

Both acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are important clinical syndromes and refer almost similar pathophysiological processes [7]. ALI is a serious clinical problem associated with pulmonary oedema and severe hypoxemia, and it is closely related with high morbidity and mortality rate [8]. ARDS,

Table 1: Characteristics of included studies in this systematic review.

References	Type and number of carnosine group	Dosage and administration type	Study duration	Main conclusion
Aydin et al. [20]	Rats (n=6)	100 mg/kg/day, oral	4 weeks	Carnosine reduced oxidative stress, and apoptosis and restored histopathological changes.
Cuzzocrea et al. [16]	Mice (n=15)	150 mg/kg/day, oral	1 week	Carnosine reduced lung injury, lung oedema, neutrophil infiltration, levels of lung MPO, TGF- β , iNOS, and TGF- β levels, apoptosis, mortality rate and improved histopathological impairments.
Kadry et al. [19]	Rats (n=10)	250 mg/kg, intraperitoneal injection		Carnosine reduced TNF- α , IL-6, CRP, VEGF, HSP-70 and degeneration of lungs and cellular infiltration.
Ohata et al. [21]	Mice (n=6)	10–50–100 mg/kg, oral		PZ reduced production of NO, TNF- α , iNOS mRNA gene expression. Pretreatment with PZ also improved lung damages.
Sun et al. [17]	Rats (n=6)	25–50 mg/kg/day, oral	30 days	Carnosine reduced levels of MDA, MPO, TNF- α and IL-8, NF- κ B p65, pulmonary oedema. It was also decreased protein concentration and levels of leukocytes in BAL. Attenuated histological changes and increased SOD activity and GPx level in the lungs.
Perel'man et al. [15]	Guinea pigs (n=90)			Carnosine alleviated the pulmonary wounds by activating intracellular regeneration, proliferation of fibroblasts, and connective tissue formation.
Tanaka et al. [18]	Mice	10–50–100 mg/kg, oral		Carnosine suppressed lung injury, alveolar haemorrhage, vascular permeability, lung interstitial oedema, leukocyte and neutrophil infiltration, MPO activity, ROS, apoptosis, and levels of IL-6, CXCL1 and CXCL2. It also decreased levels of proteins in BAL.
Xu et al. [22]	Mice (n=16)	10 mg/kg/day, oral	7 days	Carnosine decreased loss of body weight, lung oedema, levels of MDA. Carnosine also reduced MPO activity, levels of WBC, TNF- α , IL-1 β and protein concentration in BAL. It also decreased virus proliferation and TLR-4 in the lungs.
Kimura et al. [23]	A549 cells	0–40 μ M		PZ decreased cytotoxicity by suppressing LDH release, cell death and ROS level. It also increased mitochondrial activity and intracellular ATP levels.

which is a severe form of ALI, is acute respiratory failure caused by non-cardiogenic pulmonary oedema that is defined by bilateral infiltration of lungs on radiology and severe hypoxemia. ARDS is also a serious morbidity and mortality burden similar with ALI [9, 10]. There are several factors that lead to ALI and/or ARDS, including pneumonia, sepsis, acute pancreatitis, trauma, inhalation of gastric contents, and intrinsic or extrinsic oxidants [11, 12]. Both ALI and ARDS are characterized by diffuse alveolar damage (DAD), pulmonary oedema, neutrophil infiltration of lungs, and pulmonary surfactant dysfunction [11].

When the lung is injured, regardless of the cause of ALI/ARDS, inflammatory processes are activated [8, 10]. In the pathogenesis of ALI, neutrophils, which play a main role in formation of microvascular and the lung tissue injury, macrophages, and proinflammatory mediators such as tumor necrosis factor- α (TNF- α) and nitric oxide (NO) are activated [8]. On the other hand, in the pathogenesis of ARDS, inflammation can lead to DAD, which is a result of alveolar epithelial barrier dysfunction, endothelial dysfunction, and protein-rich alveolar oedema [9, 10]. As a result of these changes, hypoxemia and acute respiratory failure are observed when pulmonary oedema accumulates in the interstitium and alveoli [10].

In the light of all these knowledge, we aimed to examine the effects of carnosine on lung injury. To our knowledge, this is the first systematic review that investigates effects of carnosine on lung injury. We think that this paper can be beneficial for developing novel treatments for pulmonary diseases.

Methods

Search strategy

An electronic search was performed in three databases: Pubmed, Web of Science and Scopus until October 19th, 2020. There was no time restriction for publications. The searching keywords were “carnosine” AND “lung injury” for all databases. Procedures of the PRISMA guideline were followed for searching and reporting the data [13].

Study selection criteria

All English language original studies which investigated the effect of carnosine on lung injury were included in this review.

Reviews, abstracts, meetings, hypothesis were excluded in this systematic review.

Figure 1: Flow diagram of studies included in the systematic review.

Analysis of the data

The titles and abstracts were screened to be sure that included studies had the true scope of this systematic review. For further assessment, the full text of the papers were taken. All sections of each papers (abstract, results, tables and figures) were reviewed independently for eligibility and data extraction. Studies not relevant to the topic, reviews, abstracts, meetings, and hypothesis were removed. Publications that met the inclusion criteria were mentioned in Figure 1.

Risk of bias assessment

Bias assessments were determined as described in the Cochrane guideline. Selection bias, performance bias, detection bias, attrition bias, and reporting bias were evaluated as low, unclear, or high risk according the information given in the studies [14]. Bias analysis was done with RevMan 5.3 software (Cochrane Collaboration, Copenhagen, 2014). GraphPad Prism 6 software was used for the figures.

Results

As shown in Figure 1, we screened totally 162 publications and then excluded 20 duplicate articles. Of the 142 remaining publications, 133 of them were excluded; 68 of them were irrelevant, six of them were not in English, 49 of them were review, and 10 of them were meeting abstracts, editorial, conference paper, case report and hypothesis. The remaining nine articles were used in the final analysis of this systematic review (Table 1).

Animal studies

Eight animal studies were included and all of them demonstrated that carnosine could decrease lung injury. Perel'man et al. examined the role of carnosine on an experimental model, which is penetrating incised wound of the lung. They injected 12 mg carnosine solution into the lung. In addition, they injected each 4 mg carnosine into muscle and skin. They observed that carnosine alleviated the pulmonary wounds in guinea pigs by activating intracellular regeneration, proliferation of fibroblasts, and connective tissue formation in 7–8 days [15].

Cuzzocrea et al. investigated the effects of orally intake carnosine on bleomycin-induced lung injury in male CD mice. They demonstrated that carnosine reduced lung injury, lung oedema, infiltration of lungs by neutrophils, levels of lung myeloperoxidase (MPO), transforming growth factor- β (TGF- β), nitrotyrosine, inducible nitric oxide synthase (iNOS). It was also seen that carnosine decreased TGF- β levels in bronchoalveolar lavage (BAL), apoptosis and mortality rate through its antioxidative properties. Carnosine also improved histological findings of lung injury [16]. In another study, orally administration of two different doses of carnosine for consecutive 30 days on cecal ligature puncture-induced sepsis model in male albino Wistar rats showed that carnosine reduced levels of MDA, pulmonary oedema, proinflammatory cytokines levels such as TNF- α and interleukin-8 (IL-8), and MPO. In addition to these effects, carnosine also reduced levels of leukocytes and protein concentration in BAL. In addition to these effects, it was also seen that carnosine decreased levels of nuclear factor kappa B (NF- κ B) p65. In this study, it was also found that carnosine attenuated histological changes and increased superoxide dismutase activity (SOD) and glutathione peroxidase (GPx) level in the lungs [17]. Tanaka et al. showed that oral administration of carnosine suppressed lung injury, alveolar haemorrhage, vascular permeability, lung interstitial oedema, ROS, and levels of IL-6 and chemokines such as C-X-C motif ligand 1 and 2 (CXCL1 and CXCL2). Carnosine also suppressed protein concentration in BAL of mice with lipopolysaccharide (LPS)-induced lung injury model. Carnosine also suppressed leukocyte and neutrophil infiltration and MPO activity as well as decreasing apoptosis by suppressing endoplasmic reticulum (ER) stress response in this study [18].

In another study that evaluating the efficacy of pretreatment administration of carnosine with intraperitoneal injection on sodium nitrite (NaNO₂)-induced lung injury in male Wistar albino rats showed that carnosine

reduced TNF- α , IL-6, C-reactive protein (CRP), vascular endothelial growth factor (VEGF), heat shock protein-70 (HSP-70) and degeneration of lungs and cellular infiltration [19].

Aydin et al. examined the effects of carnosine supplementation on lung tissues of male Sprague-Dawley rats exposed to different doses of formaldehyde. They found that carnosine decreased oxidative stress and positive terminal deoxynucleotidyl transferase dUTP nick-end labelling (TUNEL) staining, which is an indicator of apoptosis. It was also showed that carnosine intake restored histopathological changes in this model [20].

In a study that investigates the efficacy of pretreatment orally utilization of polaprezinc (PZ), which is a chelate compound consisting of zinc and carnosine, in LPS-induced endotoxin shock male ddY mice found that PZ reduced production of NO and TNF- α , iNOS mRNA gene expression. It was also showed that pretreatment with PZ improved lung damages such as alveolar haemorrhage, infiltration of inflammatory cell infiltration and peri-vascular oedema in these mice [21].

In another study that investigating the effect of carnosine on H9N2 swine influenza virus-induced acute lung injury in female specific-pathogen-free BALB/c mice demonstrated that carnosine decreased loss of body weight, lung oedema, levels of MDA (while increasing total superoxide dismutase). There was also reduced levels of TNF- α , IL-1 β , white blood cells (WBC) count, MPO activity and protein concentration in BAL. In addition to these effects, carnosine also significantly reduced virus proliferation and Toll-like receptor-4 (TLR-4) in the lungs [22].

In vitro studies

One *in vitro* study was included to this systematic review. Kimura et al. examined the efficacy of PZ on cadmium-induced human lung epithelial cells. They showed that PZ decreased cytotoxicity by suppressing lactate dehydrogenase (LDH) release, apoptosis by suppressing ER stress response and production of ROS. It was also showed that PZ increased mitochondrial activity and intracellular ATP levels [23].

Risk of bias analysis

Bias analysis of each study were given with risk of bias summary and risk of bias graph (Figure 2). The risk of selection, performance, detection, attrition and reporting

Figure 2: A. Risk of bias summary of the included studies for the systematic review. B. Risk of bias graph summary of the included studies for the systematic review.

bias of the studies were analyzed according to the Cochrane Handbook [14].

Discussion

In this systematic review, we demonstrated that carnosine has beneficial effects on improving lung tissue injury by suppressing proinflammatory cytokines, certain chemokines, oxidative agents, and apoptosis.

In a study by carried out by Lamb et al. demonstrated that patients with ARDS had higher levels of oxidant agents in their BAL compared to healthy controls [24]. In addition, Bunnell et al. found that ARDS patients had lower levels of glutathione (GSH) in the alveolar fluid [25]. In addition to ARDS, also patients with IPF exhibited lower levels of GSH in their epithelial lining fluid [26].

Several research showed that carnosine has important antioxidant activities. Boldyrev et al. indicated that carnosine suppressed the lipid peroxidation towards the end of 20th century [27]. In another study, Caruso et al. found that carnosine reduced intracellular levels of superoxide anions in a murine model that used RAW 264.7 macrophages by suppressing TNF- α and IL-6 mRNAs, and enhancing antiinflammatory mediators such as IL-4, and IL-10 [28]. In another study of Caruso et al. demonstrated

that carnosine inhibited total NO levels in a murine model induced by LPS and IFN- γ [29]. More recently, the effects of carnosine for modulation of antiinflammatory and proinflammatory roles on RAW 264.7 macrophages were evaluated and found that carnosine reduced levels of MDA, expression of prooxidant enzymes, IL-1 β and IL-6 and expression of antioxidant enzymes [30].

Carnosine also plays another important role against virus infections, too. Rothan et al. examined the antiviral activities of carnosine on Dengue virus and Zika virus in Huh7 cells, which are human liver cells. At the end of the investigation, they found that exogenous carnosine significantly suppressed viral infection by inhibiting virus entry to the host cells and viral genome replication [31].

Influenza A virus (IAV) is a common causative agent of pneumonia-related death worldwide and it can cause a significant increase in mortality, especially during pandemics. After the IAV infection, increase in the activation of NF-K β , releasing of proinflammatory cytokines and chemokines are observed. These responses to the viral infection can contribute to lung tissue damage by inducing TNF- α and iNOS, which underlie the IVA-related alveolar injury [32].

As we all know, we live extraordinary times worldwide since December 2019 because of the COVID-19 (SARS-CoV-2), which is a member of the genus Betacoronavirus [33]. In the COVID-19 infection, cytokine storm is one of the most encountered and most serious problem. Several cytokines and chemokines, including TNF- α , TGF- β , IL-1 β , IL-8, macrophage inflammatory protein-1 α (MIP-1 α) are observed in this cytokine storm. However, IL-6 is one of the most major cytokine involved in this cytokine storm and it plays a central role. It was shown that cytokine storm is associated with severe lung injury by impairing the integrity of endothelial and epithelial cells, thus causing vascular permeability and pulmonary oedema, neutrophil and macrophage infiltration to the lungs, and hypoxia [34].

Previously, we mentioned many features of carnosine before. We think that carnosine may also be beneficial in the treatment of COVID-19. Firstly, one of the most important activities of carnosine is inhibition of angiotensin converting enzyme activity, which plays a central role in COVID-19 infection. Nakagawa et al. showed that carnosine inhibited ACE activity *in vitro* even at lower doses than those normally found in muscles and neuronal tissues [35, 36]. Secondly, carnosine is also important as a result of chelate formation with metal ions as mentioned before. PZ, which is a chelate with carnosine and zinc, can boost the inhibition of proinflammatory processes closely related with COVID-19 [33, 35]. Thirdly and finally, carnosine can decrease oxidative stress by suppressing levels of NO and iNOS, which are worsening viral infections [33].

As a result, in this comprehensive systematic review, we investigated the activity of carnosine in lung injury. It must be emphasized that included studies in this review are animal models or *in vitro* cell samples. Unfortunately, no human studies are available to ensure correctness of these results. Further studies, especially carried out in human, are needed to confirm these effects of carnosine.

Strength and limitation of included studies

There are certain strengths in our study. One of them is that our study includes animal and *in vitro* studies, which can control in terms of physiological conditions. Another advantage of the study is that the animal studies have a control group, which provides comparison and reduced systematic bias. Finally, the duration of included studies was found to be appropriate.

The study also has certain disadvantages. The major limitation is that lack of human studies in this systematic review. Human studies are the most suitable data to confirm mechanisms of such molecules. The effects of carnosine in human studies are changeable, thus further studies are needed to investigate exact effects in humans.

Conclusion

All of the articles included in the systematic review demonstrated that carnosine has positive effects to alleviate lung injury. However, the effects of carnosine are still unclear. Thus, human studies are needed to elucidate the action mechanisms of carnosine.

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