Regulating Effect Of Carnosine And /Or L- Arginine On The Expression Of Inflammatory Molecules Induced Nephropathy In The Hypoxic Rat Model

Nouf M. Al-Rasheed[1], Laila Fadda[1] , Azza M Mohamed*[2,3], Hala A. Attia[1,4],   Nawal M. Al-Rasheed[1]

[1]Department of Pharmacology and Toxicology, College of Pharmacy, King Saud University, Riyadh, Kingdom of Saudi Arabia. [2]Biochemistry Department, Faculty of Science – Al Faisaliah, King Abdulaziz University, Jeddah, Saudi Arabia. [3] Theraputic Chemistry Department, National Research Center, Dokki, Egypt. [4] Department of Biochemistry, College of Pharmacy, Mansoura Univrsity, Mansoura, Egypt.

ABSTRACT

This study aimed to explore the effective role of carnosine and /or L- arginine in down regulation of the inflammatory molecule   expression caused   renal damage in response to sodium nitrite (NaNO2) induced hypoxia in rats . NaNO2 was administered subcutaneously (s.c.) to rats as a single dose (60 mg/kg body weight). L-arginine (200mg/Kg body weight) and carnosine   (250 mg/ Kg body weight) were administered (i.p.) as a single dose , 24 h before NaNO2 injection. The results revealed that pre-administration of arginine and /or carnosine to NaNO2 hypoxic rats, significantly modulated the increases in serum markers of renal function (creatinine and urea) as well as the decrease in hemoglobin (Hb) level versus hypoxic rats.   The two agents each alone or in a combination, markedly down regulated   the   serum pro-inflammatory molecules, including tumor necrosis factor-α (TNF- α) , C-reactive protein (CRP), vascular endothelial growth factor (VEGF) and heat shock protein -70 (HSP-70) as well as interleukin-6 (IL-6) in renal tissue compared to NaNO2 hypoxic rats . Also, the two agents successfully down modulated the alteration in the serum hypoxia inducible factor 1α (HIF 1α) . The present biochemical results were also supported by histopathological examination. In conclusion, the current data revealed that although the efficacy of arginine or carnosine each alone, their combination was more effective in ameliorating the renal damage induced by inflammatory molecules in response to NaNO2 hypoxia . This may support the use of this combination   as an effective drug   to treat hypoxic renal damage

Key words: hypoxia, arginine , carnosine , inflammatory molecules , renal damage

INTRODUCTION

Oxygen homeostasis is critical for many physiological and developmental processes, and, its disturbances have key roles in the pathogenesis of many human diseases, including renal disease (Semenza 2011). Chronic renal disease (CRD) is an important risk factor causing mortality (Go et al. 2004). There are various causes for the CRD, represented by interstitial fibrosis, glomerular sclerosis, and nephron destruction (Remuzzi and Bertani 1998).). The kidney is sensitive to oxygen supply. Increasing evidence indicated that a reduction in renal oxygen tensions plays an important role in the progression of chronic renal disease (Eckardt et al. 2005). The kidney needs a complicated vasculature to maintain its architecture and function and is thus highly susceptible to hypoxic insults. Hpoxia causes a a rapid decline in capillary density which provides the structural basis for adequate oxygen delivery to tubular cells. Also low oxygen tensions impairs energy generation and induces a proinflammatory state via the expression of certain pro-inflammatory gene products in the endothelium, such as leukocyte adhesion molecules and proinflammatory cytokines, leading to the end-stage feature in CRS (Bohle et al. 1996; Eckardt et al. 2005; Basuroy et al. 2006). Some authors reported that hypoxia is a potential cause of tissue inflammation through activation of nuclear factor κB (NFκB), in the tissue macrophages (Rius et al. 2008) .
Sodium nitrite (NaNO2) is an inorganic salt used as a food additives and can be found in drinking water (Fewtrell 2004; Habermeyer et al. 2015). The salt is one of the toxic agents that induces hypoxic organ damage and failure . The hazardous effect of NaNO2 is derived from the reaction of nitrite with amines and amides in food to produce nitrosamines and nitrosamides, respectively, which play vital roles in posing toxic effects in different organs (Tong et al. 2010; El-Sheikh and Khalil 2011). NaNO2 is highly reactive with hemoglobin causing methemoglobinemia , a condition in which there is a reduction in hemoglobin stability to transport oxygen leading to hypoxia (Craun et al. 1981). The administration of sodium nitrite causes dysregulation of inflammation, hypoxia, ischemia , oxidative stress and impaired energy metabolism which finally aggravate organ damage , including renal damage (El-Sheikh and Khalil 2011; Salama et al. 2013; Abu Aita and Mohammed 2014; Al-Gayyar et al. 2014; 2015).
Previous studies have shown that many antioxidant compounds are able to reduce the inflammatory reactions, thereby reducing the risk of tissue injury and organ dysfunction (Ivanov et al. 2008, Tsai et al. 2010)
L-Arginine is a basic natural amino acid and has important roles in many metabolic pathways within the human body. It serves as a precursor for the synthesis of biologically important molecules, including proteins, polyamines, creatine, agmatin, proline and glutamate (Morris 2006). L-arginine is an essential component of the urea cycle, the only pathway for ammonia elimination and detoxification . L-Arginine is the only substrate in the biosynthesis of NO that has diverse physiological roles, including neurotransmission, vasorelaxation, vasodilatation, and regulation of the immune system (Bogdan 2001; Gad 2010). NO within its physiological concentration, exerts protective antiapoptotic actions (DeNadai et al. 2000) . L-Arginine also has antioxidant and anti-inflammatory potential actions (Ivanov et al. 2008). It can attenuate the inflammatory reactions by suppressing the generation of inflammatory mediators

such as inflammatory cytokines and C-reactive protein, which play the major role in the progression of tissue damage and organ dysfunction (Wu et al. 2001). Arginine is essential for the biosynthesis of parliament that strongly involved in the enhancement of protein synthesis (Moinard et al. 2005) and may facilitate healing during inflammation (Chung et al. 1993). L-arginine has been found to improve renal function (Klahr 1999).

Carnosine (beta-alanyl-L-histidine) is an endogenous synthesized dipeptide that is present in different human tissues, including the kidney (Kiliś-Pstrusińska 2012). L-carnosine is known to possess antioxidant and anti-inflammatory properties (Tsai et al. 2010). It has free radical scavenging functions (Hartman et al. 1990), can suppress lipid peroxidation, promote the expression of antioxidant enzymes and inhibit the inflammatory cytokine generation (Tsai et al. 2010). It has a cardioprotective impact against hypoxia-induced expression of hypoxia inducible factor in cardiomyoblasts (Bharadwaj et al. 2002). It can reduce rat mortality exposed to brain ischemia (Stvolinsky et al. 2000) and protect against ischemia/ reperfusion -induced acute renal failure in rats (Fujii et al. 2003).

The aim of this study is to explore the effective role of the antioxidants , L-arginine and/ or carnosine against the inflammatory reactions induced renal tissue damage in rats exposed to hypoxia.

MATERIAL AND METHODS

Chemicals

Carnosine , L- arginine and sodium nitrite used in this study were analytically pure products of Sigma- Aldrich Chemical Co., St. Louis, MO, United States. All other chemicals were of high analytical grade, product of Sigma and Merck companies. Sodium nitrite and carnosine were dissolved in normal saline, while, idebenone and arginine were suspended in 1% gum acacia in normal saline.

Animals and treatments

Fifty Wistar adult male albino rats weighing 170-200 g were used in this study. The rats were obtained from the Experimental Animal house, Faculty of Pharmacy, King Saud University, Saudi Arabia. Animals were housed in special clean cages, and maintained at standard conditions (12-h light/dark cycle, temperature ranging 20–22°C and 60% humidity). Rats were fed with standard rat pellet chow with free access to tap water *ad libitum* for one week before the experiment for acclimatization. The animal Experimental protocol was approved by the Experimental Animal Ethics Committee at King Saud University, Faculty of Pharmacy, Saudi Arabia. After one week acclimation, the rats were kept fasting over night before treatment and randomly divided into five groups, each of ten rats Group 1, served as control . Group 2 : NaNO2-treated animals. Group 3 : NaNO2-treated animals and pre-injected with arginine (200 mg/kg, i.p. Ali et al. 2012) Group 4: NaNO2-treated animals and intraperitoneally injected with carnosine (250mg/kg, Al-Rasheed et al. 2015) Group 5: NaNO2-treated animals and intraperitoneally injected with a combination of arginine (200 mg/kg, i.p.) and carnosine (250 mg/kg, i.p.) Hypoxia was induced in rats by NaNO2 (60 mg/kg,). NaNO2 was administered subcutaneously (s.c.) as a single dose .L- arginine and carnosine were administered intraperitoneally, 24 h before NaNO2 injection. After one hour of NaNO2 injection, the rats were sacrificed under ether anesthesia , then blood samples were collected and divided into two parts . One part was

collected into tubes containing heparin for hemoglobin determination. The other part was allowed to coagulate and centrifuged for serum separation and use for serum biochemical analysis . After blood collection, the kidneys were removed and placed overnight in phosphate-buffered 10% formalin for fixation and histopathological examination.

Determination of Hb
Hb was determined colorimetrically using Drabkin's reagent according to the method of Kjeldsberg (1993) .

Biochemical serum analysis
Blood urea nitrogen (BUN) and creatinine concentration in serum as renal function parameters were estimated using a commercial assay kit (Wako Pure Chemicals, Osaka, Japan).
IL-6 was measured using a high sensitive rat Enzyme-linked immunosorbent assay (ELISA) kit (IBL International GmbH, Flughafenstr, Hamburg, Germany) following the instructions of the manufacturer**.** TNF-α was measured using the ELISA assay kit following the instructions supplied by the manufacturer (DuoSet kits; R&D Systems, Minneapolis, MN, USA). C-reactive protein (CRP) was estimated by immunonephelometric (Dade Behring N Latex High Sensitivity CRPTM mono assay) on a Behring Nephelometer II analyzer. In this method, polystyrene beads coated with rat monoclonal antibodies bind to serum CRP forming aggregates. The intensity of the scattered light is directly proportional to CRP concentration. The level of VEGF was assayed by calorimetric, quantitative, sandwich ELISA (R&D Systems, UK) at 492 nm, following the manufacturer's instructions. VEGF content was estimated using a standard curve generated with specific standards provided by the manufacturer. For the quantitative

determination of HSP70, a sandwich rat HSP 70 ELISA Kit was used (Kamiya Biomedical, Washington, USA). ELISA kit was used to measure serum level of HIF-1α (Cayman Chemical Co, Ann Arbor, Michigan, USA)

Histopathological examination
A small pieces of kidney were fixed by 10% formalin and then embedded into paraffin, sectioned for 5–6-μm thick, and mounted on the glass microscope slides using standard histopathological techniques. The sections were stained with hematoxylin-eosin and examined by light microscopy.

Statistical analysis
Data were analyzed by comparing values for different treatment groups with the values of individual controls. Results are expressed as mean ± SD. Significant differences among values were analyzed using one-way analysis of variance (ANOVA) followed by Bonferroni's test post-ANOVA.

RESULTS

Biochemical observations
Figure 1 shows the effect of arginine and /or carnosine on serum levels of kidney function biomarkers (creatinine and urea) in control and hypoxia experimental groups. Induction of hypoxia in rats caused pronounced increases in serum creatinine and urea compared with control animals ($P \leq 0.001$), and the injection of arginine and /or carnosine, significantly ($P \leq 0.001$) down-modulated the deviation in these markers compared with hypoxia group.
The protective effect of arginine and /or carnosine on blood Hb concentration in control and hypoxia experimental groups is shown in Figure 3. The result revealed that induction of hypoxia in rats caused a significant decrease in Hb compared with control group ($P \leq 0.001$) . Pre-treatment of hypoxic rats with arginine and /or

carnosine markedly modulated the deviation in blood Hb versus hypoxia untreated animals.

The levels of some immunological pro-inflammatory biomarkers, including TNF-α, IL-6 and CRP in the serum of control and hypoxia rat groups are illustrated in Figure 4 . These biomarkers were dramatically elevated in the sera of hypoxic rats compared with the control group ($P \leq 0.001$). Administration of arginine and /or carnosine before the induction of hypoxia , markedly inhibited the induced inflammatory mediators compared with hypoxic animals .

The levels of VEGF (angiogenic factor), HSP70 and HIF 1 α (index of hypoxia) were significantly increased in the sera of hypoxic rats compared with the control animals (Fig.5, $P \leq 0.001$). Preadministration of arginine and /or carnosine, markedly reduced the dramatic increases in these parameters compared with hypoxic, untreated animals ($P \leq 0.001$). The synergestic pre- treatment of hypoxic animals with the combination of arginine

and carnosine was more effective in modulating most of the studied parameters near the normal levels.

Histo-pathological observations

The results of the biochemical markers were supported by the histopathological examination of renal tissues (Fig. 2). This examination revealed that the hypoxia induced animals showed degeneration of many renal corpuscles and degeneration of the epithelia of the tubules . Foci of cellular infiltration was also observed. Pre administration of either arginine or carnosine showed marked improvement of the renal corpuscles and tubules with a marked decrease of the cellular infiltration. However, Kidney of rats treated with the combination of the two agents showed apparently normal histology of renal corpuscles and tubules with absence of cellular infiltration.
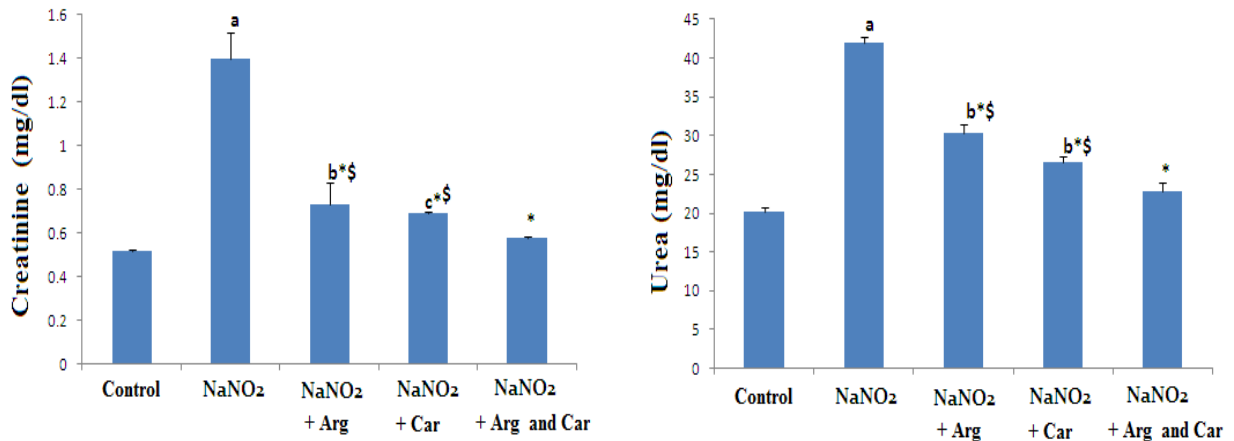

Figure 1- Effect of L-arginine (Arg) and/ or carnosine (Car) on serum kidney function markers (creatinine and urea) in control and NaNO2 induced hypoxia groups. Data are expressed as means ± S.D (n=10). [a] $P \leq 0.001$, [b] $P \leq 0.01$, [c] $P \leq 0.05$ compared with the control group, * $P \leq 0.001$, compared with NaNO2 induced hypoxia group, [$] $P \leq 0.05$ compared with the combination group (NaNO2 + Arg + Car), using ANOVA followed by Bonferroni as a post-ANOVA test
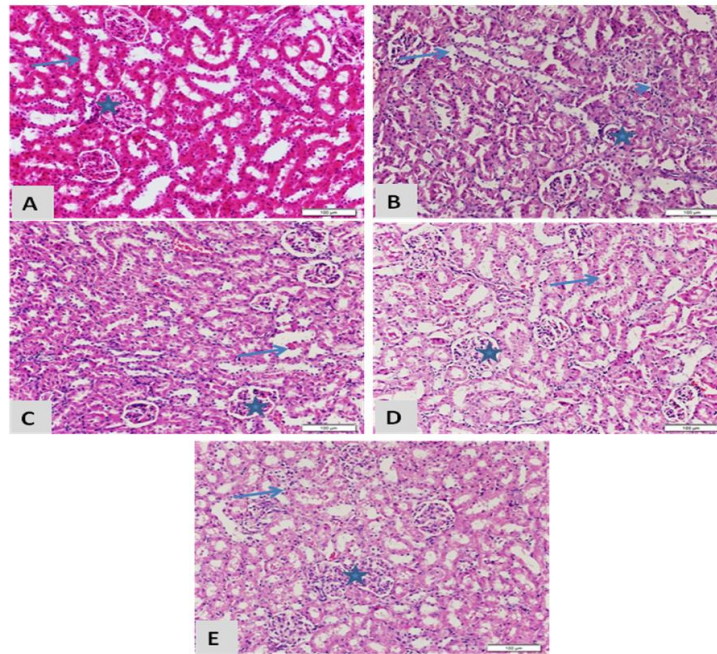
Figure 2 - Light photomicrographs from the kidney of rat stained with Hematoxylin and Eosin (Scale bar: 100µm), in which (A), represent normal renal corpuscles (star) and renal tubules(arrow). (B) Section of rat kidney   exposed to hypoxia, showing marked degeneration of many renal corpuscles (star) and degeneration of the epithelia of the tubules (arrow). Also, there are foci of cellular infiltration (arrow head). (C and D) are sections of kidney from rats exposed to hypoxia and received arginine alone or carnosine alone respectively, showing a marked improvement of the renal corpuscles (star) and the tubules (arrow) and a marked decrease of the cellular infiltration. (E) Kidney of rat exposed to hypoxia and received a combination of arginine and carnosine, showing apparently normal histology of renal corpuscles (star) and tubules (arrow) and absence of cellular infiltration.
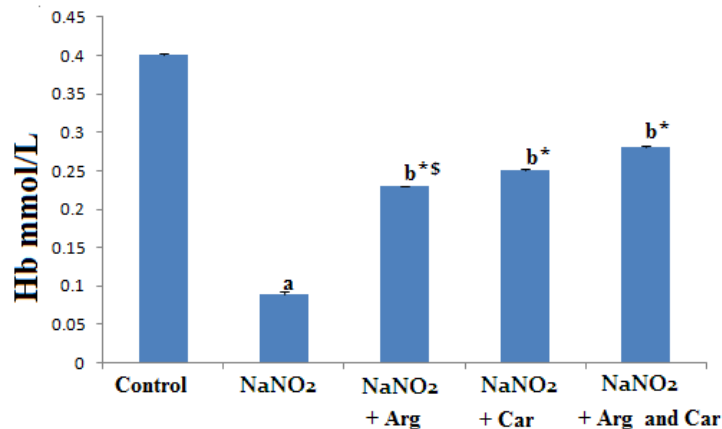

Figure 3- Effect of arginine (Arg) and/ or carnosine (Car) on blood Hb in control and NaNO2 induced hypoxia groups. Data are expressed as means ± S.D (n=10). [a] $P \leq 0.001$, [b] $P \leq 0.01$, compared with the normal group, * $P \leq 0.001$, compared with NaNO2 induced hypoxia group, [$] $P \leq 0.05$ compared with the combination group (NaNO2 + Arg + Car), using ANOVA followed by Bonferroni as a post-ANOVA test
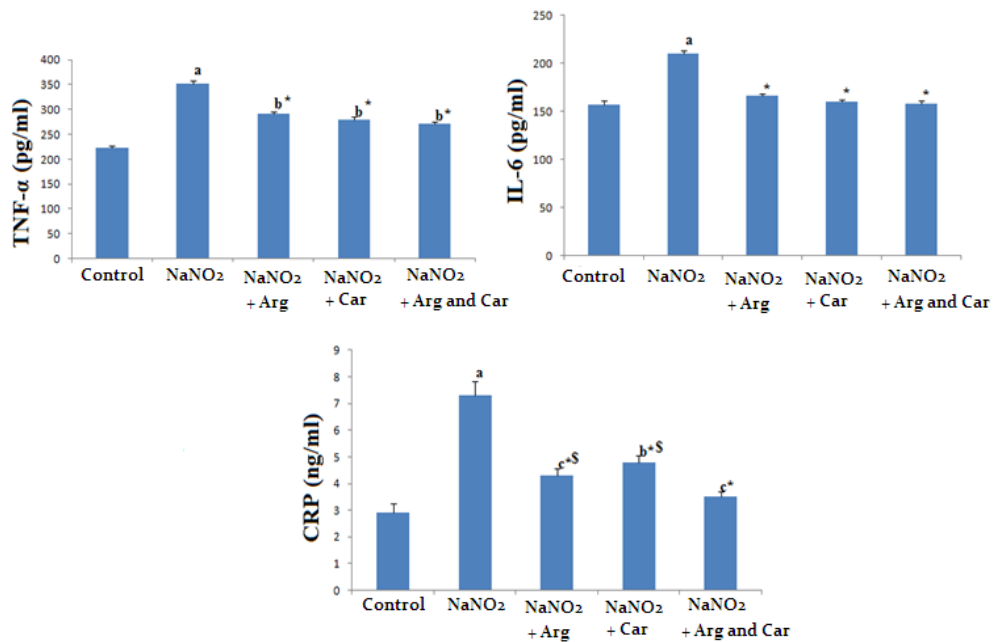
Figure 4 - Effect of arginine (Arg) and/ or carnosine (Car) on serum inflammatory markers (TNF-α, IL-6 and CRP) in control and NaNO2 induced hypoxia groups. Data are expressed as means ± S.D (n=10). [a] $P \le 0.001$, [b] $P \le 0.01$, , [c] $P \le 0.05$ compared with the normal group, * $P \le 0.001$, compared with NaNO2 induced hypoxia group,[$] $P \le 0.05$ compared with combination group (NaNO2 + Arg + Car) , using ANOVA followed by Bonferroni as a post-ANOVA test
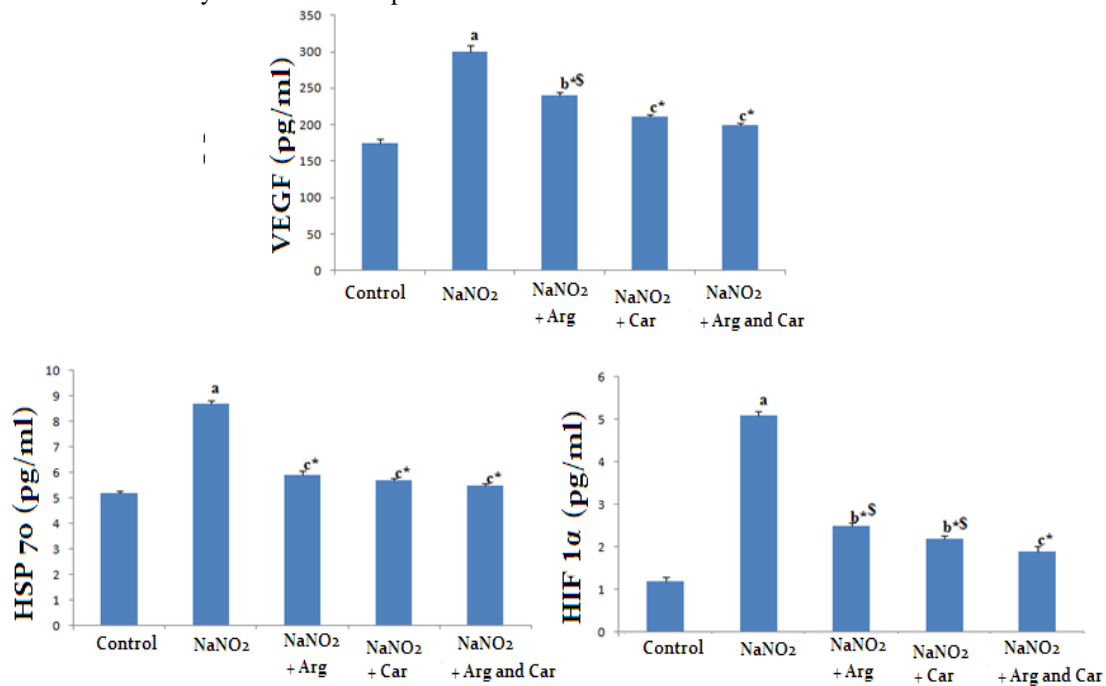

Figure 5- Effect of arginine (Arg) and/ or carnosine (Car) on serum VEGF, HSP70 and HIF1α in control and NaNO2 induced hypoxia groups. Data are expressed as means ± S.D (n=10). [a] $P \le 0.001$, [b] $P \le 0.01$, , [c] $P \le 0.05$ compared with the control group, * $P \le 0.001$, compared with NaNO2 induced hypoxia group,[$] $P \le 0.05$

compared with combination group (NaNO2 + Arg + Car) ,   using ANOVA followed by Bonferroni as a post-ANOVA test

DISCUSSION

Several studies have found that the deleterious impact of the hypoxia induced by NaNO2 is associated with oxidative stress, inflammation and methaemogobenemia which may have the principle role of organ damage and dysfunction , including renal damage (Hassan et al. 2009; El-Sheikh and Khalil 2011; Salama et al. 2013; Al-Gayyar et al. 2014).

In parallel with previous investigation, the current study revealed that induction of hypoxia in rats caused renal damage and dysfunction as indicated by the elevations in serum renal damage markers, namely creatinine and urea compared with control rats (Hassan et al., 2009). This result may indicate that exposure of renal tissue to hypoxia caused changes in the threshold of tubular re-absorption, renal blood flow and glomerular filtration rate. The deleterious impact of hypoxia induced by NaNO2 was further confirmed by the severely destructed renal tissue, as observed by the present histological examination which showed a marked degeneration of many renal corpuscles and epithelia of the tubules with foci of cellular infiltration. Administration of carnosine and/or arginine to hypoxic rats, significantly reduced the serum biomarkers of renal function compared with hypoxic untreated rats. This biochemical result was confirmed by histological observation which showed a marked improvement of the renal corpuscles and the tubules with a decrease in the cellular infiltration in rats pre-treated with either carnosine or arginine , however treatment of hypoxic rats with the combination of the two agents showed more or less normal histology of renal corpuscles and tubules with no cellular infiltration. This result may predict the beneficial synergistic protective impact of the combination of arginine and carnosine

against renal damage induced by hypoxia. This beneficial effect of both carnosine and arginine was previously documented in animals that underwent experimental renal damage (Klahr 1999; Fujii et al. 2003)

In line with previous studies , the present study demonstrated that induction of hypoxia in rats by NaNO2, caused a decrease in blood Hb level compared with normal animals (Gluhcheva et al 2012 ; Abu Aita & Mohammed , 2014). This result may indicate the development of anemia in rats in response to hypoxia . The present decrease in Hb level may be attributed to a decrease in red blood cell count in response to NaNO2.   Previous preliminary study declared a significant reduced red blood cell count in rats exposed to NaNO2 toxicity (Gluhcheva et al., 2012). Nitrite in toxic doses has been reported to induce hemic hypoxia. The underlying mechanism of such effect is mainly due to increased methemoglobin formation (Ger et al. 1996) .Some investigations reported that NaNO2 can induce oxidative damage and free radical generation that stimulates the oxidation of ferrous ions in oxyhemoglobin to form methemoglobin and erythrocyte lysis (Rahman et al. 2009; Abdel Baky et al. 2010) .

Administration of carnosine and/or arginine to hypoxic rats, significantly ameliorated the reduced level of blood Hb compared with the hypoxic untreated animals. The modulating effect of arginine and carnosine on blood Hb may contribute to their potential anti-oxidative stress due to antioxidant impacts as well as their free radical scavenging activity (Hartman et al. 1990; Giriş et al. 2014). Tarumoto et al. (2007)   reported that L-arginine administration to anemic elderly patients suffering from renal disease, resulted in an increase in their hemoglobin level and improvement in their renal function.

The present study also showed marked increases in the serum immunologic proinflammatory biomarkers, including TNF-α, IL-6, and CRP, in hypoxic rats versus the control rats. The induction of such biomarkers may play a principle role in renal damage and dysfunction induced by hypoxia. Similar result has been obtained by some studies that revealed increases in inflammatory mediators, including TNF-α , IL-1β , TGF-β1 and CRP in rat livers and human adipose tissue in response to hypoxia (O'Rourke et al. 2011, Sherif and Al-Gayyar 2013; Al-Gayyar et al. 2014).

Pre-injection of carnosine and/or arginine to hypoxic rats, successfully attenuated the production of the inflammatory mediators, TNF-α, IL-6, and CRP, suggesting that their reno-protective effect against the adverse impact of hypoxia . This beneficial impact of the two agents may be related to their anti-inflammatory and immunomodulatory beneficial actions. This result is confirmed by previous investigations, reporting that supplementation of either carnosine or L-arginine could protect against the inflammatory responses caused by different pathological conditions by inhibiting the expression of these mediators (Huang et al. 2008; Lucotti et al. 2009; Tsai et al. 2010).

The present study showed a marked increase in the angiogenic index, VEGF, in the sera of hypoxic rats. Previous study declared that overproduction of inflammatory mediators induces VEGF expression by immune and inflammatory cells (Verheul et al. 2000; Lingen 2001). Overproduction of VEGF has been reported to be a major contributor in stimulating vasculogenesis and angiogenesis to restore oxygen supply to tissues during hypoxia (Ding et al 2004; Prior et al. 2004). On the other hand, some studies reported that TNF-α and VEGF up-regulation promote a procoagulant state by increasing expression of tissue factor on endothelial cells and/or monocytes (Clauss et al. 1996; Mechtcheriakova et al. 2001). Increased tissue factor expression is thought to play a significant role in the development of multiorgan system failure in acute injury (Mechtcheriakova et al. 2001). This may suggest that overproduction of TNF-α and VEGF in hypoxic rats, presented in the current study , act synergistically to promote renal dysfunction. Pre-administration of the studied agents alone or in a combination, significantly down-regulated the increase in VEGF in the sera of hypoxic rats, suggesting their beneficial anti-angiogenic potential action. This result is supported by some investigations which revealed the role of carnosine and arginine in reducing VEGF expression (Heffernan et al. 2006; Yeha et al.2010; Ali et al. 2015).

The current study also demonstrated a significant increase in the serum HSP-70 of hypoxic rats. The increased serum level of this protein may be related to its leakage out the tissue in response to tissue injury. HSPs are groups of intracellular proteins, classified, according to their molecular weight, into five groups, namely HSP27, HSP60, HSP70, HSP90, and HSP110. HSP60 (Joly et al. 2010) . Studies on HSPs have been shown that overexpression of the HSP gene is induced in response to environmental stress (Putnak and Schlesinger 1990; Schlesinger 1990). These proteins function as cytoprotectants, preserving cell survival by maintaining the vital functions of proteins among various cell types in pathological states (Oka et al. 2013; Li et al. 2013). They regulate the response to any detrimental factors, including temperature, radiation, hypoxia, toxins or infectious agents, by controlling the three-dimensional structure of the newly synthesized proteins, preventing their misfolding or degradation (Giffard et al. 2004). It was reported that HSP70 prominently induced after stress and has long been shown to contribute to cell survival in many pathological conditions (Thomas et al. 2002). Some authors have shown that Hsp70 can protect the tissues by inhibiting various inflammatory mediators (Zheng et al. 2008). However, cell

disintegration due to damage, or necrosis may evoke the early release of HSP outside the cell (Calderwood et al. 2007) . Extracellular HSP act as a danger signal to the system of the innate immunity (Matzinger 1994) . HSP can be recognized by antigen presenting cells (APC) and their interaction subsequently triggers APC to produce the proinflammatory cytokines and to activate the nuclear factor (NF)-κB, thus initiating the adaptive immune response and the presentation of antigens to the cytotoxic T cells (Srivastava 2002). HSP70 can also stimulate the production of proinflammatory cytokines (IL-6, TNF-α) by monocytes and macrophages, as well as the expression of the adhesion molecules on the endothelial cells (Zhang et al. 2010) .

From the previous information, the present result may suggest that the increased level of serum HSP70 in hypoxic rats may have the major role in renal damage and dysfunction through inducing the overproduction of proinflammatory cytokines. Previous clinical study reported that the early release of HSP into the bloodstream after injury was associated with the development of severe tissue damage (Pespeni et al 2005) . Administration of carnosine and/or arginine to hypoxic rats, significantly reduced the serum HSP70 level . This study provides the first evidence that carnosine and arginine can reduce the endogenous cellular leakage of HSP70 into the blood stream, thus preventing its deleterious effects. This result may indicate the cytoprotective beneficial impact of these agents against hypoxia induced renal tissue injury. There is an evidence that carnosine and arginine can regulate intracellular HSP- 70 expression which is essential for preventing organ dysfunction (Chatterjee et al. 2005; Mikami et al. 2006;Wu et al 2013) .

The current result also revealed that a marked elevation in the serum HIF-1α of hypoxic rats compared with normal animals. Up-regulation of HIF-1α in different models of acute renal injury was also documented (Rosenberger et al. 2002; 2003).

HIF-1α is a transcription factor induced in response to hypoxic condition (Wenger et al., 2002). This transcription factor activates the expression of genes that are needed to maintain cellular homeostasis in the hypoxic state (Semenza et al. 2002). However, previous work postulated that induction of HIF-1α in vivo is secondary to oxidative stress and inflammatory cytokines (Haddad & Harb 2001; James et al. 2006) and its overexpression induces the expression of fibrogenic cytokines and collagen III in renal epithelial cell which play an important role in the pathogenesis of tubulointerstitial fibrosis (Basu et al. 2011). Administration of carnosine and/or arginine to hypoxic rats , significantly reduced the serum HIF-1α level compared with the hypoxic untreated group. The ability of carnosine and /or arginine to suppress the production of HIF-1α may correlate to their anti-inflammatory and anti-oxidant roles. Previous study found that carnosine could reduce the HIF-1α stability and induced its proteasome degradation (Iovine et al. 2014). On the other hand, carnosine could act on HIF-1α signaling, decreasing its protein level and consequently its transcriptional activity (Iovine et al. 2014). Also , experimental data demonstrated the ability of some other antioxidants to inhibit HIF-1α expression (Gao et al. 2007) .

CONCLUSION

The present data showed that pre-treatment with either L- arginine and/ or carnosine was beneficial in attenuating inflammation induced renal damage in response to NaNO2 induced hypoxia in rats . The combination of the two agents was the most effective one . This may support the use of this combination as an effective drug to prevent renal damage induced by hypoxic conditions.

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Erratum

In the 01 page, that read:

"**Nouf M. Al-Rasheed[1], Laila Fadda[1] , Azza M Mohamed*[2,3], Hala A. Attia[1], Nawal M. Al-Rasheed[1]**

[1]Department of Pharmacology, King Saud University, Riyadh, Saudi Arabia. [2]Biochemistry Department, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia. [3] Theraputic Chemistry Department, National Research Center, Dokki, Egypt."

Read:

"**Nouf M. Al-Rasheed[1], Laila Fadda[1] , Azza M Mohamed*[2,3], Hala A. Attia[1,4], Nawal M. Al-Rasheed[1]**

[1]Department of Pharmacology and Toxicology, College of Pharmacy, King Saud University, Riyadh, Kingdom of Saudi Arabia. [2]Biochemistry Department, Faculty of Science – Al Faisaliah, King Abdulaziz University, Jeddah, Saudi Arabia. [3] Theraputic Chemistry Department, National Research Center, Dokki, Egypt. [4] Department of Biochemistry, College of Pharmacy, Mansoura Univrsity, Mansoura, Egypt."