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ORIGINAL ARTICLE

Anxious phenotype potentiates damage in peripheral organs of animals submitted to sepsis

Fenótipo ansioso potencializa danos em órgãos periféricos de animais submetidos à sepse

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Abstract

Introduction: Anxiety and sepsis are important public health problems that present high morbidity, mortality and significant economic repercussions. The present study investigated the presence of oxidative damage in peripheral organs in two lines of animals that are bred for high and low freezing responses to contextual cues that are previously associated with foot shock (Carioca High-conditioned Freezing [CHF] and Carioca Low-conditioned Freezing [CLF]) associated to sepsis. **Methods**: Animals were subject to sepsis by the cecal ligation and perforation (CLP) or sham operated. 24 hours and 10 days after sepsis animals were euthanized and removed adrenal, kidney, lung, serum, heart for the determination of carbonyl protein levels and adrenal for check weight this structure. **Results**: Sepsis increased oxidative damage in different systemic organs, included serum. There wasn't a significant increase in protein carbonyls in heart and kidney. Anxious phenotype potentiates this damage. **Conclusion**: These findings suggest that an anxious phenotype plus sepsis may induce more pronounced organs damage, and promote more alterations in the HPA axis. These findings may help to explain, at least in part, the common point of the mechanisms involved with the pathophysiology of sepsis and anxiety.

Key words: Anxiety. Stress. Sepsis. Carioca high-freezing. Carioca low-freezing.

Resumo

Introdução: Ansiedade e sepse são importantes problemas de saúde pública que apresentam alta morbidade, mortalidade e repercussões econômicas significativas. O presente estudo investigou a presença de dano oxidativo em órgãos periféricos em duas linhagens de animais criados para respostas de alta (CHF) e baixa (CLF) ansiedade associado a sepse. **Métodos**: Os animais foram submetidos a sham (controle) ou sepse por ligação e perfuração cecal (CLP). 24 horas e 10 dias após a sepse os animais foram eutanasiados e estruturas foram removidas: adrenal, rim, pulmão, soro e coração para a determinação dos níveis de proteínas carboniladas e adrenal para verificação do peso dessa estrutura. **Resultados**: A sepse aumentou o dano oxidativo em diferentes órgãos sistêmicos, incluindo o soro. Não houve um aumento significativo de proteínas carbonilas no coração e nos rins. Fenótipo ansioso potencializa esse dano. **Conclusão**: Esses achados sugerem que um fenótipo ansioso associado a sepse pode induzir dano mais pronunciado aos órgãos e promover mais alterações no eixo HPA. Esses achados podem ajudar a explicar, pelo menos em parte, o ponto comum dos mecanismos envolvidos na fisiopatologia da sepse e da ansiedade.

Palavras-chave: Ansiedade. Estresse. Sepse. Cariocas de alto congelamento. Cariocas de baixo congelamento.

INTRODUCTION

Anxiety is an emotional disorder that affects the population's quality of life. Patients may develop psychological problems such as depression or post- traumatic stress disorder (PTSD), which can have a profound effect on their everyday functioning and the possibility of returning to work[1]. Anxiety disorders are the most prevalent psychiatric disorders[2]. In anxiety, activation of the HPA axis by repeated exposure to stress causes an increase in levels of circulating hormones[3]. When this activation remains triggered for a long time, damage begins to occur[4]. Such deleterious effects have been associated with increased generation of reactive species, which may cause oxidative damage to various structures when in excess, affecting their function[5,6].

In animals, anxiety can be studied by the freezing behavior[7,8], and rats selectively bred for high (Carioca high freezing – CHF) and low (Carioca low freezing – CLF) levels of defensive freezing behavior in response to contextual cues previously associated with foot shock were described[7,8].

Sepsis and its complications are important causes of mortality in intensive care units and sepsis survivors may present long-term cognitive and behavioral impairments, including memory deficits and anxiety symptoms[9]. Some studies have demonstrated the involvement of oxidative stress as a major step in the development of multiple organ failure and recovery

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from sepsis [9,10,11,12]. Oxidative damage, energetic metabolism impairment, and cytokine level alteration seen in early times in an animal model of sepsis may persist for up to 10 days. Oxidative stress influences the molecular mechanisms that control inflammation and directly cause tissue damage.

Oxidative damage is proteins is already well demonstrated in sepsis and according to some studies can predict mortality since the increase of carbonylated proteins indicates tissue injury. In proteins, the amino acids proline, histidine, arginine, cysteine and methionine are particularly susceptible to attack by free radicals (mainly hydroxyl radical). Oxidation of amino acids leads to fragmentation, carbonylation and protein aggregation with consequent loss of function and proteolysis[13].

Anxiety and sepsis are important public health problems that present high morbidity, mortality and significant economic repercussions[14]. Our proposal is to verify the oxidative damage in animals anxious, since anxiety for being poorly adaptive can worsen the stress caused by sepsis.

METHODS

Animals

All experimental procedures reported here in were performed under the guidelines for the use of animal experimental research established by the Brazilian Society of Neuroscience and Behavior (SBNeC), in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications) and also with approval by the local Ethics Committee (Universidade do Extremo Sul Catarinense) under protocol number 075/2016-1. Experimental animals (Carioca High-Freezing [CHF], a line selectively bred for high contextual fear conditioning, and Carioca Low-Freezing [CLF], a line selectively bred for low contextual fear conditioning) were obtained from the Pontifical Catholic University of Rio de Janeiro (PUC-Rio) according to procedures described in previous work[7,8]. Rat's control does not evidence anxious phenotype.

Males from both groups were born in the same animal room and housed in acrylic cages (31 cm × 38 cm) in groups of 3–6, under a 12 h light/dark cycle (lights on at 8:00 h), with food and water provided ad libitum. 2–3-month-old animals were used in both groups.

Experimental design

Animals were divided in six groups: Control + sham; Control + CLP (these animals don't have anxious phenotype); CHF + Sham; CHF + CLP (these animals have high anxious phenotype); CLF + Sham; CLF + CLP (these animals have low anxious phenotype).

Rats were subjected to CLP as previously described[15]. Briefly, they were anesthetized with a mixture of ketamine (80 mg/kg) and xylazine (10 mg/kg), given intraperitoneally. Under aseptic conditions, a 3 cm midline laparotomy was performed to expose the cecum and adjoining intestine. The cecum was ligated with a 3.0 with a silk suture at its base, below the ileocecal valve, and was perforated once with 14-gauge needle. The cecum was then squeezed gently to extrude a small amount of feces through the perforation site. The cecum was then returned to the peritoneal cavity, and the laparotomy was closed with 4.0 silk sutures. Animals were resuscitated with regular saline (50 mL/kg) subcutaneously (s.c.) immediately after and 12 h after CLP. All animals received antibiotic (ceftriaxone at 30 mg/kg) every 6 h, s.c. for a maximum of 3 days. In the sham-operated group, the rats were submitted to all surgical procedures but the cecum was neither ligated nor perforated. To minimize variability between different experiments, the CLP procedure was always performed by the same investigator. We had extensively characterized long-term cognitive impairment using this animal model[9,10,11]. Animals (n=8) were killed by euthanasia 24 hours and 10 days after sepsis and removed kidney, lung, serum, heart, and adrenal for the analyses described below.

Adrenal weight

Adrenal was removed, dried and weighed (g) with analytical balance of precision (Shimadzu).

Protein Carbonyls

The oxidative damage to proteins was assessed by the determination of carbonyl groups based on the reaction with dinitrophenylhidrazine (Sigma-Aldrich, Saint Louis, USA) as previously described[16]. Briefly, proteins were precipitated by the addition of 20% trichloroacetic acid and redissolved in dinitrophenylhidrazine, and the absorbance was read at 370 nm. Results were expressed as protein carbonyls/mg of protein.

Statistical analysis

Data were expressed as means ± S.D. and analyzed by one way ANOVA followed *pos hoc* Tukey test. All tests were analyzed with SPSS version 22 and/or GraphPad Prism 4.0. In all comparisons $p<0.05$ indicated statistical significance.

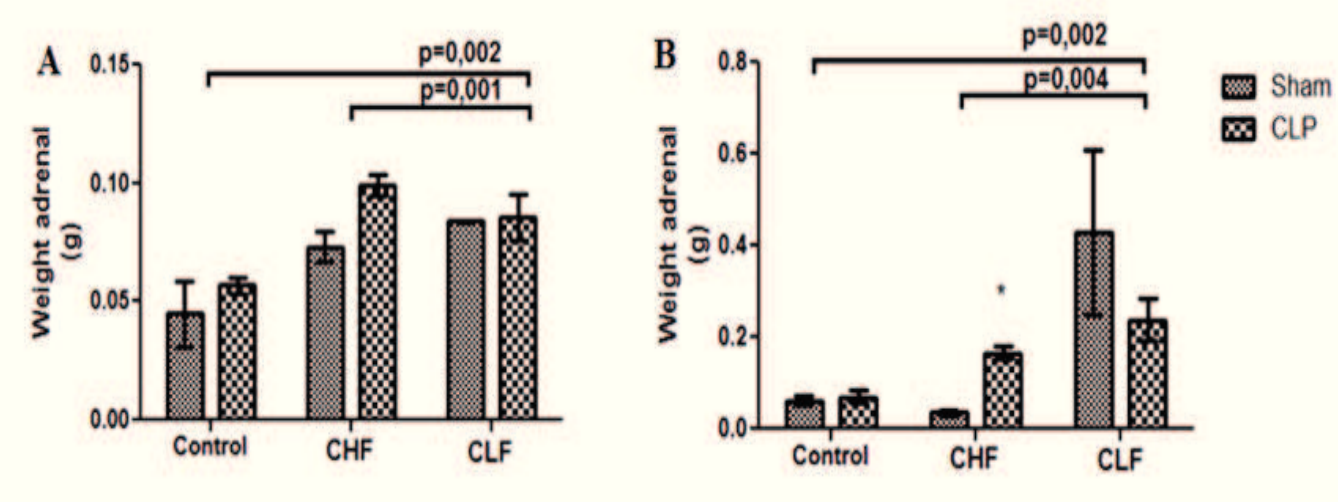
RESULTS

Adrenal Weight

Figure 1A shows the results of adrenal weight 24 hours after sepsis in control animals, CHF and CLF. Adrenal weight increased in anxious animals (CHF p=0.001 and CLF p=0.002) when compared to control. However, there was no acute effect of sepsis neither in control nor in CHF or CLF animals (Figure 1A). Similar behavior was noticed in adrenal weight 10 days after sepsis (Figure 1B). CLF and CHF increased the weight of the adrenal when compared to their control (p=0,002; p=0,004

respectively). However, there was an additional effect of sepsis CLP in CHF, but not CLF, animals (p=0,002).

Figure 1. Adrenal weight in animals with an anxious phenotype plus sepsis. Animals were submitted to CLP or sham-operated and 24h or 10 days after surgery animals were euthanized and the adrenal was removed to the determination of weight. A) adrenal weight 24h and B) adrenal weight 10 days after sepsis. Data were expressed as mean + SD. n=8 each group. p<0.05 denoted statistically difference between groups. * different from sham.



Systemic oxidative damage early (24h) after sepsis

As expected, sepsis itself increased oxidative damage in serum and different systemic organs. There was a significant increase in protein carbonyls in serum (Figure 2A), adrenal (Figure 2B) and lung (Figure 2C), but not heart (Figure 2D) and kidney (Figure 2E). In all organs that were observed oxidative damage in proteins, the CHF phenotype potentiates the damage (Figure 2A to 2C). Interestingly, there wasn't significant effect of CHF phenotype in organs were sepsis itself didn't induce oxidative damage (heart and kidney). In contrast, the CLF phenotype only potentiates oxidative damage in the kidney.

Systemic oxidative damage late (10 days) after sepsis

It was measured protein damage in serum (Figure 3A), adrenal (Figure 3B), lung (Figure 3C), heart (Figure 3D) and kidney (Figure 3E) 10 days after sepsis in control animals, CHF and CLF. In all CLP groups was showed protein damage in this time.

DISCUSSION

This study aimed to investigate early and late the damage in protein as a marker of oxidative stress in animals with anxious phenotype submitted to sepsis. This lineage of animals is well studied by investigators who are interested in better understanding the mechanisms of anxiety. Adrenal was weighed in control group, CHF and CLF groups 24 hours and 10 days after sepsis (as indirect marker of the levels of corticosterone). It was noticed that the adrenal in CHF and CLF animals are increase in 24 hours after sepsis, what was expected, but interestingly it was notice that it becomes heaviest 10 days after sepsis, demonstrating that sepsis contributes to this increase.

Mousovich et al. (2015), measured the corticosterone levels in CHF animals and noticed an increase in three times this hormone when compared to control group[17]. Glucocorticoids (cortisol in humans and corticosterone in rodents) are metabolically active hormones that play an important role in the stress response and act on different biological systems. In humans, individuals with anxiety disorders have high serum glucocorticoid levels[18,19]. Although the mechanism is not completely understood, this increase suggests possible deregulation of the HPA axis[17].

Some authors have demonstrated adrenal insufficiency in sepsis; but no author has shown that the inflammatory process in sepsis can cause an increase of the gland. Therefore, we can conclude that this increase is actually due to the levels of cortisol caused by the anxious phenotype[20,21].

Sepsis is the result of an overwhelming inflammatory response to infection or an insult that is characterized by leukocyte infiltration, followed by a massive release of inflammatory mediators such as cytokines, reactive oxygen species and nitric oxide (NO)[14]. Stress involves the activation of the HPA axis with its key effector organ: the adrenal gland. In response to adrenocorticotropic hormone (ACTH), the adrenal cortex produces high amounts of cortisol, which exerts activation of catabolic pathways, strong antiinflammatory, and immune-modulating actions[22]. Rapid activation of the HPA axis resulting in increased production of glucocorticoids is crucial to survive sepsis[22,23].

Figure 2. Oxidative damage in animals with an anxious phenotype plus sepsis (24 hours). Animals were submitted to CLP or sham-operated and 24h after surgery animals were euthanized and the (A) serum, (B) adrenal, (C) lung, (D) heart and (E) kidney were removed to the determination of carbonylated proteins. Data were expressed as mean + SD. n=8 each group. $p<0.05$ denoted statistically difference between groups. * different from sham.

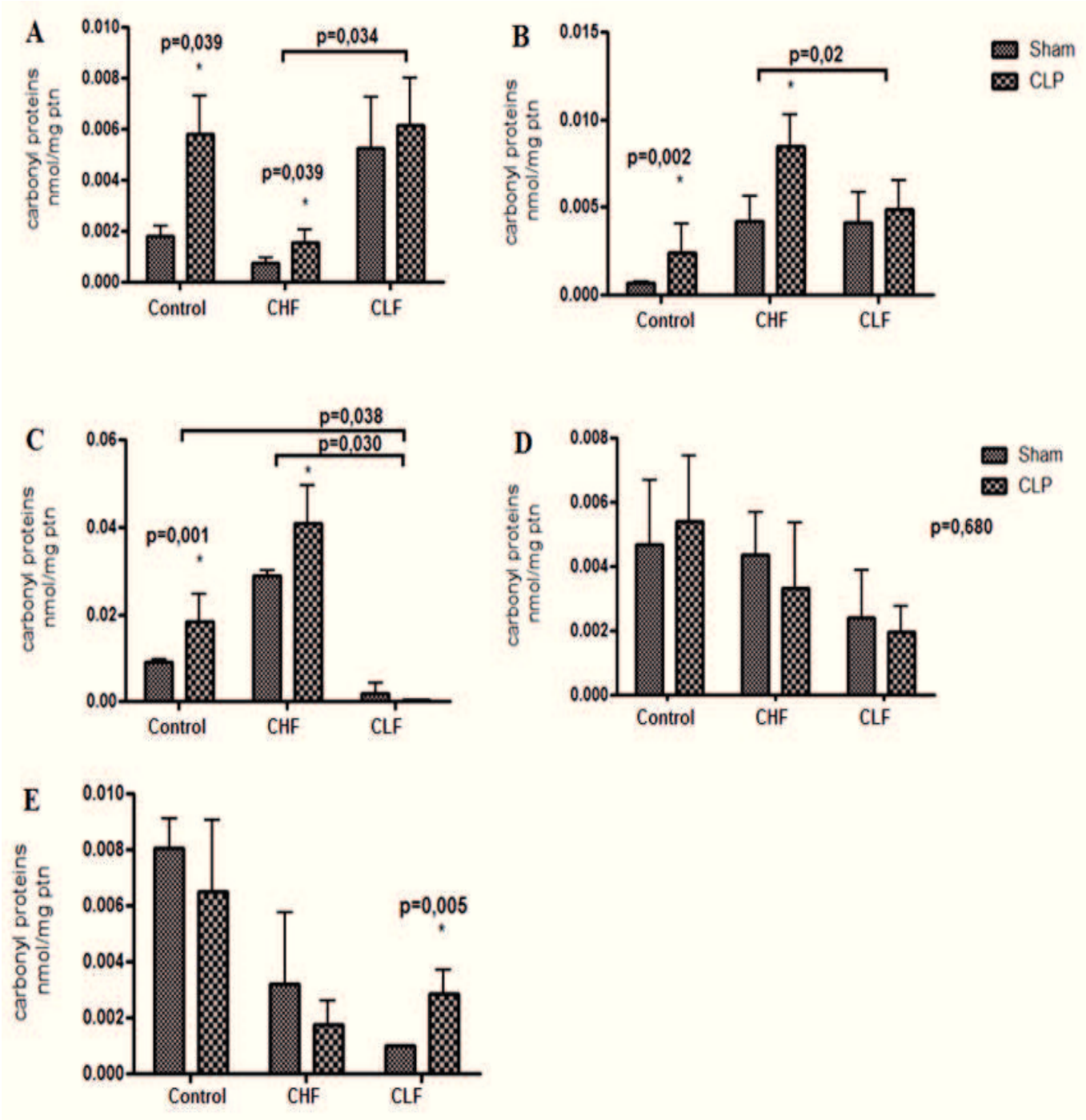
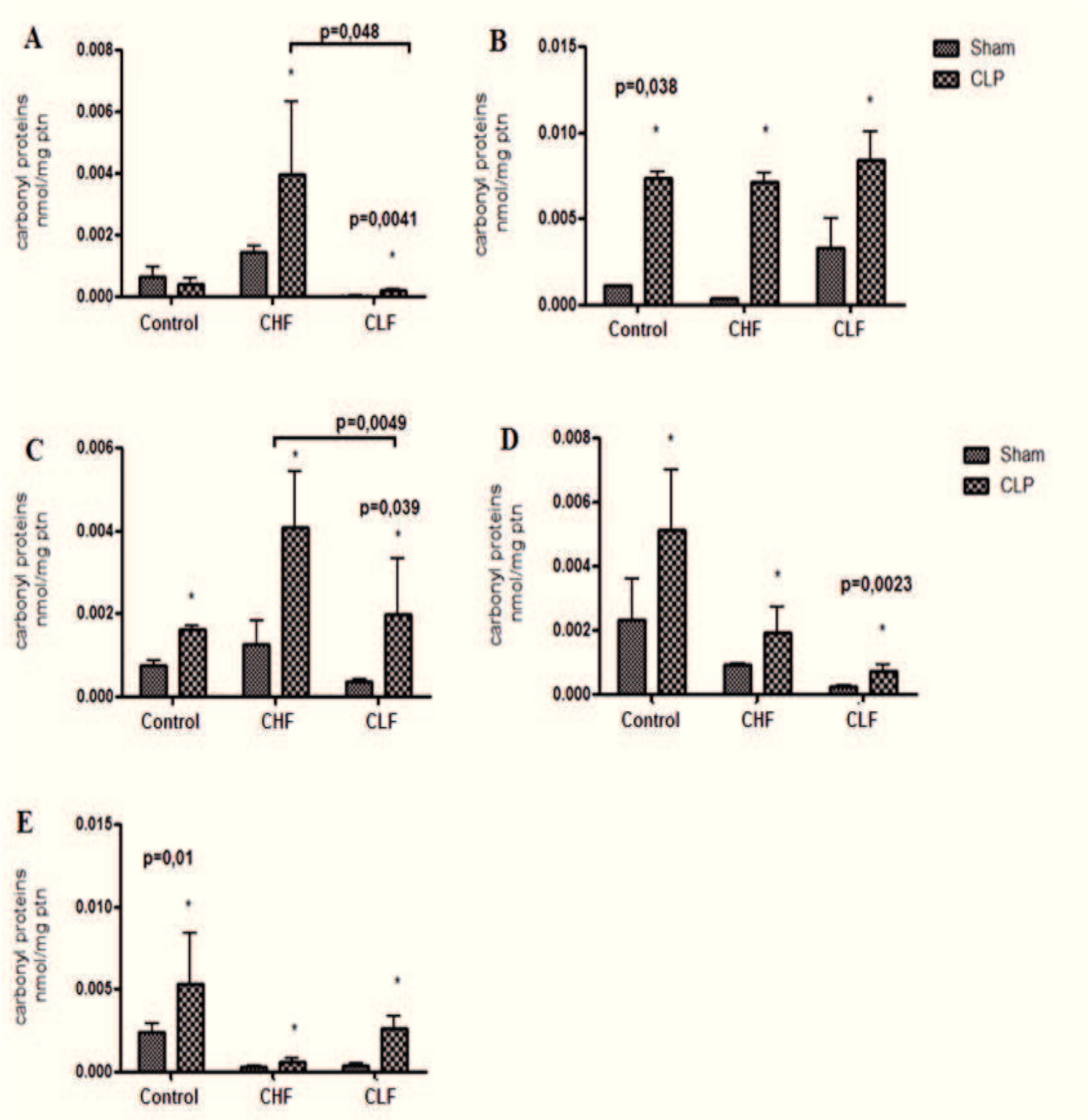


Figure 3. Oxidative damage in animals with an anxious phenotype plus sepsis (10 days). Animals were submitted to CLP or sham-operated and 10 days after surgery animals were euthanized and the (A) serum, (B) adrenal, (C) lung, (D) heart and (E) kidney were removed to the determination of carbonylated proteins. Data were expressed as mean + SD. n=8 each group. $p<0.05$ denoted statistically difference between groups. * different from sham.



In general, glucoA coordinated interaction of numerous cell types and systems within adrenal microenvironment were found to be involved in sustained adrenal glucocorticoid production during sepsis. Among these, adrenocortical–chromaffin cell interactions, the immune–adrenal crosstalk, adrenal vascular system as well as the innervation play the major role[24]. Consequently, any impairment in function of one of these systems can lead to alterations of adrenal glucocorticoid production and ultimately may contribute to the HPA axis dysfunction[22].

Reports in the literature suggest an important association between anxiety and oxidative stress. Recent studies have shown the direct involvement of oxidative stress in anxiety-like behavior in rodents[25,26,27]. In this work it was evaluated the presence of oxidative damage in serum and peripheral organs

of animals with phenotype anxious early and late.

Carbonyl proteins have long been used as a marker of oxidative stress by measure damage in protein[16]. It was noticed the presence of carbonyl proteins in serum of CLP animals and CLP plus CHF 24 hours after sepsis. 10 days after surgery it wasn't difference in carbonyl proteins in CLP control, but this damage occurs in CHF and CLF, thus proving that damage remains because the anxious phenotype.

In adrenal, this damage is perceived in all CLP groups. Sepsis alone changes the adrenal metabolism[24], so it was expected that the CLP animals showed carbonylated proteins. CHF plus CLP presents more damage when compared CLP plus CLF. It was noticed in this study that the damage remains after sepsis late (ten days). Maybe anxiety is not a determining factor for damage in the adrenal, because it is perceived increase in protein carbonyls 10 days in animals that didn't have anxious phenotypes, but others consequences are perceived, for example corticosterone levels[17] and interleukins[14].

When verified carbonyl proteins in lung 24 hours it was noticed increase in CLP control and CLP plus CHF groups. This increase in CLP remains until 10 days in all groups. Lung is a one more vulnerable and a first organ affected in sepsis[28,29]. Following the invasion of microorganism, macrophages and neutrophils immigrate to the site of inflammation and release free radicals to destroy pathogens. Free radicals that are released following activation of immune system lead to peroxidation of lipids, proteins and DNA; moreover, reactive oxygen species (ROS) produced by macrophage cause lung tissue endothelium damage and acute respiratory distress syndrome (ARDS)[30].

Although the effects of anxiety in lung injury are not easily perceivable given that CLP control remains with damage 10 days after sepsis, many studies have reported the effects of anxiety in lung[31,32]. Survivors of critical illnesses frequently have substantial psychological distress, including clinically significant symptoms of anxiety and depression with associated decrements in functioning and quality of life[33,34]. Jutte (2015), shows a study of critically ill patients with respiratory diseases and positive relationship with depression and anxiety[35].

In heart wasn't perceived difference between groups 24 hours after CLP. Probably due to an organ affected later[36]. Oxidative tissue injury is associated with both early and late stage; whereas NO is engaged primarily in late stage cardiovascular depression[37]. Late (10 days after CLP) we noticed the presence of protein carbonyls in all CLP animals, regardless of anxious or not. Probably this damage is result of sepsis, as well control presented damage. This case anxiety seems don't have effect on the amount of protein carbonyls in the heart, but the damage is due to sepsis.

Sepsis, bacteremia and inflammation cause myocardial depression[36]. Subtle abnormalities of the hypothalamic-pituitary-adrenal axis and/or of tissue sensitivity to glucocorticoids are associated with cardiovascular risk factors in patients with the metabolic syndrome. Furthermore, glucocorticoids have direct effects on the heart and blood vessels, mediated by both glucocorticoid and mineralocorticoid receptors and modified by local metabolism of glucocorticoids by the 11 beta-hydroxysteroid dehydrogenase enzymes[38].

A similar behavior in heart it was perceived in kidney early and late. 24 hours after sepsis occurs, damage only CLF plus CLP, however 10 days after sepsis, all CLP groups showed protein damage. In sepsis the cytokine storm and ischemic process were believed as the main cause of kidney and lung failure[39]. A model of lethal sepsis showed kidney and lung dysfunction, assessed by plasma urea and protein infiltrate in BALF[40]. Once again in this case, it seems that anxiety doesn't influence damage to proteins in CLP, because control also has protein carbonyls. Some works report corticosterone effects in kidney[41], this effect may be beneficial when low doses, but in this case, where they show high doses (as shown by Mousovich-Neto et al., 2015) renal damage is evident[42,43].

These findings suggest that an anxious phenotype plus sepsis may induce more pronounced organs damage, and promote more alterations in the HPA axis. These findings may help to explain, at least in part, the common point of the mechanisms involved with the pathophysiology of sepsis and anxiety.

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