

Acute and Chronic Stress and the Inflammatory Response in Hyperprolactinemic Rats

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Key Words

Domperidone • Carrageenan • Paw edema • Cold stress

Abstract

Background/Aim: Prolactin (PRL), a hormone produced by the pituitary gland, has multiple physiological functions, including immunoregulation. PRL can also be secreted in response to stressful stimuli. During stress, PRL has been suggested to oppose the immunosuppressive effects of inflammatory mediators. Therefore, the aim of the present study was to analyze the effects of short- and long-term hyperprolactinemia on the inflammatory response in rats subjected to acute or chronic cold stress. **Methods:** Inflammatory edema was induced by carrageenan in male rats, and hyperprolactinemia was induced by injections of the dopamine receptor antagonist domperidone. The volume of inflammatory edema was measured by plethysmography after carrageenan injection. Additionally, the effects of hyperprolactinemia on body weight and serum corticosterone levels were evaluated. **Results and Conclusion:** Five days of domperidone-induced hyperprolactinemia increased the volume of inflammatory edema. No differences in serum corti-

costerone levels were observed between groups. No significant differences were found among 30 days domperidone-induced hyperprolactinemic animals subjected to acute stress and the inflammatory response observed in chronic hyperprolactinemic animals subjected to chronic stress. The results suggest that short-term hyperprolactinemia has pro-inflammatory effects. Because such an effect was not observed in long-term hyperprolactinemic animals, PRL-induced tolerance seems likely. We suggest that short-term hyperprolactinemia may act as a protective factor in rats subjected to acute stress. These data suggest that hyperprolactinemia and stress interact differentially according to the time period.

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Introduction

Much evidence has implicated prolactin (PRL) in a markedly diverse array of more than 85 different physiological functions [1], including a role in lactation, reproduction, growth and development, water and electrolyte balance, and immunoregulation [2–5]. This peptide hor-

mone has been shown to stimulate T and B cells, natural killer cells, macrophages, neutrophils, CD34+ hematopoietic cells, and antigen-presenting dendritic cells [6–9]. Additionally, we have recently demonstrated a role for PRL in in vivo and in vitro activity of peritoneal macrophages in rats [10, 11].

Although controversy still surrounds the absolute requirement of PRL in immune function, renewed interest has arisen regarding PRL as an immunomodulatory factor maintaining homeostasis under conditions of stress [1]. In this context, lactogenic and growth hormones have been suggested to be necessary for the development and function of the immune system, acting as the first signal to prepare immune cells to proliferate, differentiate, and function [12].

Conversely, stress is an innate reaction to stimuli that influence the normal physiologic balance, also known as homeostasis, and stress frequently has deleterious effects [13]. The biologic response to stress occurs independent of the type of stressor and includes norepinephrine release from different areas of the central nervous system, epinephrine secretion from the adrenal medulla, and hypothalamic-hypophysis-adrenal axis activation [13]. PRL can also be secreted in response to the stressor [14, 15].

Stress can influence or even induce many diseases, from duodenal ulcers to arterial hypertension and skin injuries to depression [16, 17]. In this context, several authors have demonstrated that some stressors, such as those with psychosocial and environmental components, can affect humoral and cellular immunity [15]. Glucocorticoids, PRL [18, 19], and growth hormone are known immunomodulators and are secreted during the stress response [14, 15]. While glucocorticoids have suppressive effects [12], PRL and growth hormone are considered to be stimulators of the immune system [1, 20].

PRL is well known to be secreted in large amounts when animals are subjected to physical or psychological stress, and a marked increase in serum PRL levels has been observed during acute stress [16, 20].

Although the release of PRL induced by the stress stimulus has been well documented [18, 19], the mechanisms that regulate this response and the role of PRL in stress-induced biological changes are still controversial. The prevailing hypothesis is that, during stress, PRL opposes the immunosuppressive effects of glucocorticoids and other inflammatory mediators to maintain homeostasis. This hypothesis is supported by in vivo studies showing a protective effect of PRL after trauma-induced hemorrhage, burn injury, and glucocorticoid administra-

tion and a regulatory effect of PRL on the production of inflammatory mediators [1].

Therefore, the aim of the present study was to analyze the effects of short- and long-term hyperprolactinemia on the inflammatory response in rats subjected to acute or chronic stress. Inflammatory edema was induced by carrageenan in hyperprolactinemic rats. Hyperprolactinemia was induced by injections of the dopamine receptor antagonist domperidone.

Materials and Methods

Animals

Male Wistar rats weighing 240–285 g were used. The animals were housed at constant temperature ($23 \pm 2^\circ\text{C}$) and humidity (70%) under a fixed 12 h light/dark cycle (lights on at 06:00 h) with free access to food and water. All procedures were performed in strict accordance with the guidelines of the Committee of Animals of the Colegio Brasileiro de Experimentação Animal (COBEA) and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. We attempted to minimize the number of rats used, and every effort was made to ensure that no rat suffered unnecessarily.

Experimental Hyperprolactinemia

Hyperprolactinemia was induced by domperidone administration. Although domperidone does not cross the blood-brain barrier, it acts on the hypophysis, increasing PRL secretion [21, 22]. Domperidone was administered at a dose of 1.7 mg/kg (s.c.) 3 times per day (07:30, 15:00, and 22:00 h). The duration of treatment was 8 consecutive days or 33 consecutive days.

Carrageenan-Induced Paw Edema

Carrageenan-induced paw edema was induced by a subcutaneous injection of 0.1 ml carrageenan per rat into the left hind paw. The volume (ml) of the induced edema was measured with a plethysmometer (model 7150, Ugo Basile). Measurements were made immediately before and 1, 2, 3, 4, 6, 8, and 24 h after carrageenan injection to determine differences in paw volume up to the tibiotarsal joint [23, 24].

Drugs

Carrageenan (κ -carrageenan, Sigma), an inducer of inflammatory responses, was suspended in 0.5% Ringer solution and subcutaneously injected (subplantar) in the cell tissue of the left paw. Sodium chloride (NaCl) was used as the physiologic saline solution. The dopamine D_2 receptor-specific antagonist domperidone, 5-chloro-1-[1-{3-(2,3-dihydro-2-oxo-1H-benzimidazole)propyl}-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one (Janssen-Cilag, Brazil), was suspended in saline solution (0.9% Tween-80; approximately 1:0.002, v:v) and administered subcutaneously at a dose of 1.7 mg/kg 3 times per day at 07:30, 15:00, and 22:00 h. Domperidone was dissolved in volumes that permitted injections of 1.0 ml/kg body weight. The control group of rats received volumes of vehicle equal to those of the experimental groups (1.0 ml/kg).

Serum PRL Level Quantification (Radioimmunoassay)

For PRL measurements, trunk blood was collected in tubes and centrifuged (250 g for 20 min), and the serum was frozen at -20°C until assayed for PRL content. PRL levels were measured by radioimmunoassay using materials supplied by the National Institute of Diabetes and Digestive and Kidney Diseases (Bethesda, Md., USA). The concentrations were measured as ng/ml, based on RP-3 as the standard. Assay sensitivity and the intra-assay coefficient of variation for PRL were 1.5 ng and 5.5%, respectively.

Serum Corticosterone Level Quantification

Trunk blood samples were collected and centrifuged (250 g for 20 min). Sera were stored at -20°C until assayed for corticosterone content. Serum corticosterone levels were measured by radioimmunoassay. Serum corticosterone levels were measured using a Universal Coat-a-Count kit (DPC, Los Angeles, Calif., USA). Serum samples for corticosterone determination were assayed in duplicate. Assay sensitivity was 1.77 ng/ml, and the intra-assay coefficient of variation was 3.98%.

Statistical Analysis

Data obtained in experiments 1 and 2, the volumes of inflammatory edema and the areas under the curve, as well as body weight and adrenal gland weight, were analyzed using ANOVA followed by the Student-Newman-Keuls test. Serum corticosterone and PRL levels were analyzed by Kruskal-Wallis test followed by Mann-Whitney U test. Data were analyzed using GraphPad InStat and GraphPad Prism software (GraphPad, San Diego, Calif., USA).

Experimental Design

Experiment 1: Effects of 5-day domperidone-induced hyperprolactinemia on carrageenan-induced inflammatory paw edema in rats subjected to acute cold stress.

40 male rats were randomly and equally divided into four groups ($n = 10$) according to treatment. Animals in group D were treated with domperidone (1.7 mg/kg, s.c.) 3 times per day (07:30, 15:30, and 22:00 h) for 8 consecutive days. Animals in group V were treated with a solution of 0.9% saline/Tween-80 following the same schedule. Animals in group VS were treated the same as group V but received cold stress. Animals in group DS were treated the same as group D but received cold stress. On the 6th day of treatment and 1.5 h after the first injection of domperidone, groups VS and D were subjected to cold stress (3°C) for 2 h, while groups V and D remained in their cages in the experimentation room. Cold stress consisted of placing animals of the stress groups inside a refrigerator at 3°C for 2 h. One hour after the end of the cold stress session, all animals received 0.1 ml carrageenan (0.5%) injection into the left hind paw for edema induction. The volume (μl) of edema was measured with a plethysmometer as described above. On the 8th day, 1.5 h after the last injection of domperidone or vehicle, all animals were weighed and decapitated, and their blood was collected for evaluation of serum corticosterone and PRL levels. Adrenal glands were then removed and weighed. The relative weight of both adrenal glands (mg) and body weight (mg) were calculated. Variations in body weight (weight on day 8 minus weight on day 1) were also calculated.

Experiment 2: Effects of 30 days of domperidone-induced hyperprolactinemia on carrageenan-induced inflammatory paw edema in rats subjected to acute or chronic cold stress.

40 male rats were randomly and equally divided into four groups ($n = 10$): vehicle + acute stress (VAS), domperidone + acute stress (DAS), vehicle + chronic stress (VCS), domperidone + chronic stress (DCS). Hyperprolactinemia was induced by domperidone administration (1.7 mg/kg, s.c.) 3 times per day (07:30, 15:00, and 22:00 h) for 33 consecutive days. Cold stress consisted of placing animals of the stress groups inside a refrigerator at 3°C for 3 h (08:00–11:00 h). Animals of the acute stress groups were subjected to a single session of cold stress on the 31st day after domperidone injection. Animals of the chronic stress groups were subjected to cold stress sessions for 25 consecutive days, from the 6th to 31st days of treatment. On day 31 and 1 h after the end of the stress session, all animals were injected with carrageenan into the left hind paw as previously described. On the 33rd day and 1.5 h after the first daily injection of domperidone or vehicle, all animals were decapitated, and their blood was collected to quantify serum corticosterone and PRL levels.

Results

Effect of Short-Term Hyperprolactinemia and Stress on Inflammatory Response

The volume (μl) of inflammatory edema induced by carrageenan in rats previously treated for 5 days with domperidone and subjected to 2 h of acute cold stress was determined. Differences among groups were found 1 h ($F_{3,36} = 9.282$, $p = 0.0001$), 2 h ($F_{3,36} = 5.937$, $p = 0.0021$), 3 h ($F_{3,36} = 5.364$, $p = 0.0037$), 4 h ($F_{3,36} = 4.470$, $p = 0.0091$), 6 h ($F_{3,36} = 7.040$, $p = 0.0008$), 8 h ($F_{3,36} = 8.765$, $p = 0.0002$), and 24 h ($F_{3,36} = 7.656$, $p = 0.0004$) after carrageenan injection. After 1 h, the volume of inflammatory edema induced by carrageenan was greater in animals in group D compared with groups V ($p < 0.001$), VS ($p < 0.001$), and DS ($p < 0.05$). After 2 h, group VS exhibited a less intense inflammatory response than groups D ($p < 0.01$) and DS ($p < 0.01$). After 3 h, group VS exhibited a less intense inflammatory response compared with groups D ($p < 0.01$) and DS ($p < 0.05$). Moreover, the inflammatory response in group VS was less intense than group V ($p < 0.05$). After 4 h, both groups D ($p < 0.01$) and V ($p < 0.05$) exhibited inflammatory responses greater than group VS. After 6 h, the volume of inflammatory edema remained smaller in group VS than in groups D ($p < 0.001$), DS ($p < 0.05$), and V ($p < 0.05$). After 8 h, the inflammatory response in group VS was smaller compared with groups D ($p < 0.001$) and DS ($p < 0.001$). Group V exhibited a less intense inflammatory response compared with groups D ($p < 0.05$) and DS ($p < 0.05$). Finally, 24 h after carrageenan injection, the volume of inflammatory edema

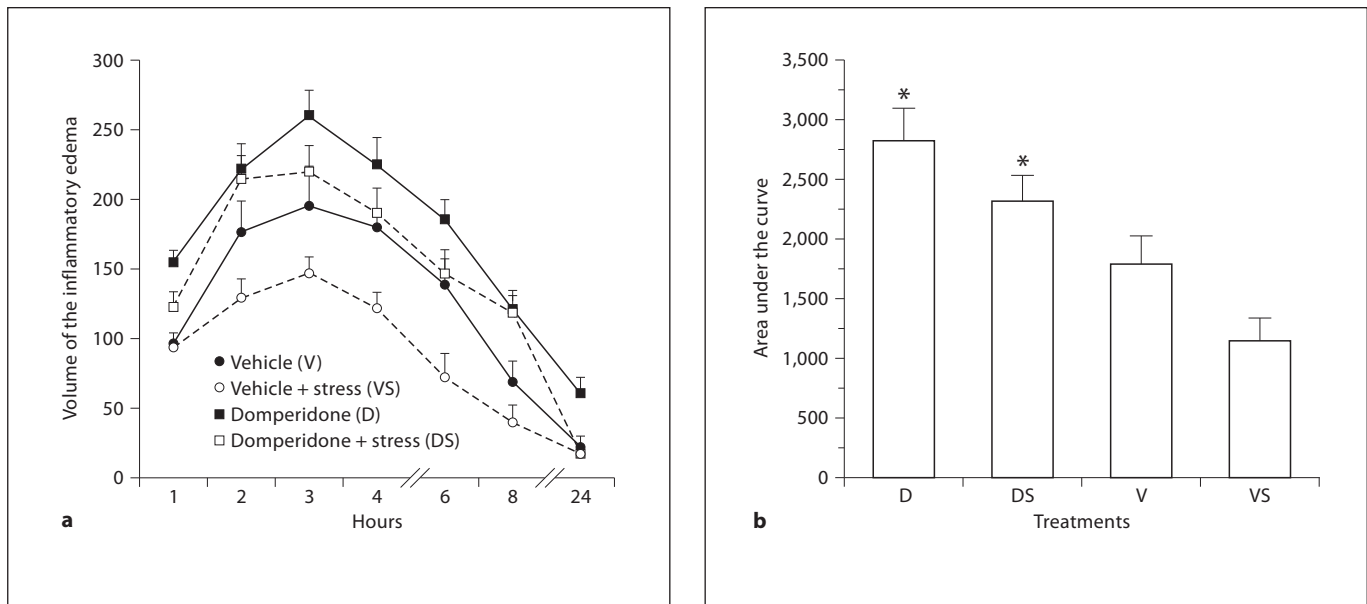


Fig. 1. Effects of hyperprolactinemia induced by 5-day domperidone treatment on carrageenan-induced inflammatory paw edema in rats subjected to cold stress (3°C): **a** kinetics and **b** area under the curve. Data are expressed as mean $\pm$ SE. * $p < 0.05$ as compared with respective vehicle group (ANOVA followed by Student-Newman-Keuls test; $n = 10$).

Table 1. Serum corticosterone and PRL levels (ng/ml) in rats 8 days after the beginning of domperidone (DOMP) treatment and submitted or not to cold stress (3°C) (mean $\pm$ SE, $n = 10$)

Parameter	Groups			
	no stress		stress	
	vehicle	DOMP ¹	vehicle	DOMP ¹
Corticosterone ²	289.8 $\pm$ 47.7	299.6 $\pm$ 43.1	276.4 $\pm$ 47.7	202.5 $\pm$ 21.2
PRL	9.4 $\pm$ 2.1	24.9 $\pm$ 4.2**	6.9 $\pm$ 1.6	32.2 $\pm$ 8.4**

** $p < 0.01$ (Mann-Whitney U test) as compared with the respective vehicle group.

¹ DOMP 1.7 mg/kg, s.c., 3 times per day (07:30, 15:00, and 22:00 h).

² There were no significant differences among the experimental groups and their corresponding controls ($p > 0.05$), Kruskal-Wallis test.

ma was greater in group D compared with groups VS ($p < 0.001$), DS ($p < 0.01$), and V ($p < 0.01$). The analysis of the areas under the curves also showed significant differences ($F_{3,36} = 9.83$, $p < 0.0001$) (fig. 1).

Effect of Short-Term Hyperprolactinemia and Stress on Weight of Adrenal Glands

No significant differences in the absolute weight of the adrenal glands were observed between groups ($F_{3,36} =$

1.246, $p = 0.3076$). However, the relative weight of the adrenal glands in group VS was less ($F_{3,36} = 3.106$, $p = 0.0384$) than groups V ($p < 0.05$) and DS ($p < 0.05$) (fig. 2).

Effect of Short-Term Hyperprolactinemia and Stress on Serum Levels of Corticosterone and Prolactin

No significant differences in serum corticosterone levels were observed between groups (KW = 3.88, $p = 0.28$). However, domperidone administration significantly in-

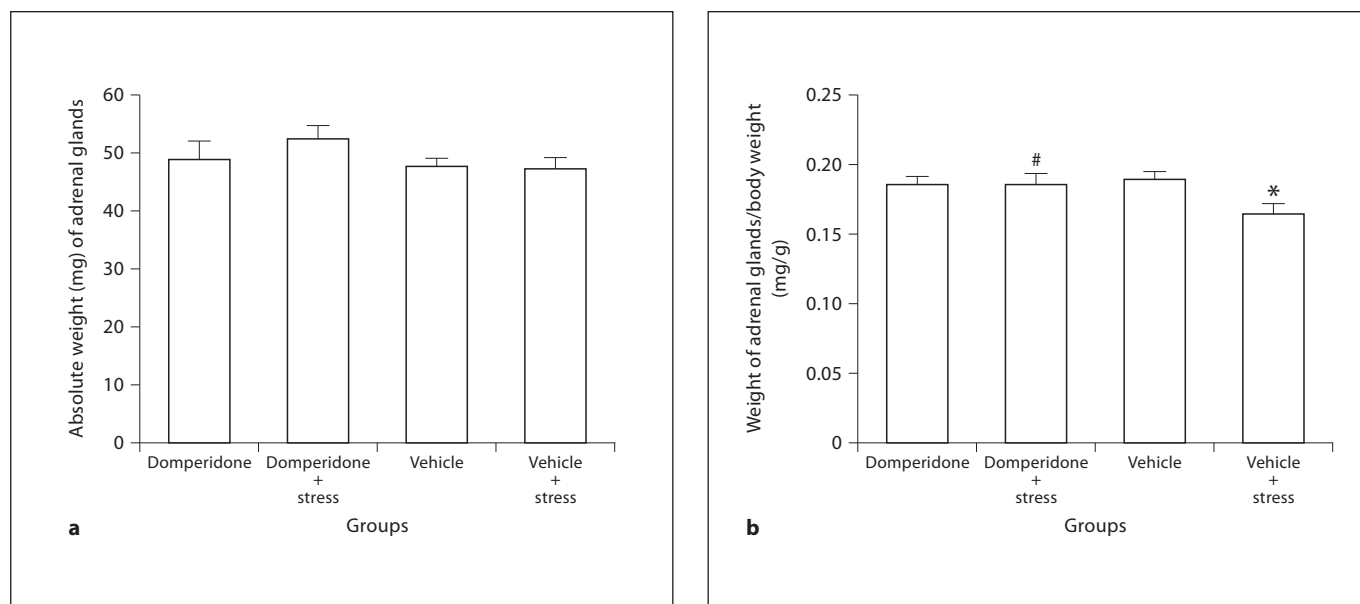


Fig. 2. Absolute weight (mg) of the adrenal glands (**a**) and weight of the adrenal glands (mg/g) relative to corporeal weight (**b**) in rats treated for 8 days with domperidone or vehicle and subjected to cold stress (3°C). Data are expressed as mean $\pm$ SE. * $p < 0.05$ as compared with vehicle group; # $p < 0.05$ as compared with vehicle + stress group (ANOVA, Student-Newman-Keuls; $n = 10$).

Table 2. Body weight (g) of rats treated with domperidone (DOMP) for 8 days and submitted or not to cold stress (3°C) (mean $\pm$ SE, $n = 10$)

Parameter	Groups			
	no stress		stress	
	vehicle	DOMP ¹	vehicle	DOMP ¹
Initial weight, g	278.0 $\pm$ 5.1	280.0 $\pm$ 4.8	278.1 $\pm$ 4.9	279.6 $\pm$ 4.7
Weight 8 days after the beginning of treatment	283.9 $\pm$ 10.6	281.7 $\pm$ 9.6	288.1 $\pm$ 7.6	284.5 $\pm$ 7.8
Increasing of corporeal weight	5.9 $\pm$ 1.0	1.8 $\pm$ 1.9**	10.0 $\pm$ 1.4	4.9 $\pm$ 2.2

** $p < 0.01$ in relation to stress vehicle group (ANOVA followed by the Student-Newman-Keuls test).

¹ DOMP 1.7 mg/kg, s.c., 3 times per day (07:30; 15:00, and 22:00 h) for 8 days.

creased ($U = 90.5$, $p = 0.001$) serum PRL levels in animals regardless of whether they were subjected to stress (table 1).

Effect of Short-Term Hyperprolactinemia and Stress on Body Weight

No differences in body weight were observed between groups at the end of the experiment ($F_{3,36} = 1.027$, $p = 0.8419$). Paradoxically, a greater decrease in body weight

was observed in group D compared with group VS ($F_{3,36} = 3.893$, $p = 0.0165$; Student-Newman-Keuls test: $q = 4.780$, $p < 0.01$) (table 2).

Effect of Long-Term Hyperprolactinemia and Stress on Inflammatory Response

The second experiment evaluated the kinetics of acute inflammatory edema induced by carrageenan. 1, 2, 3, 4, and 24 h after carrageenan injection, no differences were

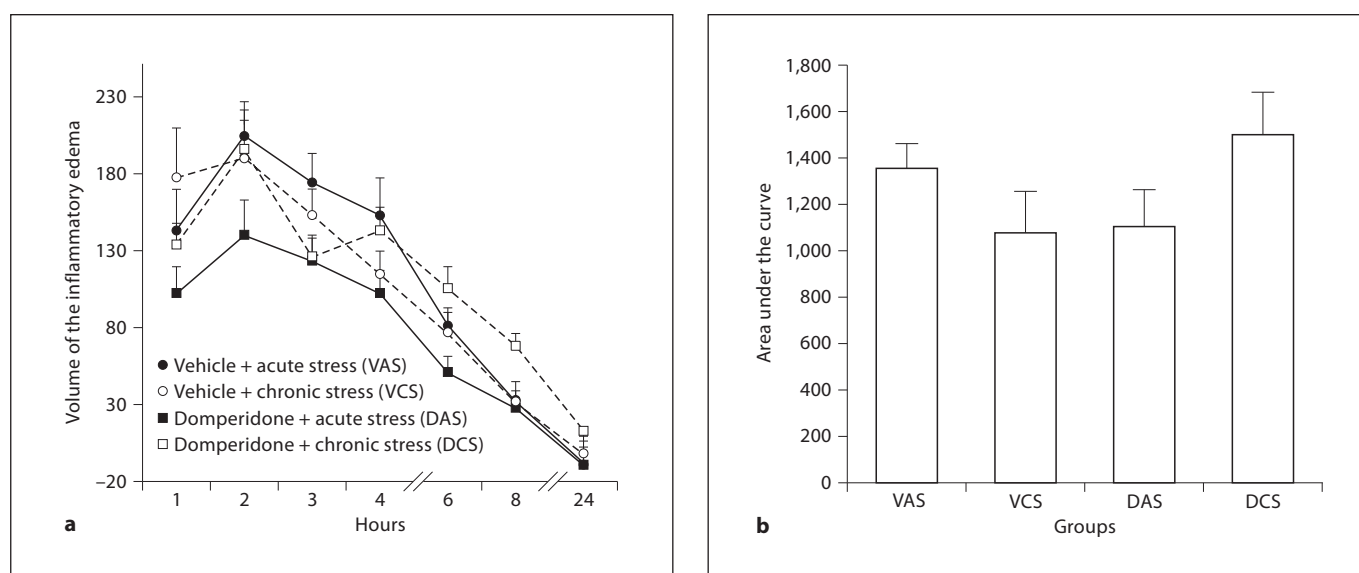


Fig. 3. Effects of hyperprolactinemia induced by 30-day domperidone treatment on carrageenan-induced inflammatory paw edema in rats subjected to acute stress or chronic stress: **a** kinetics and **b** area under the curve. Data are expressed as mean $\pm$ SE. $p > 0.05$ ($n = 10$).

Table 3. Serum corticosterone and PRL levels (ng/ml) in rats treated 33 days with domperidone (DOMP)¹ or vehicle and submitted to acute² or chronic³ cold stress (3°C) (mean $\pm$ SE, $n = 10$)

Parameter	Groups				
	vehicle			DOMP ¹	
	no stress	acute stress	chronic stress	acute stress	chronic stress
Corticosterone ⁴	242.4 $\pm$ 28.6	232.6 $\pm$ 33.5	159.0 $\pm$ 23.6	152.3 $\pm$ 29.6	132.6 $\pm$ 13.6
PRL	8.1 $\pm$ 1.5	25.5 $\pm$ 18.9	3.2 $\pm$ 0.2	81.1 $\pm$ 17.9*	119.4 $\pm$ 16.5*

¹ DOMP 1.7 mg/kg, s.c., 3 times per day (07:30; 15:00, and 22:00 h).

² Acute stress: 3 h in cold (3°C).

³ Chronic stress: 3 h in cold (3°C) per day for 25 days.

⁴ There were no significant differences among the experimental groups and their corresponding controls ($p > 0.05$), Kruskal-Wallis test.

* $p < 0.05$ (Mann-Whitney U test) as compared with respective vehicle group.

observed between groups ($p > 0.05$). However, after 6 h ($F_{3,36} = 2.961$, $p = 0.04$) and 8 h ($F_{3,36} = 3.34$, $p = 0.03$), the volume of inflammatory edema measured in group DAS was less compared with group DCS. However, the analysis of the area under the curve did not reveal any significant differences between groups ($F_{3,36} = 1.72$, $p = 0.18$) (fig. 3).

Effect of Long-Term Hyperprolactinemia and Stress on Weight of Adrenal Glands

The absolute weight of the adrenal glands ($F_{3,36} = 6.70$, $p < 0.001$), as well as the relative weight ($F_{3,36} = 3.04$, $p < 0.04$), were different between groups. The weight of the adrenal glands in group DCS was greater ($p < 0.05$) than groups VCS and VAS. Moreover, the relative weight of the adrenal glands in group DCS was greater than group VCS ($p < 0.05$) (fig. 4).

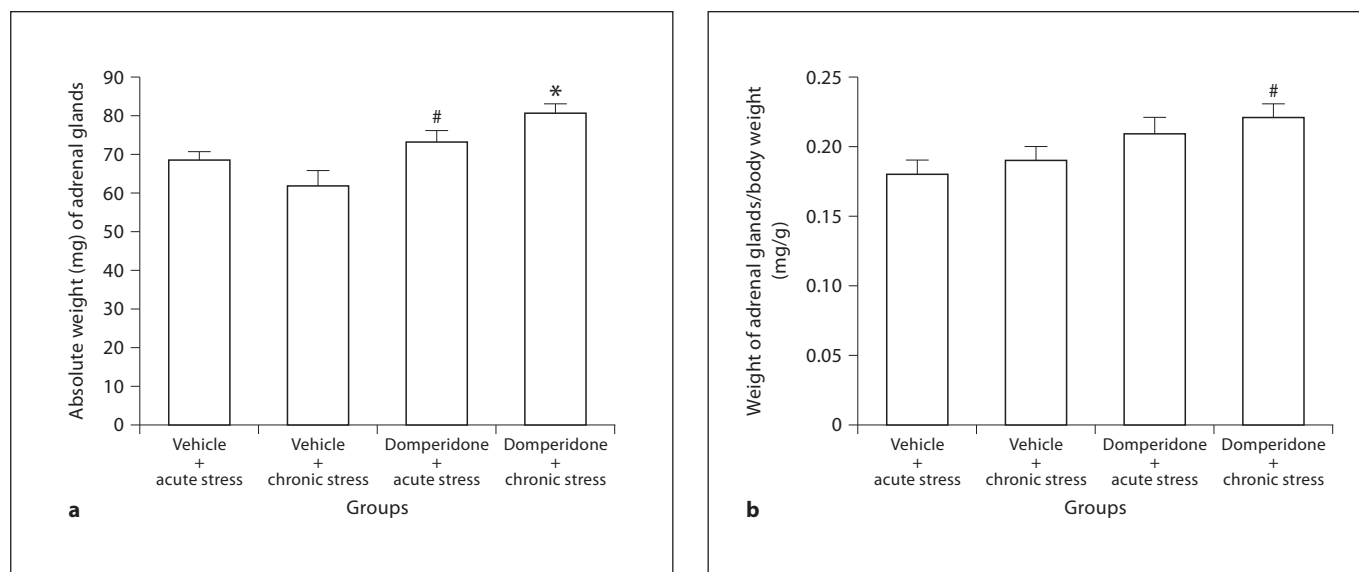


Fig. 4. Absolute weight (mg) of the adrenal glands (**a**) and weight of the adrenal glands (mg/g) relative to corporeal weight (**b**) of rats treated for 33 days with domperidone or vehicle and subjected to acute or chronic stress generated by cold (3°C). [#] $p < 0.05$ as compared with vehicle + chronic stress group; ^{*} $p < 0.05$ as compared with both vehicle groups (ANOVA followed by Student-Newman-Keuls; $n = 10$).

Effect of Long-Term Hyperprolactinemia and Stress on Serum Levels of Corticosterone and Prolactin

The change observed in relative weight of adrenal glands was not accompanied by changes in serum corticosterone levels (KW = 6.27, $p = 0.10$) (table 3). Again, domperidone administration increased serum PRL levels (KW = 23.96, $p < 0.001$) (table 3).

Effect of Long-Term Hyperprolactinemia and Stress on Body Weight

No significant differences were found in body weight during the 33 days of treatment among groups ($p > 0.05$) (table 4).

Discussion

The final response to stress may lead to changes involving homeostasis of the central nervous system, peripheral nervous system, and immune system [25, 26]. Selye [27] posited that stress is the temporary adaptability of a biologic system and can be defined as 'a nonspecific response of the organism to any demand.' This response, the so-called 'general adaptation syndrome', is characterized by stimulation of the adrenal glands, involution of lymphatic organs, the presence of gastrointestinal ulcers,

Table 4. Accumulated increasing of body weight (g) of rats treated for 33 days with domperidone¹ (DOMP) or vehicle and submitted to acute² or chronic³ stress generated by cold (3°C) (mean $\pm$ SE, $n = 10$)

Groups ⁴	Increase of weight by:		
	day 10	day 20	day 30
VAS	23.8 $\pm$ 2.2	37.1 $\pm$ 5.4	53.3 $\pm$ 5.5
VCS	9.1 $\pm$ 20.1	19.3 $\pm$ 20.5	41.8 $\pm$ 21.7
DAS	21.8 $\pm$ 2.2	35.2 $\pm$ 2.8	52.9 $\pm$ 3.2
DCS	20.5 $\pm$ 2.2	33.3 $\pm$ 3.8	53.4 $\pm$ 4.5

VAS = Vehicle + acute stress; VCS = vehicle + chronic stress; DAS = DOMP + acute stress; DCS = DOMP + chronic stress.

¹ 1.7 mg/kg, s.c., 3 times/day (07:30; 15:00, and 22:00 h).

² Acute stress: 3 h in cold (3°C).

³ Chronic stress: 3 h in cold (3°C) per day for 25 days.

⁴ There were no significant differences among the experimental groups ($p > 0.05$) (ANOVA followed by Student-Newman-Keuls test).

weight loss, and alterations in chemical mediation of the organism.

Domperidone is a peripheral dopamine antagonist that acts primarily at the chemoreceptor trigger zone on the floor of the fourth ventricle and on dopamine recep-

tors in the gut [28]. Domperidone-induced PRL release is a model of hyperprolactinemia. Therefore, domperidone was used in the present study to investigate the participation of PRL in the effects of stress on the inflammatory response. Both physical and psychological stressors lead to physiologic responses, such as increased release of PRL. Blockade of dopamine D₂ receptors by domperidone increases serum PRL levels without dramatically changing circulating levels of other hypophyseal hormones. Importantly, hyperprolactinemia induced by domperidone is far above the physiologic levels of male rat.

Several researchers have shown the anti-inflammatory effects of acute stress [29–31]. However, many studies using animal models revealed that different types of acute stress are accompanied by a reduction in immune system activity [32, 33]. In the present work, domperidone-induced hyperprolactinemia for 5 days increased the volume of inflammatory edema and reversed the decrease of this edema in animals subjected to cold stress. Nevertheless, no significant differences in serum corticosterone levels were observed between groups. Although these results suggest that corticosterone may not be involved in the stress-induced changes reported here, possible changes in corticosterone levels in other time points cannot be discharged. Adrenal gland relative weight was reduced in stressed animals. This stress-induced functional change in this gland might be part of the modulatory processes of the inflammatory response reported here. Concerning body weight of rats treated with domperidone during 8 days, non-stressed domperidone-treated animals presented less increase in corporeal weight as compared to stressed vehicle-treated rats. This may be due to an indirect effect of domperidone action increasing inflammatory response, perhaps interfering with food intake.

Under stressful conditions, PRL is required to equilibrate the possible negative effects of glucocorticoids and other immune or inflammatory mediators. This interpretation is supported by *in vitro* studies that demonstrated the protective role of PRL in preventing glucocorticoid-induced lymphocyte cell death, as well as by *in vivo* studies showing that PRL improves macrophage [10] and splenocyte function following trauma-induced hemorrhage and infection [9]. Moreover, PRL can reverse the physiologic inflammatory antagonist effect of adrenocorticotrophic hormone, possibly by decreasing the release of glucocorticoids [1].

The possible involvement of PRL in stress response mechanisms is supported by several findings: (1) PRL is released in response to exposure to different stressors,

(2) chronic stress induces the expression of the long form of PRL receptors (PRL-R) in choroid plexus cells, and (3) administration of PRL into the cerebral ventricles prevents the stress-induced formation of gastric ulcers and has antidepressant effects during forced swimming. Furthermore, neuroendocrine stress responses were found to be attenuated in hyperprolactinemia conditions [34]. Additionally, PRL has been shown to antagonize the immunosuppressive effects of transforming growth factor- β , tumor necrosis factor- α , and corticosterone. PRL may also enhance the recovery of the hematopoietic system [9].

The present study suggests that short-term hyperprolactinemia has a pro-inflammatory effect and that PRL may exert a protective role in organisms subjected to acute stress. Supporting this hypothesis, we have recently shown that domperidone-induced hyperprolactinemia can improve the generation of oxidative bursts and phagocytosis by peritoneal macrophages [10]. Thus, if the acute stress causes a decrease in the inflammatory response, and if one of the physiologic manifestations of this stimulation is PRL release, then a prior condition of acute hyperprolactinemia may potentiate the anti-inflammatory effects of the stress. Accordingly, the results are consistent with this possibility and demonstrate a pro-inflammatory effect of acute hyperprolactinemia under conditions of cold stress.

The effects of PRL on the edematogenic response are also consistent with previous observations showing that a few hours of systemic hyperprolactinemia do not have central or peripheral effects, although chronically hyperprolactinemic animals subjected to acute stress had an inflammatory response slightly less than chronically hyperprolactinemic animals subjected to chronic stress. This result suggests that in animals with normal serum levels of PRL, the duration of stress exposure does not have major effects on the inflammatory response. Prolonged stress, in this case 25 consecutive days, may produce an adaptive response or tolerance in animals, such that an inflammatory response may not be engaged in chronically hyperprolactinemic rats. Moreover, Young and Akil [35] showed that electroshock stress applied for 14 days did not alter PRL levels, suggesting that repeated sessions of stress exposure can induce such adaptations in animals.

Concerning the body weight of rats treated chronically for 33 days, hyperprolactinemia was not associated with increased body weight. These results are consistent with previous data. Hyperprolactinemia increases body weight in females but not in the males [22, 36–38], sug-

gesting that the effect of PRL on body weight may be gender-specific. Similarly, PRL is known to stimulate the ingestion of food, both in males and females of some animal species [39–43]. Consistently, adrenal hypertrophy shown here was previously reported in rats treated with domperidone [44].

Finally, these results suggest that short-term hyperprolactinemia has pro-inflammatory effects. Such effect might not occur in long-term hyperprolactinemic rats for edematogenic and inflammatory activity of carrageenan. In this context, we recently demonstrated the in vitro ef-

fects of PRL (10 and 100 nM) on peritoneal macrophage activity in female rats. 30 min after incubation with PRL, macrophage activity generally tended to decrease. After 2 h, PRL decreased oxidative bursts and increased the percentage while decreasing the intensity of phagocytosis. However, incubation with PRL for 4 h increased macrophage activity [11]. Taken together, these results suggest that the in vitro effects of PRL are biphasic and depend on the incubation period. Furthermore, we suggest that short-term hyperprolactinemia may have a protective effect in rats subjected to acute stress.

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Erratum

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