Clin Oral Invest (2010) 14:153–160
DOI 10.1007/s00784-009-0280-6

ORIGINAL ARTICLE

Bruxism affects stress responses in stressed rats

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Received: 29 June 2008 / Accepted: 28 April 2009 / Published online: 2 June 2009

Abstract It has been proposed that suppression of stress-related emotional responses leads to the simultaneous activation of both sympathetic and parasympathetic divisions of the autonomic nervous system (ANS) and that the expression of these emotional states has a protective effect against ulcerogenesis. In the present study, we investigated whether stress-induced bruxism activity (SBA) has a physiological effect of on the stress-induced changes of the stomach, thymus, and spleen as well as blood leukocytes, cortisol, and adrenaline. This study demonstrated that SBA attenuated the stress-induced ulcer genesis as well as degenerative changes of thymus and spleen. SBA also attenuated increases of adrenaline, cortisol, and neutrophils in the blood. In conclusion, expression of aggression through SBA during stress exposure attenuates both stress-induced ANS response, including gastric ulcer formation.

Keywords Restraint · Bruxism · Stomach ulcer · Neutrophil · Adrenaline

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Introduction

It has been proposed that the manifestation of stress-elicited emotions is beneficial because it reduces sympathetic arousal and restores autonomic balance [1]. Conversely, the suppression of stress-related emotional responses leads to the simultaneous activation of the sympathetic and parasympathetic nervous system, which may result in tension and organic disease [2].

Weiss JM et al. [3] demonstrated that the number of gastric lesions resulting from unpredictable shock were fewer in rats that were capable of an aggressive response compared with rats deprived of this option. Other studies have shown that rats allowed to gnaw a wooden block following shock and restraint had fewer gastric lesions than control rats [4–6]. Tanaka T et al. [7] demonstrated that expressing aggression during stress exposure attenuated increases in noradrenalin (NA) release in the rat amygdala as well as gastric ulcer formation. Thus, it appears that the expression of stress-induced emotion may have a protective effect in situations that may be ulcerogenic.

In animal models where an emotional state was elicited by hypothalamic stimulation, increases in masseter muscle activity associated with bruxism were observed [8–10]. Furthermore, clinical research also suggests that emotional and psychological stresses are associated with bruxism as indicated by an increase in jaw muscle electromyographic (EMG) activity and an increase of catecholamine levels [11–14].

Although previous studies suggest that there is a close relationship between emotional stress associated with bruxism and stress-induced ulcer formation [7], the physiological significance of stress-induced masticatory parafunction, such as bruxism, is not well understood. A study of masticatory parafunction in animals conditioned to an

emotionally stressful environment will further clarify the association between emotional stress and bruxism and also the physiological significance thereof.

The present study was designed to investigate stress-induced bruxism activity (SBA) in rats. Masseter muscle EMG activity during restraint stress and the physiological effect of SBA, such as the stress-induced changes of various tissues and organs, were evaluated. We hypothesized that SBA induced by restraint stress has a protective effect in ulcerogenic situations, which prevents allostatic overload.

Materials and methods

Animals

A total of 35 male Wistar rats (7–8 weeks old) were group-housed (five per cage) under controlled temperature (22±3°C) and lighting conditions (12:12 h light: dark cycle), with free access to food and water. To avoid diurnal variations in hormone expression that might effects cytokine production, we conducted all experiments between 1000 and 1500 hours.

Restraint stress and measurement of SBA

Restraint stress was induced by securing the rat on a wooden board (18×25 cm) in a supine position (20 rats). All four legs were fixed at an angle of 45° to the body midline with adhesive tape. Restrained animals were exposed to restraint stress for 360 min. Control rats were not exposed to restraint and had free access to food and water (15 rats). The experimental procedures used in this study were reviewed and approved by the Committee of Ethics on Animal Experiments of Kanagawa Dental College and were carried out under the Guidelines for Animal Experimentation of Kanagawa Dental College.

To record the length of SBA, a needle electrode was inserted directly into the masseter muscles bilaterally for recording by EMG (EMG, SN 700, Tecno Science, Tokyo, Japan). Electromyograms showed muscle activity; we measured the duration of SBA. The cut-off limit is 5% of the maximum potential of masseter muscles. Head and neck movements of the rats are picked up by the electrical measuring device.

Therefore, to obtain a true SBA, EMG activity due to head movement had to be subtracted from total EMG activity. Thus, a bruxism-monitoring system was developed to monitor head movement. This system consisted of a two-axis accelerometer (ADXL202E, Analog Devices, USA), which recorded X–Y axis body movements. A video recording system, which consisted of a time-lapse video-cassette recorder (TLV-3060, Daiwa, Tokyo, Japan), was also used. Bruxism analyzing software (G1 System, Tokyo, Japan) was developed and used to analyze the data from the bruxism-monitoring system.

Preparation of specimens

Following 360 min of restraint, rats were exsanguinated by heart puncture under general anesthesia. Blood samples were taken and allowed to coagulate for 10 min at room temperature before centrifugation to obtain serum samples. Aliquots of serum were immediately stored and frozen at −80°C until use. The spleen and thymus were removed and weighed (wet weight), then immersion-fixed in 10% formalin solution followed by histological sectioning for observation of histological changes. The stomach was also removed to evaluate ulcer formation.

Measurement of stomach lesions

The stomach was opened along the greater curvature and pinned onto a board as a fresh specimen. The severity of stomach lesions was scored while fresh under a dissecting microscope. Scoring included the number and cumulative length of the rubefacient area and discrete glandular lesions filled with clotted blood. We also measured the rubefacient area of the stomach mucosa (RAS), using a visual analysis system (WinRoof, Ver. 5.5, Mitani Shoji, Tokyo, Japan; Fig. 1). Different color values (i.e., red, green, and blue) at the most whitish as well as the blushing part of the stomach mucosal surfaces were recorded for each animal. A cut-off value was calculated by subtracting the highest blushing value from the highest whitish value. This difference was divided in half and added to the highest blushing value. Then, the blushing area of the mucosal surface was visualized as the RAS. Following RAS visualization, the stomach was immersion-fixed in 10% formalin solution followed by histological sectioning for observation of histological changes.

Measurements of blood adrenaline and cortisol levels

Serum samples were analyzed to evaluate adrenaline and cortisol levels. Cortisol levels were measured by a cortisol radioimmunoassay (RIA) kit (Immunotech, USA), using anti-cortisol mouse monoclonal antibody as described previously [15].

Catecholamines (specifically, adrenaline in the blood) were analyzed after fractionation by high-performance liquid chromatography. Samples were passed cationic exchange pre-column through to remove water soluble materials, then catecholamines were separated using HLC-8030 column (Toso, Tokyo, Japan). After that, fluorescence

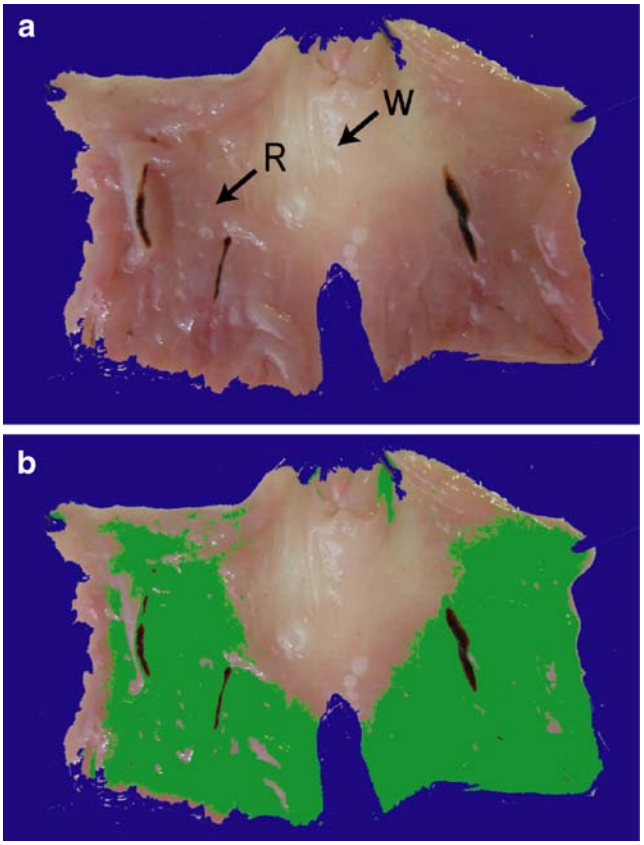

Fig. 1 Measurement of the RAS. The RAS was measured using a visual analyzing system. Different color values (i.e., *red*, *green* and *blue*) at the most whitish (**a**, *arrow with W*) and blushing (**a**, *arrow with R*) part of stomach mucosal surfaces were identified for each animal. A cut-off value was then calculated. The blushing area of mucosal surface was visualized as can be seen in (**b**)

produced by diphenyl-ethylene-diamine and potassium ferricyanide was measured with excitation wave length λex = 355 nm and emission wave length λem = 470 nm.

Measurements of blood leukocytes

Blood leukocytes, especially the ratio of neutrophils to lymphocytes, are an indicator of the immunological stress reaction of the sympathetic nervous system [16]. For the leukocyte fraction, neutrophils, lymphocytes, monocytes, and basocytes were assessed by peripheral blood smear (Wright–Giemsa stain) and microscopic cell counting. The proportion of neutrophils and lymphocytes in the leukocyte fraction was calculated.

Statistical analysis

Shapiro–Wilk tests were used to test shivering threshold data for normality ($P>0.05$). In order to locate the factors independently associated with SBA, we performed a multiple regression analysis. We used SBA as outcome variable, the others as predictor variables. Subject was treated as categorical factor using dummy variable with five degrees of freedom. And correlation coefficients were determined by the Pearson correlation analysis using SPSS software (Ver. 7.5, SPSS, Chicago, USA).

Results

SBA

Restraint stress animals showed certain length of SBA, although non-stressed animals did not show SBA. Activities were video recorded. This study was done during the period from 9:00 to 15:00, which is not an active time for rats. Non-stressed rats slept or ate mostly during this period. Masseter muscle activity associated with eating and drinking was excluded as much as possible. Individual SBA varied from 19.77 to 1.37 min (0.23–3.30 min/h) during 6 h of restraint stress (Fig. 2). Mean SBA over this period was 8.06±5.02 min.

Macroscopic observations of spleen and thymus

The spleen and thymus were markedly affected by restraint stress. Compared with controls, the weight of the spleen and the thymus was significantly lower ($P=0.05$) in rats that experienced 6 h of restraint stress (Fig. 3). In histological and macroscopic observations, decreases in thymus cortex, increases in thymus marrow, and decreases in white spleen marrow relative to controls were observed

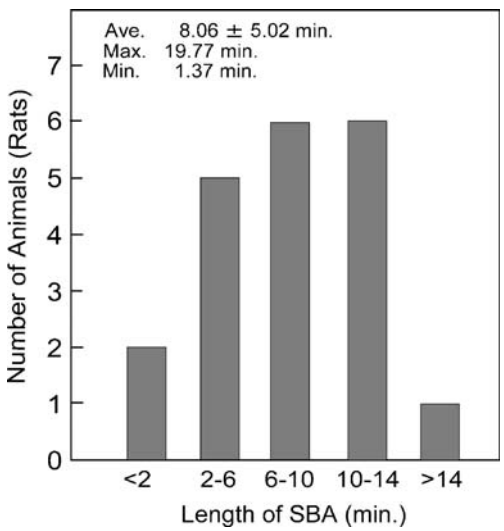

Fig. 2 Variation of SBA. The masseter muscle activity during restraint was measured by EMG. The length of the activity was calculated for each animal. The variations of individual SBA ranged from 19.77 min to 1.37 min during 6 h of restraint stress

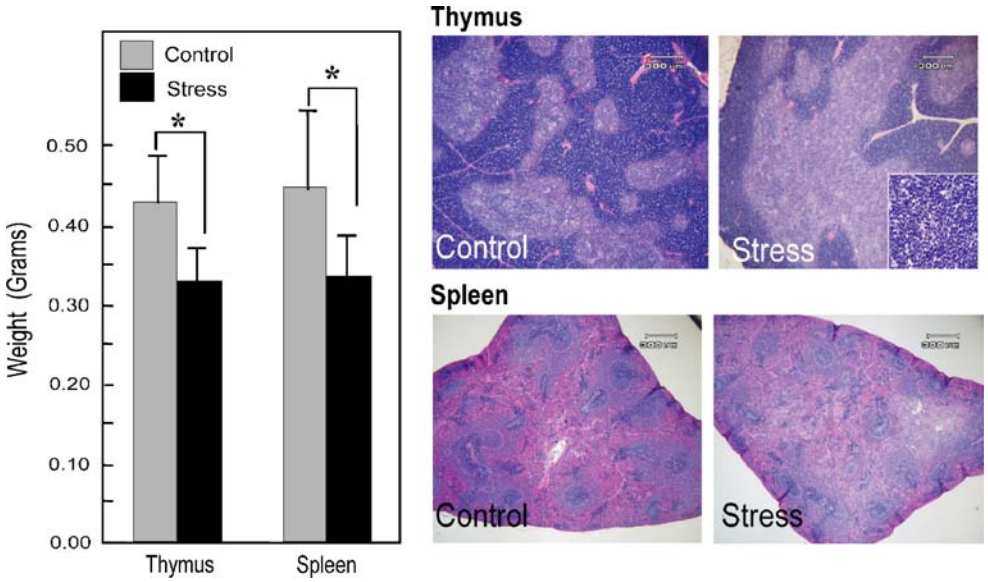

Fig. 3 Effects of restraint stress on the weight of the spleen and thymus. Stressed animals showed a significantly lower spleen and thymus weight compared with controls. In histological and macroscopic observations, decreases in thymus cortex, increases in thymus marrow, and decreases white spleen marrow compared with controls were observed. *Asterisk* (*) indicated significant difference at $p<0.05$

(Fig. 3). However, the weight of both the thymus and the spleen increased in direct proportion to the duration of SBA; this correlation was statistically significant for both the thymus ($P=0.032$) and the spleen ($P=0.0002$) (Fig. 4).

SBA and blood leukocytes

During the 360 min of restraint stress, the percentage of neutrophils progressively increased, while the percentage lymphocytes gradually decreased (Fig. 5). The proportion of neutrophils to lymphocytes in blood leukocytes inversed at 240 min of restraint stress and was sustained until the end of the trial. Conversely, SBA attenuated the stress-induced alterations of neutrophil/lymphocyte balance (Fig. 6).

SBA, blood adrenaline, and cortisol levels

Rats under restraint stress showed an increase in cortisol and adrenaline levels relative to controls (1.20±0.30), although these elevations were attenuated by SBA (Fig. 7). Blood adrenaline levels were significantly correlated with the percentage of neutrophils in blood leukocytes ($R=0.604$, $P<0.01$; Fig. 8). RAS and the percentage of neutrophils in blood leukocytes were also strongly correlated ($R=0.835$, $P<0.01$; Fig. 8).

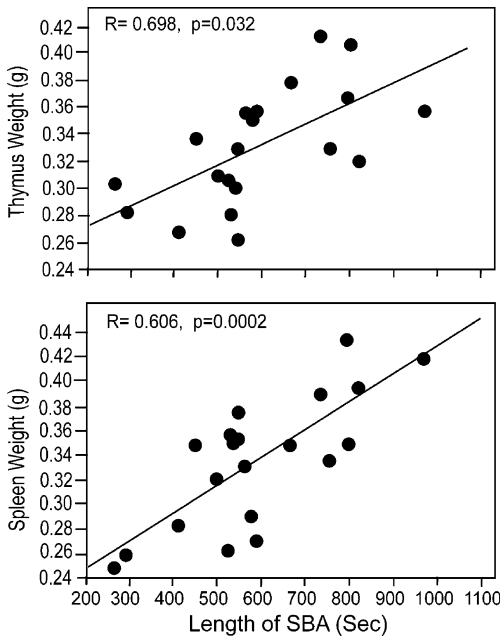

Fig. 4 Effects of SBA on the stress-induced changes of the spleen and thymus weights. Restraint stress was applied for 6 h, during which decreases in spleen and thymus weights were attenuated by SBA in a duration-dependent manner

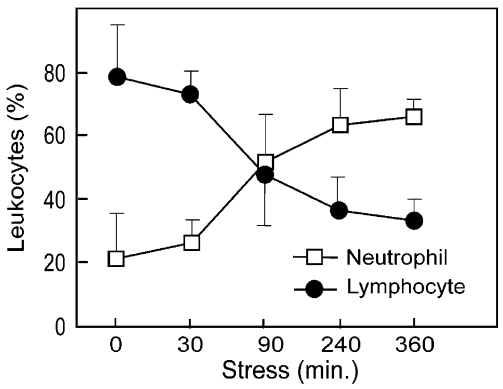

Fig. 5 Alterations of neutrophil/lymphocyte balance in the stressed animal. Restraint stress for 6 h increased the number of neutrophils, while lymphocytes decreased

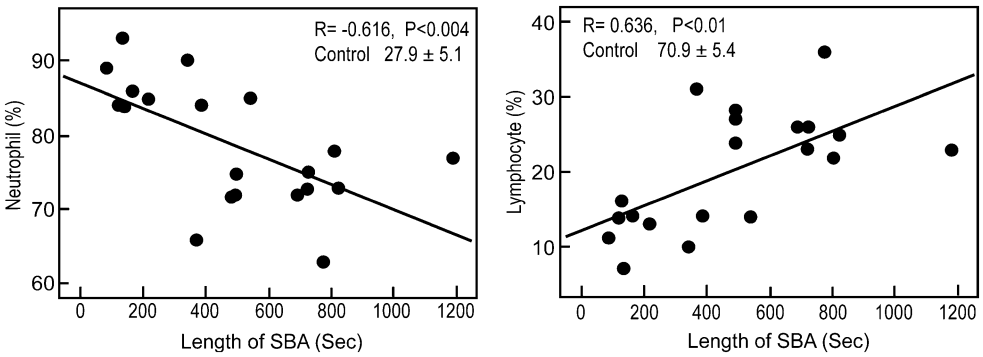

Fig. 6 Effect of SBA on the neutrophil/lymphocyte balance in the stressed animal. Stress-induced alterations in the percentage of neutrophils and lymphocytes in blood leukocytes were attenuated by SBA in a duration-dependent manner

SBA and ulcer formation

After 6 h of restraint stress, a variety of stomach ulcers formed (Fig. 9a). The duration of SBA and the RAS were significantly correlated (R=−0.6746, P<0.01), indicating that SBA had a protective effect on stress-induced ulcer formation (Fig. 9b). Additionally, in multiple regression analysis, in forced entry, there are high reference in this model (R=0.825, R^2=0.680). In stepAIC, cortisol and RAS have strong effect on SBA.

Discussion

The results of this study demonstrate that SBA attenuates emotional stress-induced ulcerogenesis.

Reductions in the weight of the thymus, spleen, and adrenal glands are usually found when stress is induced [17]. However, in this study SBA attenuated the stress-induced weight reduction in these organs. These findings further support the hypothesis that SBA may have a protective effect against stress-induced changes in physiology.

This study also demonstrated that rats that express aggression through SBA in response to restraint stress attenuated increases in blood adrenaline, cortisol, and neutrophils. These findings suggested that expressing aggression through SBA during stress may help regulate the hypothalamic–pituitary–adrenal axis and the autonomic nervous system (ANS) response.

Previous work has confirmed the down-regulating effect of masticatory parafunction on restraint-stress-induced changes of neurophysiologic events. For instance, Fos expression [18], free radical consumption [19], phosphorylated ERK 1/2 expression [20], corticotrophin-releasing factor expression [21], and neuronal nitric oxide synthase [22] expression in the rat hypothalamus and paraventricular nucleus increased as a result of restraint stress. These stress-induced changes were significantly suppressed by bruxism-like biting activity of the jaw [19–23].

Tsuda et al. [23] reported that giving rats an opportunity to express aggression (bite a wooden stick) during stress exposure resulted in a significant attenuation of stress-induced increases in NA turnover in the hypothalamus, thalamus, midbrain, and basal ganglia compared with rats that were not given an opportunity to bite. Similarly, they found a significant attenuation of stress-induced increases in NA metabolite levels in the amygdala of rats allowed to bite a wooden stick. Tsuda et al. also showed that there was a significant elevation of NA release in the non-biting rats; this elevation was significantly attenuated by biting.

It has been reported that stress-induced increases in NA turnover in the amygdala are closely related to the onset of

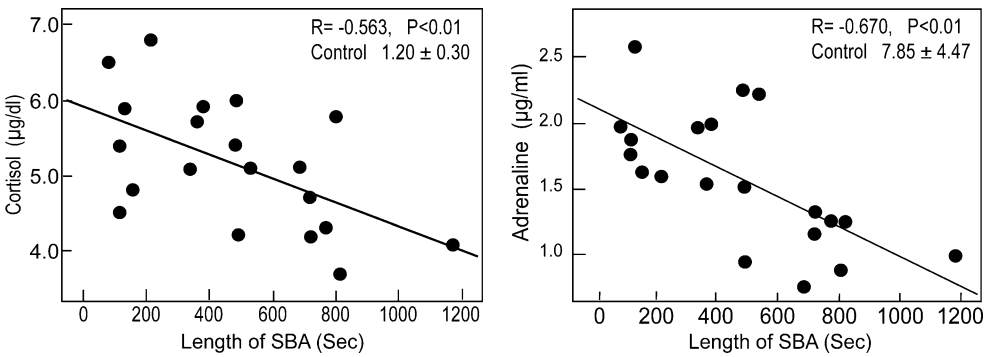

Fig. 7 Effect of SBA on blood cortisol and adrenaline levels. Stressed animal showed an increase in cortisol and adrenaline levels, although these elevations were attenuated by SBA in a duration-dependent manner

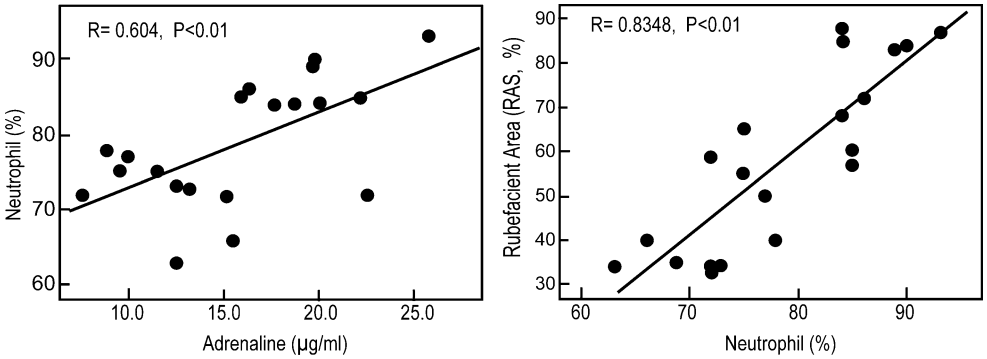

Fig. 8 Correlation between neutrophils and blood adrenaline and neutrophils and RAS. Adrenaline levels and the percentage of neutrophils in blood leukocytes were significantly correlated. Similarly, the RAS and the percentage of neutrophils in blood leukocytes were also strongly correlated

negative emotions, such as anxiety and/or fear, which have been observed in animals during stress exposure [24–27]. Such changes in NA turnover in the amygdala are considered an indicator of certain psychological characteristics, such as the ability to cope with a stressor. In light of these data, the present study may suggest that expressing aggression during exposure to stress might attenuate stress-induced fear and/or anxiety. In fact, a previous study shows that stress-induced Fos expression in amygdala was significantly attenuated by aggressive biting action [18].

The present investigation examined the effects of the SBA instead of artificial biting and support the notion that changes in the emotional state are reflected by muscle tension [28] and, in particular, by tension of the masticatory muscles [29]. The SBA observed in stress-induced rats in the present investigation may suggest that jaw muscle parafunction is a coping mechanism for stress-related events, which maintains allostasis in the body.

It has been suggested that aggression is an underlying factor in bruxism. In this study, rats under restraint stress frequently demonstrated aggressive behavior through SBA in contrast to non-stressed control animals that did not show such activity. According to Rosales et al. [30] and Pohto et al. [31], a stressful environment (e.g., communication box or foot shock) simulated oral parafunction, such as bruxism-like activity. Their results support that emotional aggression display bruxism activity.

It might be speculated that aggressive biting behavior distracts attention from the negative emotion (anxiety and/or fear) produced by stressful situations and thereby reduces the adverse effects of that stressor. If this hypothesis holds true for humans, then expression of aggression through a coping mechanism like sleep bruxism may have therapeutic benefit by attenuating the onset of psychosomatic diseases, such as stress-induced ulcer or neurosis.

Blood leukocytes, especially the ratio of granulocytes to lymphocytes, are a useful indicator of the stress reaction of the immunological system [32] because activation of the sympathetic nervous system increases neutrophils through adrenaline receptors on the cell surface. Morphologically, almost all granulocytes (>95%) are neutrophils, thus blood neutrophils were measured in this study.

It has been demonstrated that granulocytes are closely associated with the formation of gastric ulcers in animals exposed to restraint stress [33]. Strong stressors have the

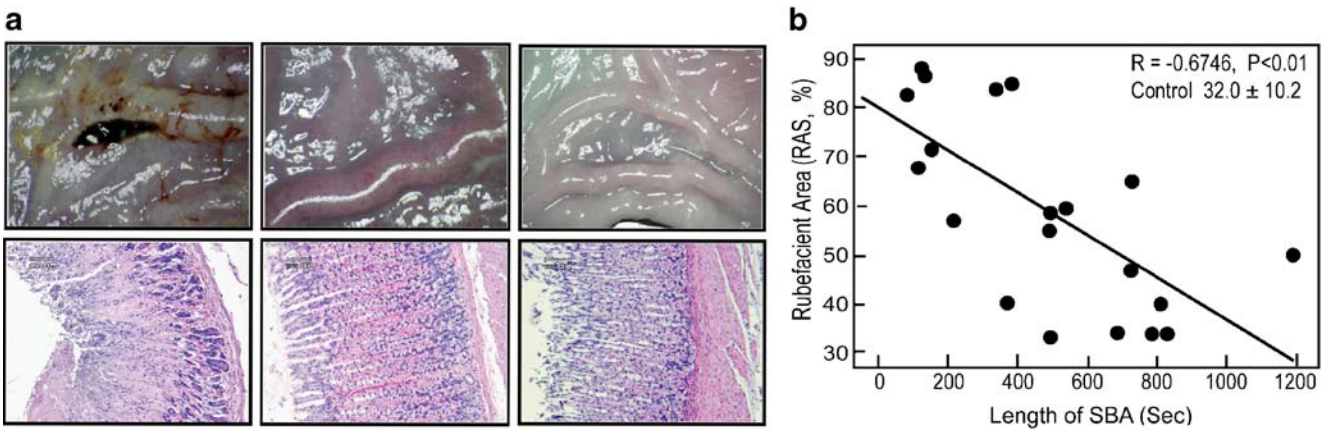

Fig. 9 Effect of SBA on stress-induced ulcer formation. Stressed animals showed a variety of stomach ulcer formations as shown by macroscopic and histological observations (**a**). The RAS decreased significantly with SBA in a duration-dependent manner (**b**)

potential to induce granulocytosis and granulocytes may subsequently induce multiple tissue (mucosal) damage if over-activated. In the present study, the neutrophil to lymphocyte ratio in blood leukocytes was reversed 240 min after restraint stress and was sustained through the end of the trial. This finding implicates sympathetic nerve activation, which may cause damage to internal organs, such as the stomach, the thymus, and the spleen. However, SBA attenuated the stress-induced alterations of the neutrophil to lymphocyte balance (Fig. 6). Histological and macroscopic observation also showed that the severity of the lesions was proportional to the duration of SBA. This significant negative correlation indicates that the stomach lesions tended to be less severe as the duration of bruxism increased and vice versa (Fig. 9). In support of this finding, the RAS in animals with a shorter duration of SBA was larger than in animals with a longer duration of SBA. Overall, these stress-induced physiologic alterations were attenuated by the SBA in a duration-dependent manner (Fig. 9).

Although it cannot be confirmed why SBA reduced ulcer formation in this study, it can be speculated that attenuation of stress-induced ANS activation, followed by increases in neutrophils, adrenaline, and cortisol, underlie the reduction in stress-induced gastric ulcer formation. In conclusion, the present study demonstrates that expression of aggression during stress exposure attenuates both stress-induced ANS responses, including gastric ulcer formation. These results strongly support the hypothesis that suppression of aggression during stress exposure may lead to psychosomatic diseases, such as peptic ulcer and/or neuroses in humans.

Acknowledgements This work was performed at the Research Institute of Occlusion Medicine and Research Center of Brain and Oral Science at the Kanagawa Dental College and was supported by a grant-in-aid for Open Research from the Japanese Ministry of Education, Culture, Sports, Science, and Technology.

Conflicts of interest We indicate that we have no financial relationship with the organization that sponsored the research.
We declare that we have no conflict of interest.

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