

Bidirectional Crosstalk between Stress-Induced Gastric Ulcer and Depression under Chronic Stress

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Abstract

Stress contributes to a variety of diseases and disorders such as depression and peptic ulcer. The present study aimed to investigate the correlation between stress ulcer and depression in pathogenesis and treatment by using chronic stress depression (CSD), chronic psychological stress ulcer (CPSU) and water immersion restraint stress models in rats. Our data showed that the ulcer index of the animals after CSD exposure was significantly higher than that of controls. Depression-like behaviors were observed in rat after CPSU exposure. Fluoxetine hydrochloride significantly reduced the ulcer index of rats exposed to CPSU stress, while ranitidine inhibited depression-like behavior of the animals in CSD group. The ulcer index of rats administered with mifepristone after CPSU stress was markedly reduced compared to CPSU group, although there was no significant difference in the depression-like behavior between mifepristone-treated CSD group and naive controls. We also found that the rats exposed to CPSU or CSD stress displayed a lower level of corticosterone than naive controls, however, the acute stress (AS) group showed an opposite result. Additionally, in order to study the relevance of H₂ receptors and depression, we treated the CSD group with cimetidine and famotidine respectively. The data showed that cimetidine inhibited depression-like behavior in CSD rats, and famotidine had no impact on depression. Overall our data suggested that the hypothalamic-pituitary-adrenal (HPA) axis dysfunction may be the key role in triggering depression and stress ulcer. Acid-suppressing drugs and antidepressants could be used for treatment of depression and stress ulcer respectively. The occurrence of depression might be inhibited by blocking the central H₂ receptors.

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Introduction

Hans Selye was a clinical endocrinologist and experimental biologist who focused his efforts on the study of stress responses [1]. He first introduced the concepts of stress, stressor, eustress, distress, and 'General Adaptation Syndrome' (GAS). He defined stress as the failed response of an individual to an emotional or physical threat [2–6]. Chronic physical and psychological stress has severe deleterious effects on an individual, and stress-related disorders have become a significant public health concern. The most common stress-related disorders impact the digestive system including stress ulcers and irritable bowel syndrome [7] as well as the central nervous system including psychiatric disorders such as depression and anxiety [8]. Although peptic ulcer was caused by disruption of the gastric mucosal defensive barrier [9,10], depression is a complicated emotional and physical response of which the underlying mechanism was still not understood.

Factors inducing either stress ulcer or depression may contain surgery, trauma and emotional stress. The hypothalamic-pituitary-adrenal (HPA) axis is a major part of the neuroendocrine system that recognizes stresses and controls the reactions. The stress response of the HPA axis involves release of multiple hormones with diverse cognitive, physical, emotional and behavioral impacts. A survey of 104 patients with various cancers identified fluctuating

corticosteroid level that was closely correlated with depression, pain and fatigue [11]. Gastric bleeding in rats exposed to acute water immersion and restraint is attributed to the decreased gastric pH and elevated adrenocorticotrophic hormone (ACTH) levels [12,13], suggesting the role of the HPA axis in stress ulcer formation and development. While multiple studies have been devoted to understand the neuroendocrine components of stress ulcers and depression, much remains unknown. Fundamental unanswered questions include whether the induction of stress ulcers and the onset of depression share a common etiology, and whether pharmacologic intervention of one stress-related disorder impacts the other or vice versa.

The H₂ receptor antagonists are a class of drugs such as cimetidine (Cim), ranitidine, famotidine and nizatidine that inhibit gastric acid secretion from parietal cells, thereby protecting the gastric mucosa. However, the role of brain H₂ receptors, specifically relating to depression and depression-like behaviors has not been disclosed yet. Histamine is known to activate HPA axis by affecting the H₂ receptor in the brain, which leads to increase serum corticosterone level and induce the depression-like behaviors. Ranitidine, cimetidine and famotidine are H₂ receptor antagonists widely used in clinical practice. In addition to their effects on the digestive system, ranitidine and cimetidine can pass across the blood brain barrier (BBB) and likely come into contact

with the brain H₂ receptors, but famotidine does not have the ability to gain access to the central nervous system by penetrating the BBB. In this scenario, the H₂ receptor antagonists would serve to suppress depression-like behaviors. Supporting this hypothesis, clinical observations of the mental state of patients suffered from duodenal ulcer reported that the anxiety and depression scale was significantly improved compared to placebo after 4 weeks of treatment with ranitidine ($P < 0.05$) [14]. Therefore, in the current study, we intended to illustrate the association of stress ulcer generation and the onset of depression utilizing the rat models of chronic stress. The results may provide novel strategies to the treatment for common chronic stress-induced disorders.

Materials and Methods

Animals

Adult male Sprague-Dawley (SD) rats weighing 200–220 g, were purchased from the Animal Center Laboratory (Laboratory Animal Centre, Academy of Military Medical Sciences). Every 9 animals were housed in polyethylene cages (485 mm × 350 mm × 200 mm) under standard housing conditions (12/12 h light-dark cycle starting at 7:00 AM, temperature 22 ± 2°C, free access to food and water) for 6–7 days before initiation of the experiment. All efforts were made to minimize animal suffering following the proposal of International Ethical Guideline for Biomedical Research (CIOMS/OMS, 1985).

Treatments

Adult male SD rats were randomly divided into 10 groups ($n = 9$ per group): control group received saline (3 ml; p.o.); chronic psychological stress (ulcer forming; referred as CPSU; treated with saline, 3 ml; p.o.); chronic stress (leading to depression; CSD; treated with saline, 3 ml; p.o.); acute stress (AS); CPSU treated with ranitidine (histamine H₂-receptor antagonist, 150 mg/kg, p.o.); CPSU treated with fluoxetine hydrochloride (selective serotonin re-uptake inhibitor, 1.8 mg/kg, p.o.); CPSU treated with mifepristone (glucocorticoid receptor antagonist, 65 mg/kg, p.o.); CSD treated with fluoxetine hydrochloride (1.8 mg/kg, p.o.); CSD treated with ranitidine (150 mg/kg, p.o.); and CSD treated with mifepristone (65 mg/kg, p.o.). A second set of studies was performed in which the SD rats were exposed to chronic stress depression in the presence of cimetidine (150 mg/kg, p.o. $n = 9$) and famotidine (150 mg/kg p.o. $n = 9$). Drugs were dissolved in saline. All drug solutions were freshly prepared and administered 1 h prior to stress exposure.

Chronic Psychological Stress Ulcer

Restraint was used to induce CPSU. Briefly, naive rats were placed in an adjustable acrylic hemi-cylindrical plastic tube (5 cm of diameter and 12 cm of length), as previously reported [15]. Rats were confined individually and exposed for a period of 4 h a day for consecutive 28 days. The major advantage of immobilization is that it produces both inescapable physical and psychological stress [16].

Acute Stress

Rats were exposed to water immersion restraint stress (WIRS) where restrained in the stainless steel cages and immersed up to their xiphoid in a water bath maintained at 23 ± 2°C. After the exposure for 4 h, the animals were sacrificed [17].

Chronic Stress Depression

CSD was performed as described with some modifications [18]. Rats were exposed to one of nine randomly assigned stressors once

daily for the next twenty-eight days. These involved food deprivation for 48 h; water deprivation for 24 h; tail pinch (1 cm apart from the end of the tail) for 5 min; overhang for 5 min; day and night reverse; 12°C cold water swimming for 5 min; shaking-crowding for 1 h; or 23 ± 2°C water swimming for 10 min.

Forced Swimming Test

Forced swimming test (FST) was performed as described [19]. Briefly, the experiment consisted of two forcing swim sessions. On the first day, the rats were individually placed in the testing cylinder (60 cm of the height and 30 cm of the diameter) filled to a 20 cm depth with water (25°C) for 15 min. The animals were placed in a plexiglas box for 30 min under a 60-W bulb to dry off following removal from the water and towel drying. Twenty-four hours after the first session, the animals were placed back in the cylinder individually for 6 min. The total period of immobility was recorded during the last 4 min of the test. The cylinders were emptied and cleaned between each animal.

Sucrose Consumption Test

Animals were first treated to consume a palatable, weak (1%) sucrose solution. Training consisted of an initial 48 hours exposure to sucrose in place of water, followed by five 1-h tests in which sucrose was presented. On the day 28 following chronic stress, sucrose consumption was measured by determination of the mass of the bottle containing the sucrose solution before and after the test period. Sucrose preference was calculated as: (sucrose consumption)/(total fluid consumption) [20].

Serum Corticosterone Analysis

Blood was collected from decapitated rats between 9:00 AM and 11:00 AM forty-eight hours after stress treatment and separated in a refrigerated centrifuge at 4°C (3,000 rpm × 10 min). Serum was stored at –80°C until the assays were performed. The serum corticosterone (CORT) was quantified by radio-immunoassay (RAI) according to the manufacturers protocols (PLA General Hospital, the RIA Technology Development Center, China).

Ulcer Index Quantification

At the end of each experiment, animals were sacrificed by deep anesthesia with 10% chloral hydrate (350 mg/kg, i.p.). The stomachs were removed, inflated by injecting 2 ml of 1% formalin, and opened along the greater curvature. The area (mm²) of each hemorrhagic lesion was measured under a dissecting microscope with 10× magnification, summed per stomach and used as the lesion score.

Statistics

Statistical analyses were performed using the SPSS 13.0 software. All data are presented as mean ± standard deviation. The Kolmogorov-Smirnov Z method was adopted for normal test, while the student's *t*-test was used to identify significant differences between two samples. $P < 0.05$ was recognized as statistically significant.

Results

Association of Stress Ulcers with Depression

Initial studies were performed to determine whether a correlation exists between the generation of stress-associated ulcers and the onset of depression. The SD rats were exposed to

a 28-day chronic psychological stress protocol. On day 28, rats were examined by the forced swimming test and sucrose consumption test (SCT). After completion of testing, the rats were sacrificed, serum was collected and ulcer index was quantified. The results of sucrose preference and immobility time of forced swimming test of the chronic psychological stress ulcer group showed no significant differences with the control group ($P>0.05$) (Fig. 1A). In contrast, scarring on the surface of the gastric mucosa was observed in rats following CPSU. Further analysis revealed diffuse congestion, erosion and bleeding of the glandular stomach, with an ulcer index significantly higher than that observed in the untreated control group ($P<0.01$) (Fig. 2A). In summary, the gastric mucosa of animals exposed to CPSU was significantly impaired, however no depression-like behavior was observed.

Rats exposed to CSD displayed significantly increased immobility time of forced swimming test compared to naive control animals as anticipated ($P<0.01$) (Fig. 1B). Similarly, sucrose preference was significantly lower in these rats compared to naive controls ($P<0.01$) (Fig. 1A). However, dotted and lineal erosion, bleeding and ulceration were clearly observed on the surface of the gastric mucosa in the rats exposed to CSD. Mucosal injury was observed primarily within the glandular stomach, and the ulcer index was significantly higher when compared with the control group ($P<0.01$) (Fig. 2B). In contrast to CPSU, CSD resulted in both depression-like behavior as well as gastric mucosal ulceration, suggesting that depression may be associated with ulcer formation in the animals.

Antidepressants Inhibit Ulcer Formation in Both CPSU and CSD Models

The administration of the selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine hydrochloride significantly reduced gastric mucosal impairment in rats with CPSU or CSD, compared to control animals ($P<0.05$) (Fig. 2). Fluoxetine hydrochloride completely eliminated gastric bleeding, with only a few scattered areas of hemorrhage and erosion were observed in the glandular stomach. The ulcer index of the fluoxetine-treated rats exposed to CPSU or CSD was significantly lower than rats that did not receive the medication ($P<0.01$ for each protocol) (Fig. 2A). These data indicate that administration of the antidepressant fluoxetine hydrochloride protects against stress-induced gastric mucosal injury.

H₂ Receptor Antagonists Impact Depression

Rats exposed to CSD were administered with ranitidine, a common H₂ receptor antagonist, or placebo. Ranitidine inhibited depression-like behavior in CSD rats. No significant differences in the immobility time of forced swimming test or sucrose preference were observed from the CSD rats administered with ranitidine compared to naive control rats ($P>0.05$ for each test) (Fig. 1).

Mifepristone Prevents Depression in Chronic Stress Models

In rats exposed to either CPSU or CSD, administration of the glucocorticoid receptor antagonist mifepristone reduced the ulcer index compared to CPSU treatment alone ($P<0.01$ for each) (Fig. 2). Interestingly, we did not observe significant differences in immobility time of the forced swimming test of mifepristone-treated rats exposed to CSD compared with naive controls ($P>0.05$) (Fig. 1B). In addition, we also did not observe any significant difference in the percentage of sucrose preference between mifepristone-treated and CSD exposed rats and the naive control group ($P>0.05$) (Fig. 1A). These results indicate that

mifepristone may prevent the occurrence of depression-like behavior in rats.

Serum Chemistry Following Stress

Serum corticosterone level was measured following stress treatments. Rats exposed to acute stress displayed significantly higher corticosterone levels than naive controls ($P<0.05$) (Fig. 3). In contrast, rats exposed to either CPSU or CSD displayed significantly lower corticosterone than naive control rats ($P<0.05$) (Fig. 3).

H₂ Receptor Antagonists have Disparate Impacts on Depression-like Behaviors and Serum Corticosterone

No significant differences in the immobility time of forced swimming test ($P>0.05$) or the percentage of sugar preference were observed between the cimetidine-treated rats with CSD and naive controls as shown in Figure 4 and Figure 5 ($P>0.05$). However, the immobility time of forced swimming test of the famotidine-treated rats was significantly increased ($P<0.01$), while the percentage of sucrose preference in this group was significantly decreased compared to naive control rats as shown in Figure 4 and Figure 5 ($P<0.01$). In summary, these data suggest that the H₂ receptor antagonist, cimetidine, which is able to pass across the BBB, has a significant inhibitive effect on depression-like behavior; while famotidine, which cannot cross the BBB, does not offer impact on depression. Serum chemistry analysis revealed that no significant differences in corticosterone levels between famotidine-treated rats and rats with CSD as shown in Figure 6 ($P>0.05$). However, serum corticosterone levels in CSD-exposed rats treated with ranitidine or cimetidine were significantly lower than these in control group alone with CSD ($P<0.05$) (Fig. 6).

In order to have a better understanding on the morphological changes of different groups with treatments, the diffuse congestion, erosion and bleeding at the glandular stomach mucosa of the SD rats could be seen in Figure 7.

Discussion

Stress-related disorders have become more important and severe in current society. There is increasing interest in deciphering the role of stress-induced factors in stress ulcer and depression. In this study, we found the bidirectional crosstalk between stress ulcer disease and major depression as well as the common mechanism of pathogenesis.

It is known that the H₂ receptor antagonists are a class of drugs inhibiting gastric acid secretion commonly used in clinical practice, which blocking the H₂ receptors on parietal cells plays a role in protecting the gastric mucosa. Ranitidine, cimetidine and famotidine are widely used H₂ receptor antagonists. It has been demonstrated that no depression-like behaviors are presented in ranitidine-treated rats with CSD; therefore we speculate that H₂ receptors in the brain plays an important role in the process of the occurrence and development of depression, consistent with previous reports [21]. Supplementary interventions with cimetidine and famotidine were conducted for further validation. The data showed that cimetidine which can easily go across the blood-brain barrier had a significant suppressing effect on depression-like behaviors but not for famotidine. As famotidine has a poor lipophilicity, its ability to penetrate the blood-brain barrier is weaker than the other H₂ receptor antagonists. It is suggested that the efficacy on depression-like behaviors of cimetidine and ranitidine is related to the H₂ receptor in the brain. Although the mechanism still remains unclear, it has been reported that H₂ receptor antagonist does prevent the occurrence of depression. To

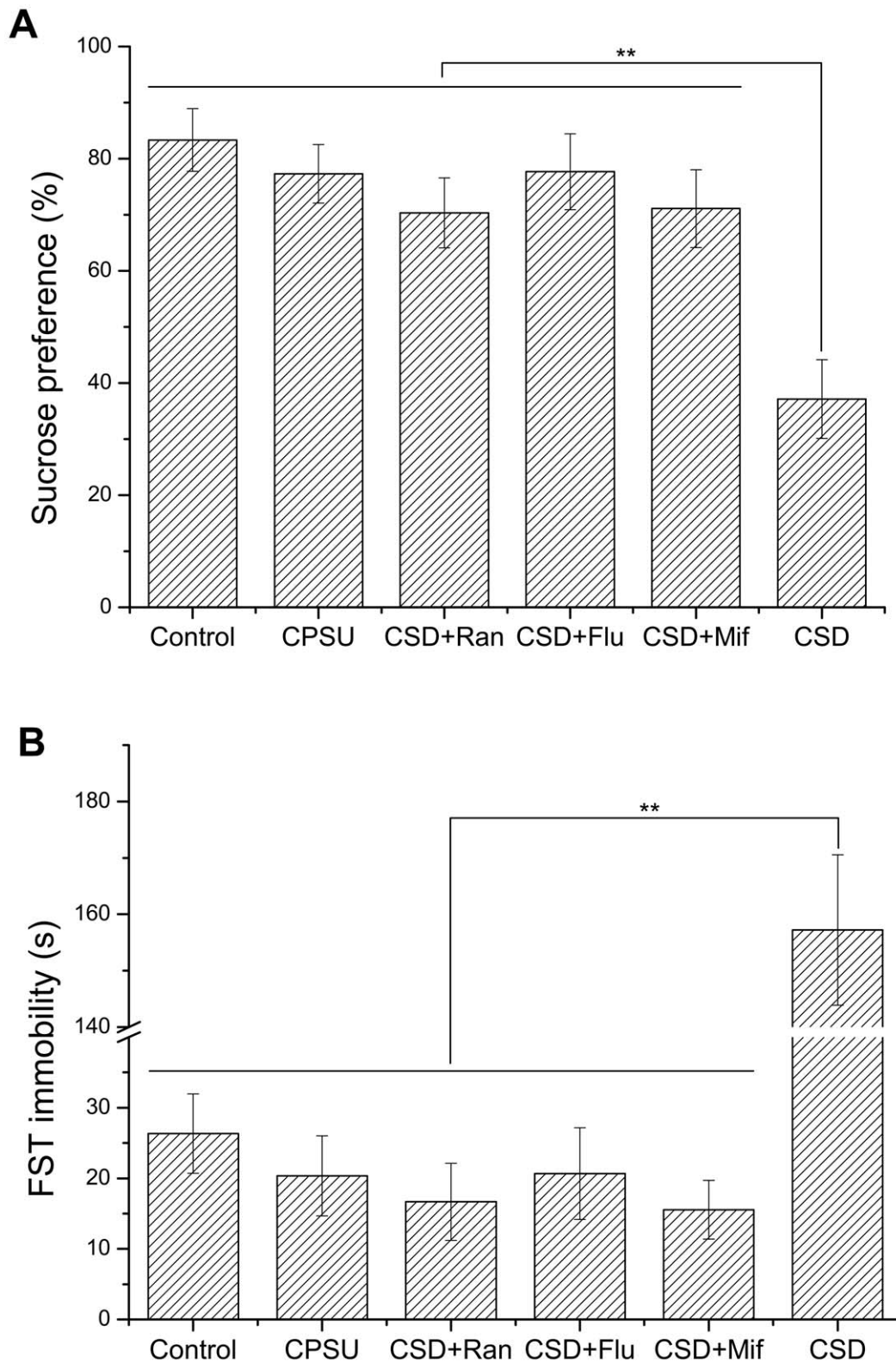


Figure 1. Effects of rat exposed to CPSU, CSD+Flu, CSD+Ran, CSD+Mif and CSD on sucrose preference of sucrose consumption test (SCT) (A) and immobility time of FST (B). The CPSU, CSD+Flu, CSD+Ran and CSD+Mif groups showed no significant difference on sucrose preference of the SCT test compared to control group. The sucrose preference of CSD animals was significantly decreased compared to control animals. The immobility time of CPSU, CSD+Flu, CSD+Ran and CSD+Mif groups showed no significant difference compared to the control group. The FST immobility time of CSD rats is significant higher than control animals. Flu: Fluoxetine hydrochloride; Ran: Ranitidine; Mif: Mifepristone. $**P < 0.01$, $n = 9$ per group.

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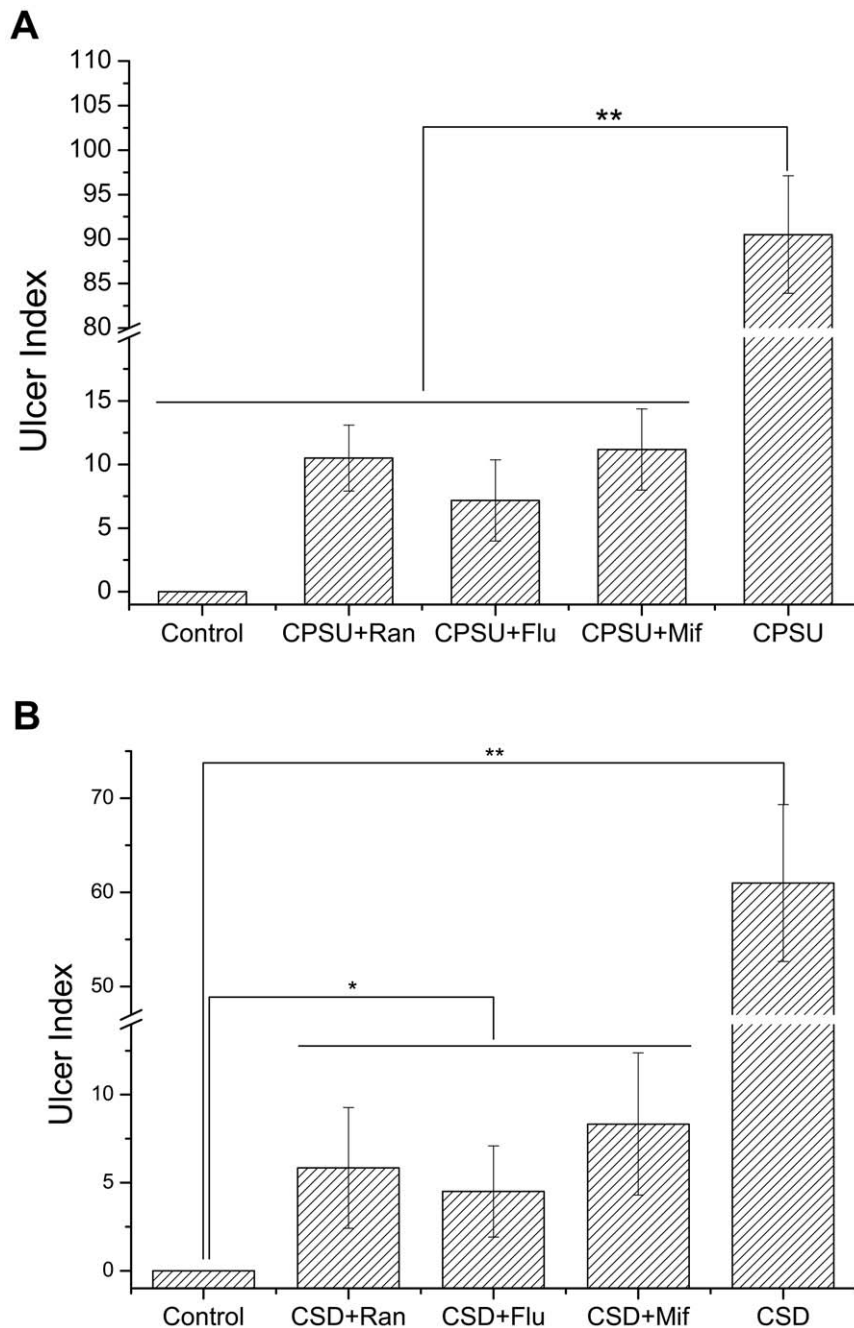


Figure 2. Effects of antagonists on ulcer index (UI) in CPSU procedure (A) and CSD procedure (B). The UIs in CPSU+Ran, CPSU+Flu and CPSU+Mif groups were significant lower than that of the CPSU treatment (A) and CSD treatment (B) groups. Flu: Fluoxetine hydrochloride; Ran: Ranitidine; Mif: Mifepristone. * $P < 0.05$; ** $P < 0.01$; $n = 9$ per group. doi:10.1371/journal.pone.0051148.g002

understand the underlying mechanism of this phenomenon, we examined the serum corticosterone level of rats exposed to CSD and treated with ranitidine or cimetidine which is significantly lower than that of the rats exposed to CSD and receiving placebo. Cerebral histamine is produced by mastocytes which can activate the HPA axis after stimulation [22]. It is possible that the H_2 receptor antagonists such as ranitidine and cimetidine may affect histamine to activate HPA axis through blocking the H_2 receptor in the brain, which decrease serum corticosterone level and suppress the depression-like behaviors. Chandishwar Nath found that central histamine plays a facilitator role in occurrence of

depression in animal. Administration with histamine can enhance immobility in the swimming despair test in mice [21]. Some researchers concluded that central histamine H_2 receptor facilitates aggressive behavior [23]. It seemed that the H_2 receptor antagonists may play an important role in suppressing the depression-like behaviors via reducing HPA axis activation and inhibiting histamine by blocking the H_2 receptor in the central nervous system. Thus our data provides new clues to the mechanism of depression for further in-depth study.

A pilot study has been conducted which showed that erosion and bleeding in CSD group was observed in glandular stomach

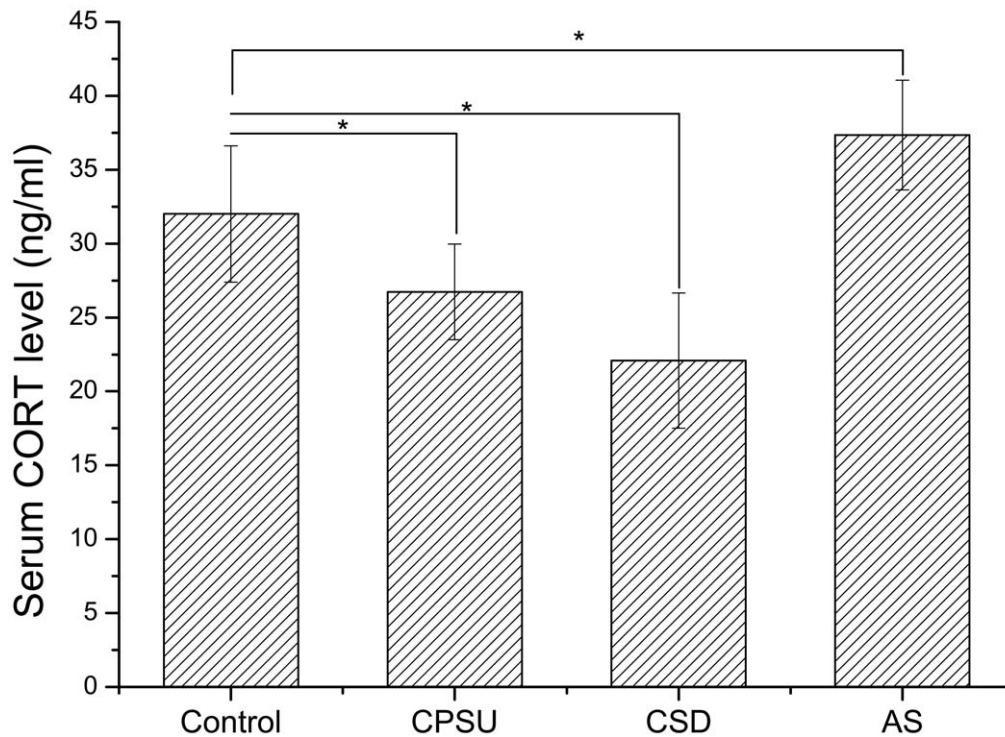


Figure 3. Serum corticosterone (CORT) level analysis of the animals received different treatments. The serum CORT levels of CPSU and CSD groups were markedly lower than control group. Acute stress (AS) resulted in a significant increase in the plasma CORT level compared to control group. * $P < 0.01$, compared to control group. $n = 9$ per group. doi:10.1371/journal.pone.0051148.g003

mucosa with ulcer index significantly higher than the control group, and depression behavior test revealed a significant depression-like behavior. Our results indicated that the rats with

depression-like behavior suffered from a severe gastric mucosal impairment. Meanwhile depression-like behavior in the CPSU group was not statistically different from the control group,

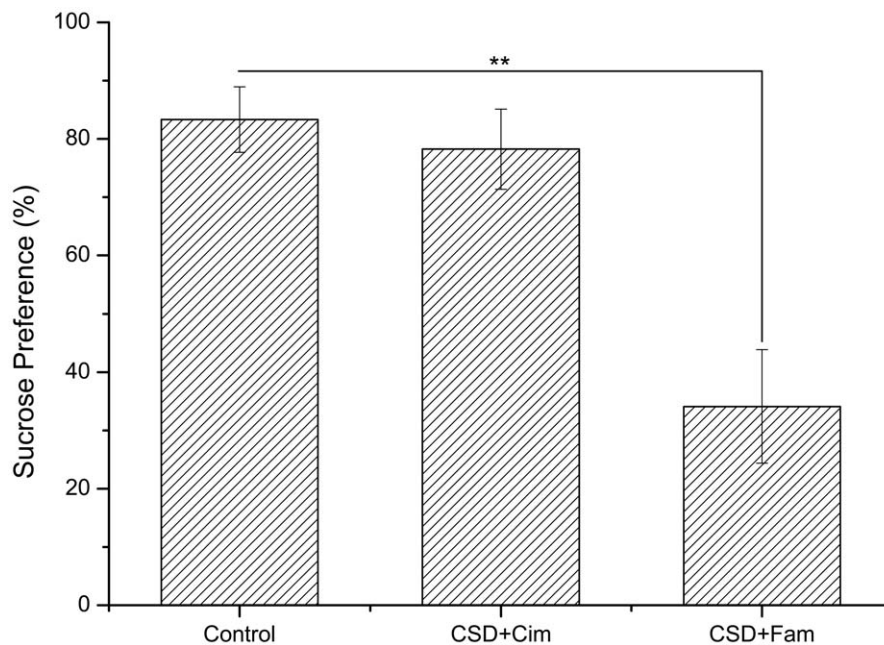


Figure 4. Effects of the histamine H₂-receptor antagonist cimetidine and famotidine on sucrose preference of SCT test. CSD+Cim animals showed no significant difference compared to control group. The sucrose preference of CPSU+Fam animals was significant decreased than control animals. Cim: Cimetidine; Fam: Famotidine. ** $P < 0.01$; $n = 9$ per group. doi:10.1371/journal.pone.0051148.g004

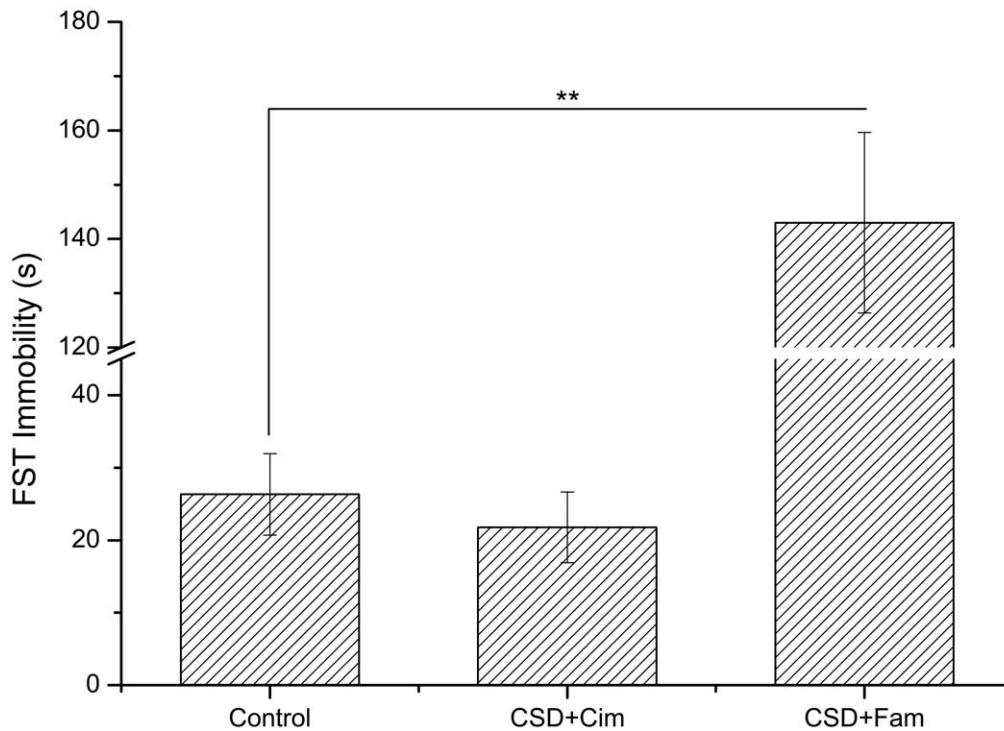


Figure 5. Effects of the histamine H₂-receptor antagonist cimetidine and famotidine on immobility time of the FST test. The immobility time of CSD+Cim group showed no significant difference compared to the control animals. The FST immobility time of CSD+Fam animals was significant higher than control animals. Cim: Cimetidine; Fam: Famotidine. ** $P < 0.01$; $n = 9$ per group. doi:10.1371/journal.pone.0051148.g005

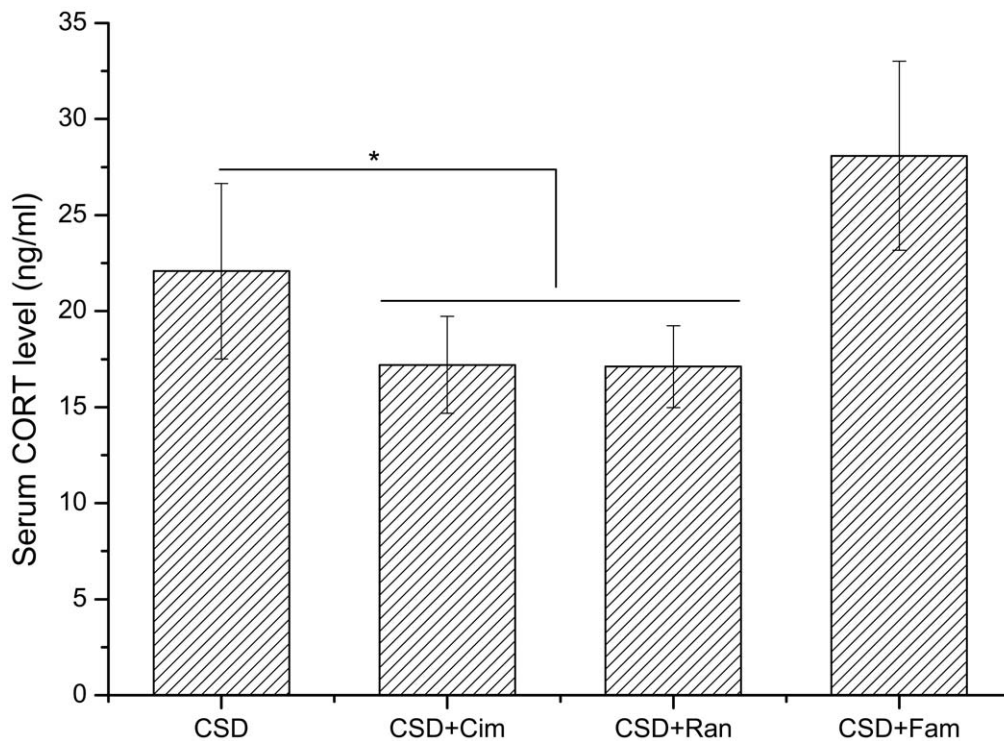


Figure 6. Effects of the histamine H₂-receptor antagonists cimetidine and famotidine on serum CORT level. The serum CORT level of CSD+Fam exposure showed no significant difference compared to the CSD group. In CSD+Ran and CSD+Cim animals, the serum CORT level was lower than control rats. Cim: Cimetidine; Ran: Ranitidine; Fam: Famotidine. * $P < 0.05$; $n = 9$ per group. doi:10.1371/journal.pone.0051148.g006

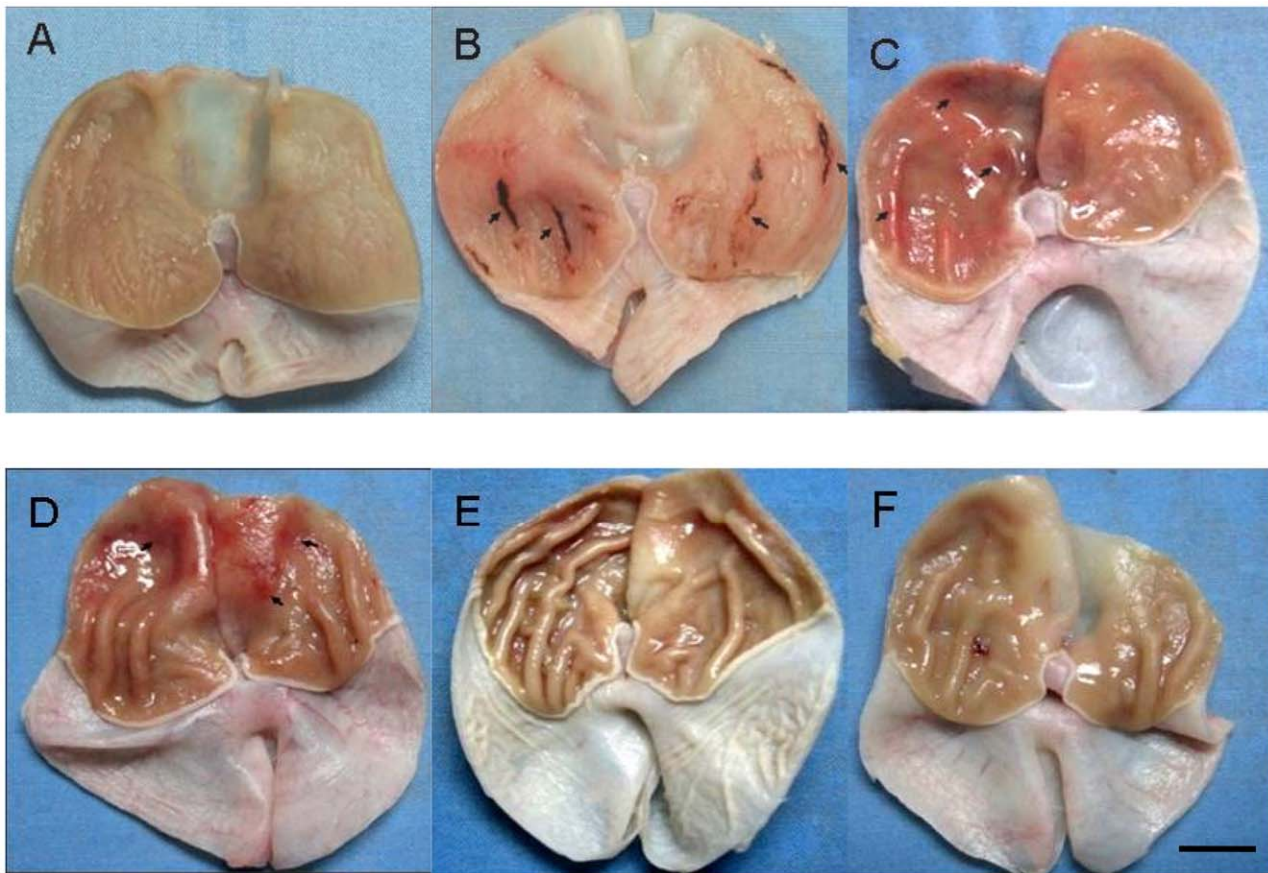


Figure 7. Diffuse congestion, erosion and bleeding at the glandular stomach mucosa of the SD rats. A: Control; B: Acute stress; C: Chronic psychological stress ulcer; D: Chronic stress depression; E: Chronic stress depression treated with fluoxetine hydrochloride; F: Chronic stress depression treated with ranitidine. Scale bar = 3 mm. doi:10.1371/journal.pone.0051148.g007

suggesting that the stress ulcer is not necessarily accompanied by the occurrence of depression. The results are consistent with previous studies [24,25], although other authors reported a different result [26]. It is known that depression is related to defective function of 5-hydroxytryptamine. Chronic restraint stress is associated with enhanced postsynaptic behavioral sensitivity to the 5-hydroxytryptamine agonist 5-methoxy-N, N-dimethyltryptamine [24,25]. Susceptibility to chronic stress is affected by multiple factors such as circadian rhythms, age, gender, strain or genomic makeup [27–30]. In conclusion, it is believed that certain relevance does exist between stress ulcer and depression, and that depression often goes with stress ulcer while stress ulcer is not necessarily accompanied by the occurrence of depression.

Previous study indicated that repeated pretreatment with antidepressant citalopram exhibited a significant gastroprotective efficacy in cold restraint model [31]. Antidepressants have been thought to relieve gastric mucosa impairment via reducing gastric acid secretion and repairing the mucus-bicarbonate barrier. Suleyman identified that administration of antidepressants increased expression of antioxidant indicators including glutathione and superoxide dismutase, while decreasing the expression of oxidative indicators such as hydrogen peroxide, malondialdehyde and myeloperoxidase [32]. Fluoxetine is believed to act as a SSRI and frequently used to treat depression [33]. It could increase cortical gamma-aminobutyric acid (GABA) levels in stressed rats [34], and gastroprotective activity of GABA appears to be mediated by increasing the gastric mucosal blood flow that was

depended on sensory neuron and NO systems [35]. A more plausible mechanism was presented by Kanof, suggesting that antidepressants could protect gastric mucosa via interactions with H_2 receptors in the brain [36]. As the H_2 receptor antagonists that pass across the BBB were able to impact depression, our data also provided further evidence for this issue. Embracing all these possibilities, a possible mechanism was proposed in Figure 8.

Stressors activate the paraventricular nucleus, giving rise to the release of corticotropin releasing hormone (CRH). CRH acts on the pituitary and stimulates the secretion of ACTH which promotes glucocorticoids release from the adrenal cortex [37]. Glucocorticoids are the end-product of the HPA axis referred to as cortisol in human and corticosterone in rodents [38]. The causal relationship between glucocorticoids and depression remains unclear. Researches on whether stressors will induce the release of glucocorticoids are inconsistent. Some studies suggest that stress triggers depression with increasing output of glucocorticoids [39,40]. In contrast to these papers, another theory considers that stress-induced decline in glucocorticoids output involves in the pathogenesis of depression [41]. Our results demonstrated the level of corticosterone was significantly increased in rats exposed to AS, on the contrary the rats exposed to chronic stress (CPSU or CSD) showed obviously lower level of corticosterone than naive controls. This situation could be considered as the influence of timing on the HPA axis. Sanne H Booij pointed out that “when chronic stress first begins, there is an initial activation of the HPA axis, which results in elevated concentrations of ACTH and

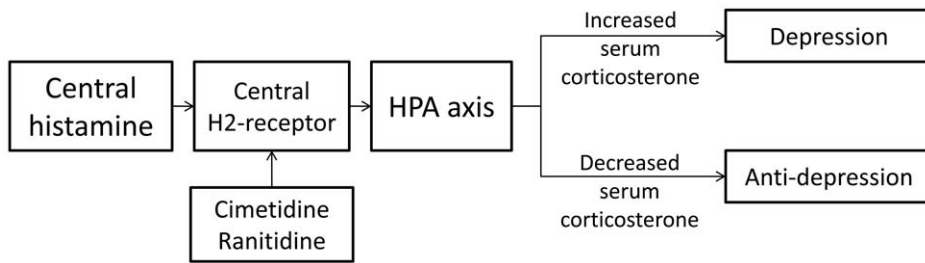


Figure 8. Diagram showing the depressant action of H₂ receptor antagonists.
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cortisol. However, the findings suggest that as time passes, this activity diminishes, and cortisol secretion rebounds to below normal” [42]. Glucocorticoids are released in response to many stressors as a protective hormone, the effect of which is the normalization of stress response, serving as adaptive factors to stress events or circumstance. Investigations showed that the experience of repeated or chronic stress can result in hypo-active state of the HPA axis [43]. We speculated that the decline in serum corticosterone level may represent an adaptive response to stress. In addition, high level of glucocorticoids can be induced by stress, which increases the sensitivity to the negative feedback in pituitary [44,45]. There is general agreement that large quantities of glucocorticoids may induce or aggravate peptic ulcer. Glucocorticoids can not only interfere with tissue repair, elevate levels of gastric acid and pepsin, but also reduce the secretion of gastric mucus, and eventually impair gastric mucosal barrier resulting in peptic ulcer. Moreover depression is characterized with reduced neurogenesis, mainly in hippocampus [46]. The elevation of glucocorticoids can interfere by a variety of adverse structural and cellular changes including neuronal damage in hippocampus [47], cause increased secretion of hypothalamic CRH, and result in impaired reactivity to stress [42,48]. Clearly neuroendocrine system that regulates stress response is extremely complex. Our data suggest the HPA axis is significantly involved in chronic stress-induced ulcer formation and the onset of depression via multiple mechanisms, among which it mediates the structural and cellular changes in hippocampus, and consequently the alterations induce hippocampus damage, which may increase the risk of depression. Furthermore, these data indicate that intervention at the level of the HPA axis may provide broad protection from chronic stress disorder.

The above experiments have confirmed that stress ulcer does correlate with depression: antidepressants can probably be used for the treatment of stress ulcer and acid-suppressing drugs can be used to treat depression, suggesting that these two diseases may share a common mechanism of pathogenesis. Mifepristone is a glucocorticosteroid receptor and progesterone receptor antagonist currently being tested as potential antidepressant [49]. We used mifepristone for better understanding the interaction between

stress ulcer and depression on the HPA axis. Our data demonstrated that rats administered with mifepristone in the two groups (CPSU and CSD) did not suffer from severe gastric mucosal damage. Compared with the control group, there was no difference in depression-like behavior in the CSD group, which was given mifepristone. These findings suggested that mifepristone significantly decreases depression-like behavior and the occurrence of stress ulcer in chronic stressed rats, consistent with an antidepressant effect. Previous study suggested that mifepristone ameliorate acute stress-induced depression-like behavior by targeting the glucocorticoid receptor [50]. Since the chronic stressors in the CPSU and CSD animal models could be understood as the integration of different acute stressors, mifepristone blocks the glucocorticoid receptor and invalidates the end-product of the HPA axis, and eventually exerts a positive effect on reducing depression-like behavior and protecting the gastric mucosa. The results have shown that glucocorticoid plays an important role in the occurrence of stress ulcer and depression by which we can conclude that interaction of these two diseases does exist on the HPA axis.

Conclusions

There is a certain relationship between stress ulcer and depression. Stress ulcer is not necessarily accompanied by the occurrence of depression while depression often goes with stress ulcer. Antidepressants and acid-suppressing drugs may probably be used for the treatment of stress ulcer and depression respectively. Acute stress activates the HPA axis and chronic stress may result in reduced HPA axis activation. Interaction exists between the occurrence of depression and stress ulcer on the HPA axis, meanwhile the H₂-receptor in the brain plays an important role in depression.

Author Contributions

Conceived and designed the experiments: SZ HL CZ. Performed the experiments: SZ ZX. Analyzed the data: SZ ZX. Contributed reagents/materials/analysis tools: YG YW ZL. Wrote the paper: SZ CZ.

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