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Original Article

Aprepitant, a NK1 receptor antagonist, improves both airway inflammation and depressive-like behaviors in a rat model with asthma and depression

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Abstract: The objectives of the study were to detect the effect of substance P receptor antagonist aprepitant on a rat model of asthma and depression. Ovalbumin (OVA)-induced asthmatic Wistar rats were exposed to a chronic mild stress (CMS) procedure which was usually used to induce depression in animals. Simultaneously with the CMS, two groups of the rats were respectively given either aprepitant or slaine (p.o.). Pulmonary inflammation was assessed with hematoxylin and eosin staining and inflammatory cell counting in bronchoalveolar lavage fluid (BALF). The depressive-like behaviors were valuated by sucrose solution consumption test and forced swim test. Besides, levels of IL-1β, IL-5, IL-6 IL-13 and IL-17A in serum and lung homogenate, as well as total IgE and OVA-specific IgE in serum were measured using ELISA analysis. We found that the OVA challenge and CMS exposure induced significant lung inflammation, higher levels of total IgE, OVA-specific IgE and inflammatory cytokines (IL-1β, IL-5, IL-6 IL-13 and IL-17A) as well as depressive behaviors in rats from the OVA-CMS group. However, NK1 receptor antagonist treatment significantly ameliorated lung inflammation, reduced the elevation of total IgE, OVA-specific IgE and inflammatory cytokines as well as attenuated depressive behaviors in the rats from the aprepitant group if compared to the OVA-CMS group. These data suggested that NK1 receptor antagonist could improve both asthma and depression in a CMS-asthmatic rat model.

Keywords: NK1 receptor antagonist aprepitant, substance P, asthma, depression, rat model, effect

Introduction

Asthma is a chronic inflammatory disease of the airway affecting millions of people worldwide [1]. The prevalence of depression, a common psychological disorder which may exacerbate asthma, is as high as 50% in asthmatic patients [2, 3]. But the treatments of asthma and depression might be contradictory in patients with both asthma and depression. Long term use of glucocorticoids which is beneficial for asthma might lead to the onset of depression [4, 5]; while long term use of serotonin reuptake inhibitors that are effective on depression can result in the elevation of serotonin levels which is involved in the exacerbation of asthma [6]. It is necessary to discover drugs that are beneficial for both asthma and depression for patients with the two conditions.

Substance P, a neuropeptide which is produced by nerve fibers and immune cells, has been shown to play important roles in chronic inflammatory diseases and psychological disorders [7, 8]. The effects of substance P on the airways and on the brain are mediated by neurokinin-1 receptor (NK-1R) [7, 9].

Higher levels of substance P have been found asthmatic subjects compared with control individuals [10]. It has also been demonstrated that substance P could exacerbate asthma by promoting airway inflammation, hyper-responsiveness and airway remodeling [11, 12]. Preclinical and clinical studies showed the NK1 receptor antagonists could improve asthma by blocking the combination of substance P with NK1 receptor [13, 14]. Besides, high levels of substance P and NK1 receptor expression are found in the emotion-related areas of the brain

and substance P has been proven to participate in the pathogenesis of depression [15]. NK1 receptor antagonists were administrated to subjects with depression in some trials, but paradoxical results were observed. Some studies showed significant therapeutic effects on depressive cases, but some other studies did not prove the effect [16, 17]. However, it is still generally accepted that substance P antagonists are a prospective anti-depression drug [17-19].

Interestingly, Tohda Y et al. reported substance P contributed to the pathogenesis of airway hypersensitivity following electric shock stress in a guinea pig asthma model [20]. Joachim RA et al. reported that NK-1 receptor plays an important role in mediating the effects of sound stress in allergen-induced airway inflammation [21]. Yet, to our knowledge, no study detected the anti-inflammatory and antidepressant effects of NK1 receptor antagonist in the subjects with both asthma and comorbid depression. It is well known that asthma and depression has opposite alternation of HPA axis activity. Further more, the co-occurrence of asthma and depression is different from the condition only with asthma or depression in the alterations of HPA axis activity, inflammatory state, clinical manifestations and some other characteristics [22-24]. All the facts indicate that individuals with comorbid depression and asthma have unique biological and clinical characters. This might lead to different responses to NK1 receptor antagonist in such individuals. Thus, it is worthwhile to investigate the possible effects of NK1 receptor antagonist in subjects with the two conditions.

Methods

Animals

Twenty-four male Wistar rats (200-220 grams) were the experimental subjects. The animals were obtained from Shandong University's animal center. They were housed 4 per cage and fed with normal food and tap water *ad* libitum on a 12 h/12 h light-dark cycle. The subjects were randomly assigned into OVA-CMS group, aprepitant group and control group with 8 rats per group. This study was approved by our university's Animal Ethics Committee. The protocols were conducted in compliance with Chinese Research Council's Guide for the Care and Use of Laboratory Animals.

OVA sensitization and challenge

The induction of asthma was conducted as described previously with slight modification [25]. Briefly, 100 mg OVA and 200 mg aluminium hydroxide suspended in 2 mL saline were given (i.p. injection) to each rat in OVA-CMS group and aprepitant group on day 1 and day 7. From day 15, the OVA sensitized animals were exposed to aerosolized OVA challenges consisting of two different challenge phases, i.e., the acute challenge phase (from day 15 to day 28) then the chronic challenge phase (from day 29 to day 56). During the acute challenge phase, the animals were exposed to 20-minute of 1% OVA aerosol (40 mL/20 min) every day; but the animals were exposed to OVA aerosol once every 5 days during the chronic challenge phase. Control rats received i.p. injection and challenge of saline only.

CMS exposure

The CMS procedure is widely used to induce depression in animals [26]. The procedure used in this study consisted of some different stressors randomly arranged across 28 consecutive days, including 24 h wet cage, 5 min cold swimming (4°C), 5 min hot room (45°C), 24 h cage tilt (45°C), 24 h food deprivation, 1 min tail pinch, 1 h physical restraint, 2 h intermittent white noise (75 Db). From day 29 to day 56, rats of the OVA-CMS group and aprepitant group received one stressor per day, rats in normal group undisturbed.

Treatment with NK1 receptor antagonist

Rats in the aprepitant group were daily given NK1 receptor antagonist aprepitant (dissolved in 1 ml saline, 10 mg/kg body weight/day, p.o.) for 28 days, starting from the day when rats received the first CMS stimulus (from day 29 to day 56). Rats in OVA-CMS group and control group orally received the same volume of saline.

Forced swim test

The forced swim test is the most commonly used behavioral test to evaluate the antidepressant efficacy of drugs in animals. Rats were individually placed into a glass cylinder which was 60 cm high and half full of water (depth at 30 cm, temperature at 25°C. All rats were forced to swim in the cylinder for 6 min.

Table 1. Effects of aprepitant on depressive-like behaviors of the rats

	FST Immobility (s)	TST Immobility (s)	Sucrose preference
Control	61.80±5.93	79.7±9.82	80.58±6.31
OVA-CMS	126.37±10.40[a]	158.2±22.06[a]	51.26±6.07[a]
Aprepitant	95.31±8.69[a,b]	103.6±14.61[a,b]	67.20±7.15[a,b]

Data is expressed as mean ± SD. [a]$P < 0.05$, if compared to the control group; [b]$P < 0.05$, if compared to the OVA-CMS group.

The behaviors were recorded via a camera and the total immobility duration during the final 4 min of the test session was scored off-line.

Tail suspension test

The tail suspension test is another commonly used behavioral test accessing depressive behaviors of animals. During the 6 min of test, the rat was suspended 30 cm above the floor by hanging on a fixed hook (positioned 3 cm from the tip of the tail) using adhesive tape. The immobility duration during the final 5 min was investigated.

Sucrose preference test

Sucrose preference test has been extensively used to assess the anhedonia which is a key component of depression. During the test, animals were given the choices between consuming sucrose solution versus water. Prior to testing, all the rats were familiarized with sucrose consumption by giving them 1% sucrose solution. On the day before the test, rats were water-deprived for 23 h. Then rats were individually housed and were given access to one bottle containing 1% sucrose solution and the other bottle with tap water for 1 hour. The intakes of sucrose solution and water were determined by volume. The percent sucrose preference is expressed by: [sucrose intake/(water intake + sucrose intake)] × 100.

Differential inflammatory cell counting in BALF

After sacrifice under deep anesthesia, the right lung was removed and BALF was prepared as previously described [25]. After centrifugation at 3000 ×g for 15 min, cells in the BALF were stained with Wright-Giemsa stain and counted.

Lung histopathology

The left lung was removed for histology after sacrifice. The tissue samples were fixed in 4% paraformaldehyde for 3 days and embedded in paraffin. Sections at 4 micron were cut and stained with hematoxylin and eosin. The pulmonary inflammation was graded on the scales 0, 1, 2, 3, 4, based on the distribution and severity of inflammation as described in [27]. Five randomly selected sections were analyzed for each rat.

Cytokine and IgE measurements

Post sacrifice, tissue samples collected from the left lung were homogenized at 4°C in PBS as described in [28]. The homogenates were centrifuged for 10 min and the supernatants stored at -80°C until used. Concentrations of cytokines IL-1β, IL-5, IL-6, IL-13 and IL-17A in serum and lung homogenates were determined using commercial ELISA kits according to the manufacturer's instructions. Levels of total IgE and OVA specific IgE in serum were also measured using ELISA.

Statistical analysis

Data was presented as mean ± SD and analyzed using SPSS 13.0. We used one-way ANOVA followed by Students-Newman-Keuls test to compare the group differences. The difference was considered statistically significant if the P value is less than 0.05.

Results

Forced swim test

The immobility time was regarded as the time that the mouse floated in the water without struggling. CMS exposure significantly increased the immobility time in the OVA-CMS group as compared to the control group ($P < 0.05$). Aprepitant produced a significant reduction of immobility duration in aprepitant group in comparison to OVA-CMS group ($P < 0.05$). The result indicated that CMS induced depressive-like behaviors in rats, while aprepitant improved the depressive-like behavior in the CMS-asthmatic rats (shown in **Table 1**).

Tail suspension test

In the tail suspension test, CMS exposure also significantly increased the immobility time in the OVA-CMS group as compared to the control group ($P < 0.05$). However, aprepitant produced

Table 2. Effects of aprepitant on lung inflammation and serum levels of IgE

	Peribronchial region	Perivascular region	Total IgE (ng/mL)	OVA specific IgE (ng/mL)
Control	0.3±0.06	0.4±0.08	30.09±5.95	0.51±0.08
OVA-CMS	4.7±0.81[a]	4.1±0.62[a]	785.25±101.39[a]	29.93±4.79[a]
Aprepitant	2.6±0.40[a,b]	2.2±0.43[a,b]	463.27±60.58[a,b]	13.09±3.16[a,b]

Data is expressed as mean ± SD. [a]$P < 0.05$, if compared to the control group; [b]$P < 0.05$, if compared to the OVA-CMS group.

a significant reduction of immobility duration in aprepitant group in comparison to OVA-CMS group ($P < 0.05$) (shown in **Table 1**).

Sucrose preference test

After the CMS exposure, rats in the OVA-CMS group consumed much less sucrose solution than control animals ($P < 0.05$). However, the aprepitant treated rats consumed much more sucrose solution than the rats in the OVA-CMS group ($P < 0.05$). The results also indicated that aprepitant improved the depressive-like behavior in the CMS-asthmatic rats (shown in **Table 1**).

Lung histopathology assessments

Histological examination was performed with hematoxylin and eosin staining to determine the recruitment of leukocytes into the lung. There was significant infiltration of leukocytes in the peribronchial and perivascular regions of the rats in the OVA-CMS group ($P < 0.05$) if compared to the controls. The aprepitant treated rats also showed inflammatory histological changes, but the inflammatory infiltration was much less than the rats in the OVA-CMS group ($P < 0.05$). The results suggested that aprepitant inhibited lung inflammation in the CMS-asthmatic rats (shown in **Table 2** and **Figure 1**).

Differential inflammatory cell counting in BALF

Rats in the OVA-CMS group showed greater numbers of macrophages, eosinophils, lymphocyte and neutrophil in BALF than the control rats (all $P < 0.05$). But aprepitant significantly reduced the elevation in numbers of these inflammatory cells in the aprepitant group if compared to the OVA-CMS group (all $P < 0.05$) (shown in **Table 3**).

IgE assessment

The production of IgE is one of the important components of allergic asthma. We examined levels of the total IgE and OVA specific IgE in serum. Animals in the OVA-CMS group produced significant higher levels of the total IgE and OVA specific IgE than the control rats (both $P < 0.05$). However, aprepitant markedly inhibited the over-production of total IgE and OVA specific IgE in the aprepitant treated rats if compared to the rats in the OVA-CMS group (both $P < 0.05$) (shown in **Table 2**).

Cytokine assessment

The rats in the OVA-CMS group showed significant higher concentrations of IL-1β, IL-5 IL-6, IL-13 and IL-17A in serum and lung homogenates than the control rats (all $P < 0.05$). However, the concentrations of these cytokines in the aprepitant group were lower than the OVA-CMS group (all $P < 0.05$) (shown in **Tables 4**, **5**).

Discussion

To our knowledge, this is the first study to show that NK1 receptor antagonist aprepitant improves depressive-like behaviors, lung inflammation and allergen reaction in a rat model of asthma and depression.

Both asthma and depression are chronic diseases with high prevalence, imposing unacceptable social and economic burdens on the public healthcare system [29]. Asthma is a respiratory disease characterized by chronic airway inflammation and poor respiratory function. Depression is a psychological disease. Yet, the association between asthma and depression has been recognized for decades [30]. Numerous studies have demonstrated the high prevalence of the co-occurrence of asthma and depression [31-33]. And it is now regarded that asthma and depression have a complex reciprocal relationship. Depression may induce poor asthma outcomes, such as severe symptoms, impaired life quality, frequent emergency department admissions and hospitalizations, and even lethal attacks [33, 34]. However, studies also have revealed that asthma could increase the risk of the occurrence of depression [35]. Investigations reported that the prevalence of depression in asthma might be as high as 45% [36]. Besides, studies

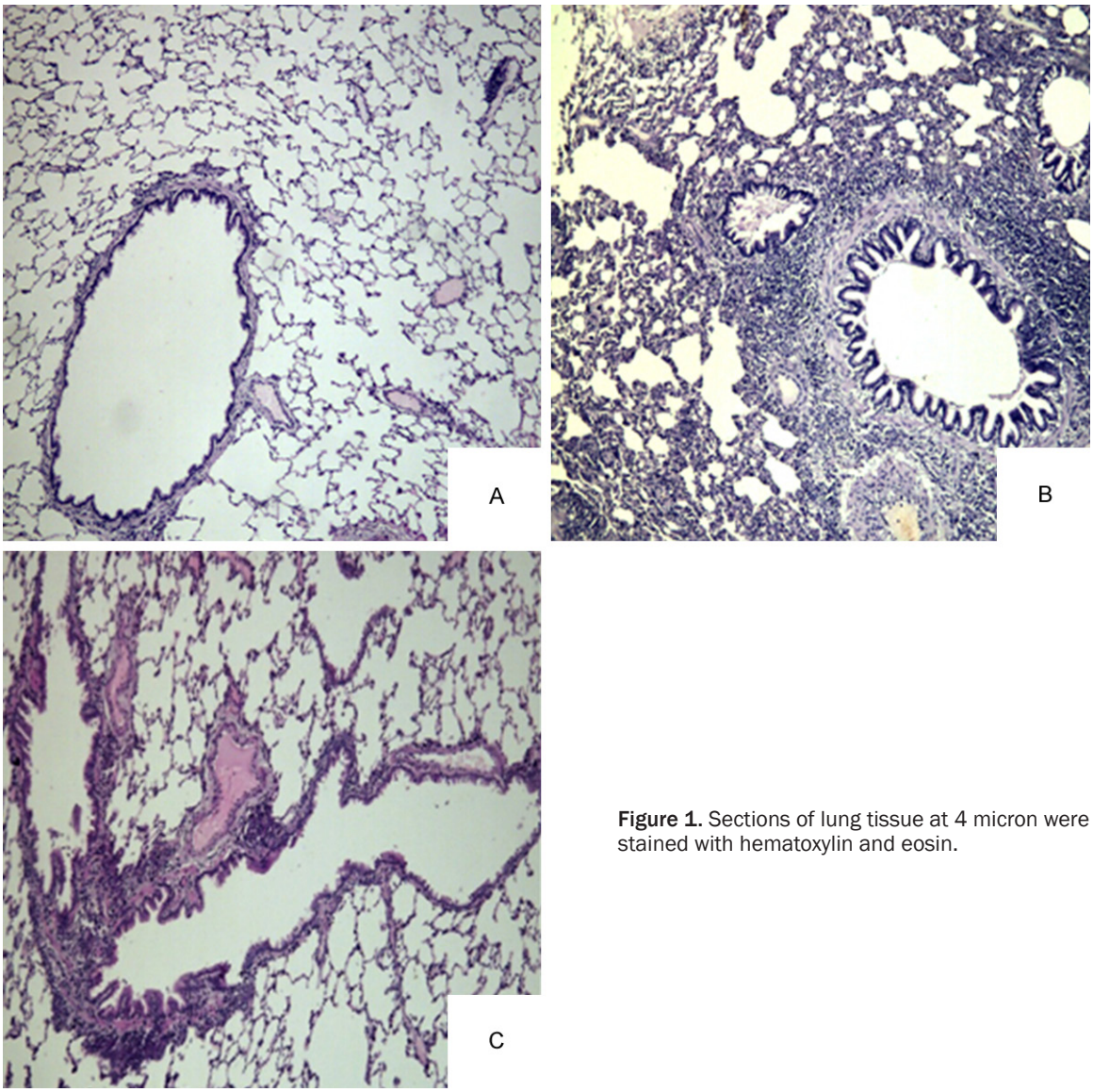

Figure 1. Sections of lung tissue at 4 micron were stained with hematoxylin and eosin.

Table 3. Effects of aprepitant on inflammatory cell counting in BALF (× 10^5)

	Macrophages	Eosinophils	Lymphocyte	Neutrophil
Control	12.07±2.59	0.08±0.01	10.62±2.08	2.12±0.51
OVA-CMS	27.20±4.83[a]	3.10±0.56[a]	23.10±4.04[a]	6.76±1.07[a]
Aprepitant	19.55±3.17[a,b]	1.76±0.33[a,b]	16.92±2.20[a,b]	4.25±0.73[a,b]

Data is expressed as mean ± SD. [a]$P < 0.05$, if compared to the control group; [b]$P < 0.05$, if compared to the OVA-CMS group.

have proved that asthma could exacerbate the depressive symptoms of the patients with depression [37, 38]. Therefore, Depressive conditions can lead to the exacerbation of asthma, and asthma can lead to worse psychological outcomes.

In order to control the asthma symptoms, glucocorticoids are repeatedly used. But studies have showed the frequent use of glucocorticoids is associated with the onset and exacerbation of depression [4, 5]. And some anti-depression drugs could increase the concentration of serotonin which is believed to have a role in the exacerbation of asthma [6]. Attention has been paid to the possible mechanisms linking between psychological disorders and asthma exacerbation and it is believed that there must be a shared way that leads to asthma and depression, which may provide a

Table 4. Effects of aprepitant on levels of cytokines in serum

	IL-1β (pg/ml)	IL-5 (pg/ml)	IL-6 (pg/ml)	IL-13 (pg/ml)	IL-17A (pg/ml)
Control	18.36±2.97	31.06±4.01	21.86±3.72	30.11±4.88	14.83±2.58
OVA-CMS	31.15±4.03[a]	56.32±4.33[a]	39.05±4.93[a]	59.3±7.22[a]	26.11±3.14[a]
Aprepitant	24.10±3.56[a,b]	41.55±6.17[a,b]	30.71±3.41[a,b]	43.92±6.31[a,b]	19.56±2.80[a,b]

Data is expressed as mean ± SD. [a]$P < 0.05$, if compared to the control group; [b]$P < 0.05$, if compared to the OVA-CMS group.

Table 5. Effects of aprepitant on levels of cytokines in lung homogenate

	IL-1β (pg/mL)	IL-5 (pg/mL)	IL-6 (pg/mL)	IL-13 (pg/ml)	IL-17A (pg/ml)
Control	118.01±15.53	164.92±22.08	71.15±9.76	192.58±23.61	30.78±4.09
OVA-CMS	271.45±32.58[a]	336.59±41.90[a]	233.27±30.14[a]	351.04±43.94[a]	59.27±8.35[a]
Aprepitant	192.01±24.80[a,b]	251.64±28.66[a,b]	160.91±21.39[a,b]	258.50±31.22[a,b]	42.01±5.63[a,b]

Data is expressed as mean ± SD. [a]$P < 0.05$, if compared to the control group; [b]$P < 0.05$, if compared to the OVA-CMS group.

new target for the treatment of these two concomitant conditions [39, 40].

Recent studies have showed that substance P, whose actions are mediated by neurokinin-1 receptor, is involved in the physiopathology of asthma and also plays a role in depression [10, 11, 15]. So we administrated aprepitant, a specific NK1 receptor antagonist [41], to the rats with comorbid depression and asthma to detect the possible effects of NK1 receptor antagonist in such subjects.

In order to detect its therapeutic effects on asthma, we analyzed the recruitment of leukocytes into the lung tissue using hematoxylin and eosin staining. We found that rats in the OVA-CMS group had significant infiltration of leukocytes to the peribronchial and perivascular regions of the lung tissue. However, rats in the aprepitant group showed much less leukocytes infiltration to the lung tissue. Besides, we found aprepitant significantly reduced the elevation in numbers of macrophages, eosinophils, lymphocyte and neutrophil in BALF. The results indicated that aprepitant could attenuate the lung inflammation caused by OVA allergy. In addition, we measured serum levels of the total IgE and OVA-specific IgE which reflect the allergic reaction towards an aeroallergen in sensitized subjects. We found that aprepitant significantly inhibited the production of both total IgE and OVA-specific IgE in the aprepitant treated rats if compared to the rats in the OVA-CMS group. All the findings suggested that the aprepitant could attenuate the asthmatic reaction in rats with comorbid depression and asthma. The effects observed in our study were similar to the previous literatures which reported the anti-asthmatic activity of NK1 receptor antagonist. But unlike the subjects used in the current study, the models used in the previous studies were animals only with asthma or animals with asthma and obesity [14, 42].

To evaluate the effects of the NK1 receptor antagonist on the depressive behaviors in rats with asthma and depression, some behavioral tests were performed. The forced swim test and the tail suspension test are most commonly used behavioral tests assessing the antidepressant efficacy of agents in preclinical studies. Immobility time of the animal in the tests can be used to quantify the depressive behaviors. In the current study, much longer immobility time of the rats was observed in the OVA-CMS groups if compared to the control group, indicating the CMS exposure induced depressive symptoms. However, rats in the aprepitant group showed much shorter immobility time than the rats in the OVA-CMS group, indicating that aprepitant attenuated the depressive behaviors of the animals. Anhedonia, which means the loss of the ability to experience pleasure, is also one of the core symptoms of depression and can be evaluated by sucrose preference test [43]. In this study, the rats in the OVA-CMS group consumed less sucrose solution than control animals; while the aprepitant treated rats consumed much more sucrose solution than the rats in the OVA-CMS group. The data also supported the antidepressant activity of aprepitant in rats with asthma and depression. Our findings were consistent with the earlier studies that reported the antidepressant efficacy of NK1 receptor antagonist

[16, 44]. But in those studies, the subjects receiving NK1 receptor antagonist were only with depression, which were different from the subjects in our study. However, unlike our findings, some other previous studies did not proved the antidepressant effects of the NK1 receptor antagonist [45].

In addition to assessing the anti-asthmatic and antidepressant effects of aprepitant in rats with asthma and depression, we also investigated the effects of aprepitant on cytokines that involved in the pathogenesis of asthma and depression. Pro-inflammatory cytokines IL-1β and IL-6, Th2-associated cytokines IL-5 and IL-13 and Th17-related cytokine IL-17A are believed to play roles in asthma and in depression [46-48]. Managements targeting at reducing the over-production of the cytokines were shown to be beneficial for the improvement of asthma or depression. Furthermore, our previous study showed the rats with asthma and depression had high serum levels of IL-1β, IL-6 and IL-17A compared to rats only with asthma [49]. In the current study, the results showed that rats in the OVA-CMS group had significant higher serum levels of IL-1β, IL-5, IL-6 IL-13 and IL-17A than the control rats. Yet, aprepitant markedly reduced the elevation of the cytokine production in the aprepitant group if compared to the OVA-CMS group. We supposed that the reduction of the cytokine production might contribute to the amelioration of asthma and depression.

Thus, aprepitant could ameliorate lung inflammation, improve allergen reaction, attenuate depressive behaviors and inhibit the over-production of cytokines IL-1β, IL-5, IL-6 IL-13 and IL-17A in a rat model with asthma and depression. NK1 receptor antagonists might be a potential drug for the subjects with asthma and comorbid depression. But the effects of NK1 receptor antagonists on the other asthmatic changes in subjects with asthma and depression, such as bronchial hyper-responsiveness and airway remodeling, were not investigated in the current study. Furthermore, the effects we observed on rats need further study in clinic.

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Disclosure of conflict of interest

None.

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