Stress ›
The International Journal on the Biology of Stress
Volume 20, 2017 - Issue 1

Original Research Report

Toll-like receptor 4 protects against stress-induced ulcers via regulation of glucocorticoid production in mice

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Pages 19-26 | Received 10 Sep 2015, Accepted 11 Aug 2016, Published online: 06 Dec 2016

Cite this article https://doi.org/10.1080/10253890.2016.1224843 Check for updates

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showed expression in the adrenal of P450scc (CYP11A1), the first rate-limiting enzyme in the synthesis of steroids, was increased 4 h after water immersion restraint stress or LPS treatment in WT mice, but was conversely decreased in TLR4$^{-/-}$ mice after either stressor. Furthermore, in adrenal glands of TLR4$^{-/-}$ mice, structural distortion of mitochondria (which contain CYP11A1) was found with electron microscopy, and lack of lipid-storing droplets was found using light microscopy on adrenal cryosections stained with Oil red O. These data indicate that TLR4 plays a protective role in stress-induced gastric ulcer that is exerted via impacting synthesis of glucocorticoid in the adrenal gland.

Keywords:

Cortisol glucocorticoid LPS stomach ulcer stress TLR4

Introduction

Stress may affect different physiological functions of the gastrointestinal tract including gastric secretion, motility, permeability and barrier function, visceral sensitivity, and mucosal
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Moreover, intra-hypothalamic dexamethasone implantation which induces long-lasting stress-induced glucocorticoid deficiency results in aggravation of stress-induced gastric injury (Filaretova & Filaretov, 1992). The gastroprotective effects of glucocorticoids during acute stress involve multiple mechanisms, including the maintenance of glucose homeostasis, gastric mucosal blood flow, mucus production, and attenuation of gastric motility and microvascular permeability (Filaretova et al., 2004; Kuo et al., 2015; Podvigina et al., 2009), as well as changes in the gastric microcirculation (Filaretova et al., 1999). Although circulating corticosterone is considered to be the main glucocorticoid in the regulation of stress in rodents, cortisol also has a corresponding response to stimulation by stress in mice (Gong et al., 2015). Whether it impacts stress-induced gastric ulcer in mice remains to be determined.

TLR4 is an innate immune pattern recognition receptor, which is part of the Interleukin-1 Receptor/Toll-like Receptor Superfamily containing a toll-like/IL-1 Receptor (TIR) domain and a Leucine-rich repeat motif in the extracellular domain (Nardone & Compare, 2014). As the receptor for lipopolysaccharide (LPS), TLR4 can be activated by the LPS-lipopolysaccharide-binding protein (LBP)-myeloid differentiation protein 2 (MD2) complex, thus passing this signal to the downstream nuclear factor (NF)-kb pathway (Akira & Takeda, 2004). Several studies have reported that downregulation of NF-kb or inflammation mitigates gastric ulcer (Kang et al., 2014; Mahmoud-Awny et al., 2015; Sinha et

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Methods

Animals and management

The study was approved by the Institutional Animal Care and Use Committee (IACUC) of the Second Military Medical University in Shanghai (IACUC-2012-XuSG) in accordance with the U.S.A. National Institutes of Health guidelines for the care and use of laboratory mice. TLR4 knockout ($TLR4^{-/-}$; C57BL/10ScNJU) and wild-type (WT;C57BL/6_129) mice were obtained from the Jackson Laboratory (Bar Harbor, ME, U.S.A.). The $TLR4^{-/-}$ mice were genetically identified in the Nanjing Biomedical Research Institute of Nanjing University (Nanjing, Jiangsu, China). Male WT and $TLR4^{-/-}$ mice bred under specific pathogen-free conditions aged 6–8 weeks were used for experiments. Mice were housed three to five per cage and acclimatized to standard laboratory conditions (lights on between 08:00 h and 19:00 h, temperature 20 ± 1 °r, free access to food and water) for 7 days before the experiment.

Induction of ulcers by exposure to combined water immersion and restraint stress

WT and $TLR4^{-/-}$ mice were fasted for 24 h before experiments but given free access to tap wate ely. WT and $TLR4^{-/-}$ mersed in 23 °C wa of the xiphoid p 007b). After the indic jection of sodium p d from the inferior v . Blood sampl ugation for 15 m d at −80 °C until ass

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water immersion restraint stress (Jia et al., 2007b), mice were anesthetized with sodium pentobarbital (as above) for blood sampling and stomach removal for the estimation of cortisol level and gastric injury, respectively.

Endotoxemia model

WT and TLR4$^{-/-}$ mice were randomized (n = 5 per group) and injected intraperitoneally with LPS (0.2 mg/ml, 2 mg/kg) (Sigma-Aldrich Corp., St. Louis, MO) or isotonic saline and killed 4 h later to determine the effect of TLR4 (receptor for LPS) on the regulation of endogenous glucocorticoids.

Corticotropin (adrenocorticotropic hormone, ACTH) test

WT and TLR4$^{-/-}$ mice were randomized and injected intraperitoneally with corticotropin (5 IU/ml, 50 IU/kg) (Shanghai NO.1 Biochemical & Pharmaceutical Co., LTD, Shanghai, China) or isotonic saline and killed after 4 h to measure serum cortisol and corticosterone.

Assessment of gastric damage

Stomachs were removed and filled with 2 ml of 1% formalin and immersed in formalin for 24 h. The stomachs then were cut along the length of the greater curvature and examine erosions was mea tor blinded to the tr tissue sample

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<8%, and inter-assay <10%) (Cusabio, Wuhan, China) and the mouse LBP enzyme-linked immunosorbent assay kits (sensitivity: 3.12 ng/ml; coefficient of variation: intra-assay <8%, and inter-assay <10%) (Cusabio, Wuhan, China).

Western blotting

Whole adrenal glands were lysed in protein extraction buffer [20 mM Tris (pH7.5), 150 mM NaCl, 1%Triton X-100, 1 mM EDTA] followed by centrifugation at 12,000 × g for 15 min at 4 °C. The supernatant was removed and total protein was determined (Bradford assay). Samples containing 40 µg protein were loaded, separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (90 V), and blotted onto nitrocellulose membrane. The blots were probed with anti-CYP11A1 antibody (1/1000; Cell Signaling Technology) and with horseradish peroxidase-conjugated anti-rabbit secondary antibody (1/2000; Santa Cruz Biotechnology). After extensive washing, protein bands were visualized by chemiluminescence staining. Blots were also probed with anti-glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (1/1000; Sigma–Aldrich) to confirm equal loading of protein. Expression of proteins was then calculated semiquantitatively as integrated optical density (IOD) ratio of CYP11A1 to GAPDH.

Electron microscopy

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Statistical analysis

Data were analyzed by two-way ANOVA, one-way ANOVA, or Tukey's test of variance using SPSS v.20.0 software (SPSS Inc., Chicago, IL). Differences between groups were calculated using the least significant differences method, and significance level was defined as $p < .05$. Results are expressed as mean ± SEM.

Results

TLR4 deficiency exacerbates stress-induced gastric mucosal injury and modulates serum glucocorticoid concentrations

Gastric mucosa. Gastric mucosal injury was exacerbated in WT mice as a function of water immersion restraint time. Cellular swelling, hypochromia of the cytoplasm, stenosis, and erythropenia in the mucosa appeared starting 0.5 h after stress application. Atrophy and exfoliation of mucosal cells, and increased gastric stromal cell erosion was observed at 1 h. After 2 h, mucosal erosion became more severe, and ulceration appeared at 4 h. The pathological changes induced by water immersion restraint stress were more severe in $TLR4^{-/-}$ than in WT mice (Figure 1(A)), and more ulcers were observed grossly in the gastric mucosa of the mutants after 4 h (Figure 1(B)

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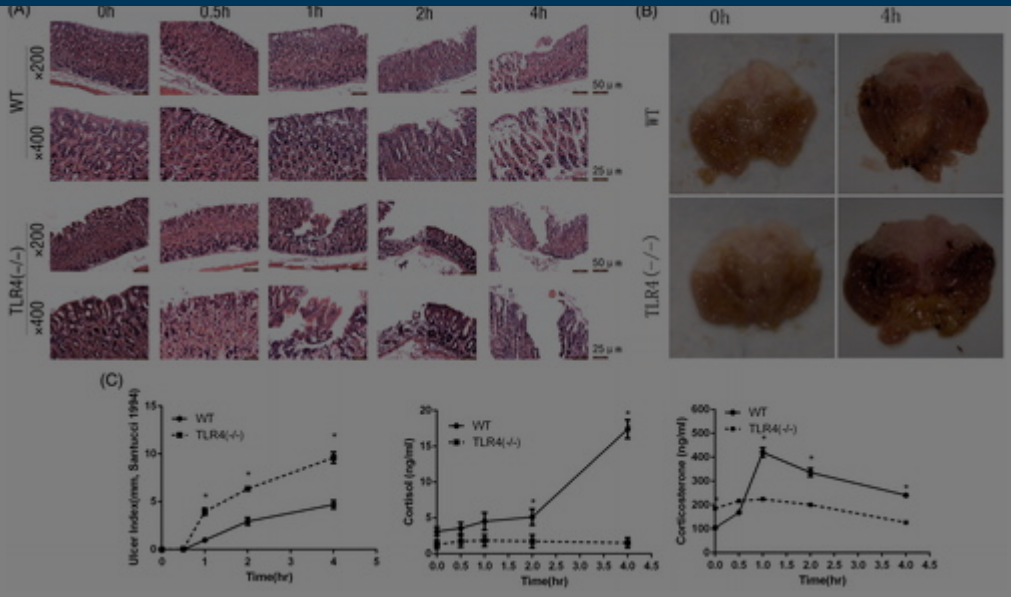

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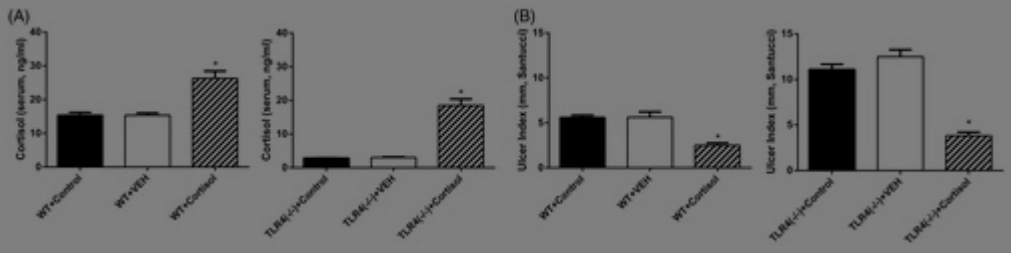
Serum cortisol. Serum cortisol concentrations were increased in WT mice starting from 2 h after the application of the stressor and peaked at the 4-h time point (two-way ANOVA, $F_{mice\text{-}type} = 109.4$, $p_{mice\text{-}type} < .001$; $F_{time} = 29.8$, $p_{time} < .001$; $F_{mice\text{-}type \times time} = 30.7$, $p_{mice\text{-}type \times time} < .001$; one-way ANOVA after two-way ANOVA, df = (9,40), F = 39.0, $p < .001$; Tukey's test, $p_{WT0h/WT0.5\,h} = 1.000$, $p_{WT0.5\,h/WT1h} = .39$, $p_{WT1h/WT2h} = .001$, $p_{WT2h/WT4h} = .005$). In contrast, cortisol concentration remained lower in $TLR4^{-/-}$ mice during exposure to stress (one-way ANOVA after two-way ANOVA, df = (9, 40), F = 39.0, $p < .001$; Tukey's test, $p_{WT0h/TLR4-/-0\,h} = .8$, $p_{WT0.5\,h/TLR4-/-0.5\,h} = .8$, $p_{WT1h/TLR4-/-1\,h} = .3$, $p_{WT2h/TLR}$

Serum c… by the stressor …pes of mice (two-way … $F_{mice\text{-}type \times time} = 62$… = (9,40), F = 75.7, p… $_{h/WT2h} < .001$, $p_{WT2h/}$… $_{TLR4-/-1\,h/WT2}$…ed a higher basal va…e to the stressor …001; Tukey's test, p_{WT}…01, $p_{WT\,2\,h/TLR4-/-}$…

Admini…osal injury

As expected, serum cortisol concentrations were increased in WT and TLR4$^{-/-}$ mice upon injection of exogenous cortisol as compared to the vehicle-injected and uninjected control groups (WT: $F = 2.98$, $df = (2, 12)$ $p = .0001$; TLR4$^{-/-}$: $F = 67.18$, $df = (2, 12)$, $p < .0001$) (Figure 2(A)) and was associated with a lower UI (WT: $F = 19.02$, $df = (2, 12)$ $p = .0002$; TLR4$^{-/-}$: $F = 60.13$, $df = (2, 12)$, $p < .0001$) (Figure 2(B)). Hence, cortisol administration alleviated stress-induced gastric mucosal damage, in both WT and TLR4$^{-/-}$ mice.

Figure 2. Effect of cortisol administration on stress-induced ulceration. WT and TLR4$^{-/-}$ mice were evaluated for (A) serum cortisol concentrations, and (B) gastric ulcer index (UI) after pretreatment with cortisol. Results represent mean ± SEM ($n = 5$ mice per group). *$p < .05$ (one-way ANOVA, Tukey's test) versus vehicle group (dimethylsulfoxide in saline, 1:200) and control groups (without any treatment).



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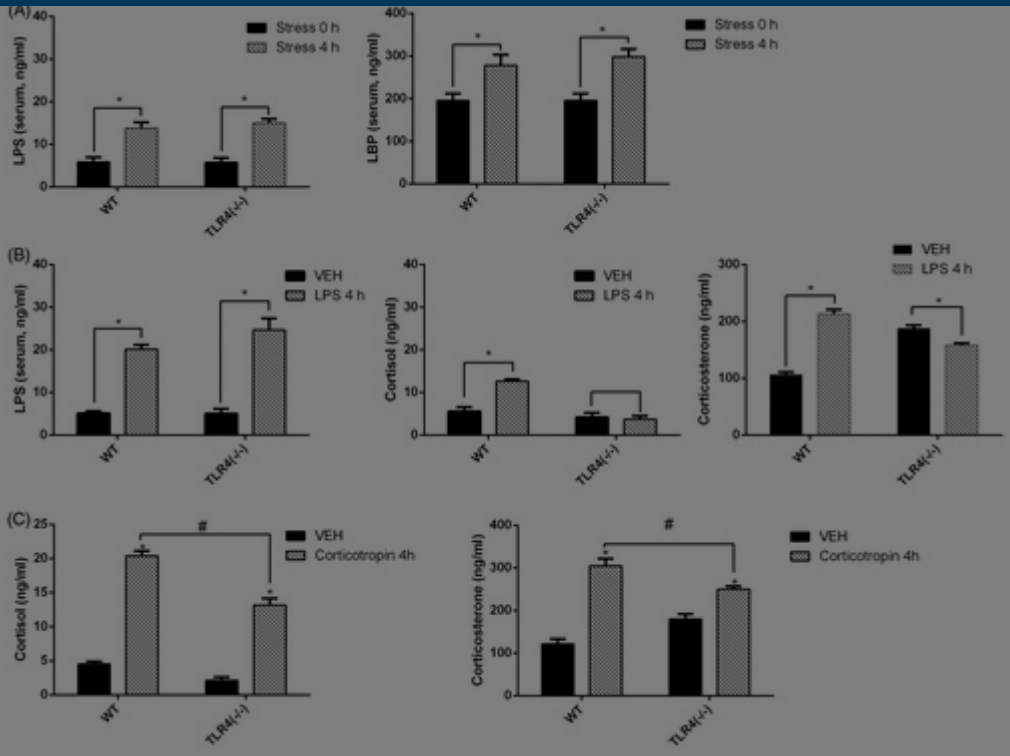

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Cortisol and corticosterone concentrations were measured in mice pretreated with LPS (1% w/v, 2 mg/kg) for 4 h. Serum LPS concentration increased compared to the vehicle-treated group in both WT and TLR4$^{-/-}$ mice (WT: $F = 123.4$, $p < .0001$; TLR4$^{-/-}$: $F = 35.14$, $p = .0004$. All df are (3, 16)), while cortisol concentrations were elevated in LPS-treated as compared to vehicle-treated WT but not TLR4$^{-/-}$ mice (WT: $F = 33.03$, $p = .0004$;

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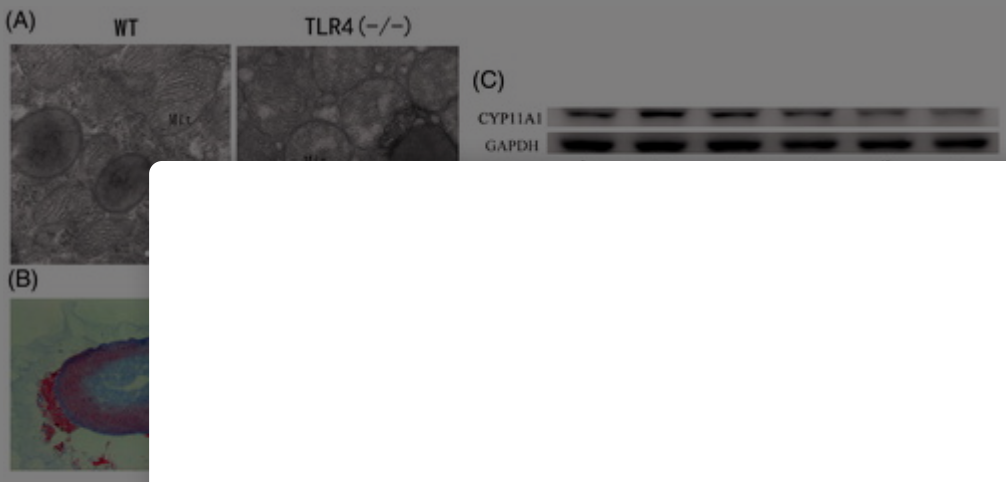
microscopy, obvious reduction in density of lipid-storing droplets was seen in Oil red O-stained whole adrenal frozen section in unstressed TLR4$^{-/-}$ mice (Figure 4(B)).

Figure 4. Ultrastructure, lipid storage, and steroidogenic enzyme content in WT and TLR4$^{-/-}$ mouse adrenal glands. (A) Electron micrographs of adrenocortical cells in the zona fasciculata. Mitochondria (MIT), smooth endoplasmic reticulum, and liposomes (LIP) are visible in the cytoplasm of WT and TLR4$^{-/-}$ mice. Note the round shape, disorganized arrangement of tubulovesicular cristae, and presence of metrical vacuoles in the mutant. Scale bar 1 µm. (B) Cryosections of whole adrenal gland stained with Oil red O in WT and TLR4$^{-/-}$ mice without any treatment showing fewer red-stained lipid-droplets in TLR4 mutant mice. Scale bar 200 µm. (C) Western blotting of adrenal gland protein samples and the corresponding integrated optical density (IOD) ratio values (CYP11A1/glyceraldehyde 3-phosphate dehydrogenase [GAPDH]). The expression of CYP11A1 (P450scc) increased 4 h after stress or lipopolysaccharide (LPS) treatment in WT but decreased in TLR4$^{-/-}$ mice. Results represent mean ± SEM (n = 5 mice per group). *$p < .05$ versus WT vehicle group (isotonic saline). #$p < .05$ (one-way ANOVA, Tukey's test) versus TLR4$^{-/-}$ vehicle group (isotonic saline).



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Discussion

The activation of the inflammatory response and ensuing release of pro-inflammatory cytokines are features of stress-induced peptic ulcers (McGettrick & O'Neill, 2004). The innate inflammatory/immune response is activated after exposure to stressful stimuli. Cold restraint stress can induce a rapid activation of nuclear factor (NF)-κB in rats, the inhibition of which alleviates inflammation and injury (Jia et al., 2007a). The deletion of the NF-κB p50 subunit can alleviate gastric injury by inhibiting NF-κB activation and consequent inflammation (Ye et al., 2013). We previously demonstrated that the activation of the mitogen-activated protein kinase (MAPK) p38 by reactive oxygen species may also play a role in stress-induced gastric damage in rats (Jia et al., 2007b). TLR4 protein is a positive regulator of inflammation (Szumilas et al., 2013). Signaling pathways activated by Toll-like receptors (TLRs) in the innate immune system are linked to the induction of pro-inflammatory cytokines. NF-κB, p38, and the MAPK family member c-Jun N-terminal kinase are the major factors activated by TLR4 (O'Neill, 2006) which, along with its co-receptor MD-2 and some inflammatory mediators, is upregulated by chronic mild stress (Garate et al., 2011). Hence it is a plausible hypothesis that TLR4 may increase gastric injury through the activation of inflammatory pathways in stress ulcer. However, we found just the opposite. In this study, it was observed that water immersion restraint stress-induced gastric ulceration was mor ng inflamm ess condition

Many stu ease in response d ulceration (Filareto n the present s in TLR4$^{-/-}$ mice acharowski et al., 20 corticost er research reported corticoid involved asma cortisol a been determin nermore,

WT and TLR4$^{-/-}$ mice. This indicates that the release of glucocorticoid during acute stress plays an important role in indicating injury and protecting the gastric mucosa during acute stress in mice.

Previous research showed that TLR4 signaling is sufficient to cause glucocorticoid release from adrenal cells (Vakharia & Hinson, 2005). LPS from Gram-negative bacteria, which act via TLR4, stimulates glucocorticoid release (Zacharowski et al., 2006). In addition, translocation from the intestinal flora of bacterial LPS occurs during chronic mild stress (Garate et al., 2011). LBP is essential for the recognition of LPS by TLR4 (Palsson-McDermott & O'Neill, 2004), and it has been found that plasma LPS and LBP expression is upregulated after cold restraint stress, which has been linked to changes in intestinal permeability and bacterial translocation (Garate et al., 2011). In this study, we also found that serum concentrations of LPS and of LBP were upregulated after 4-h water immersion restraint stress. Also, the serum cortisol and corticosterone concentrations both increased 4 h after LPS treatment in this study in WT, but importantly not in the TLR4$^{-/-}$ mice. In contrast, the corticotropin test showed increased circulating glucocorticoid (corticosterone and cortisol) concentrations in both types of mice, although the response was less in TLR4$^{-/-}$ mice. Hence, TLR4 in the adrenal gland is not essential for a response to ACTH, but has an important role in regulating the extent of glucocorticoid release during acute stress.

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the differences in the synthesis and secretion of corticosterone and cortisol by adrenocortical cells between WT and TLR4$^{-/-}$ mice.

Exposure to low concentrations of endotoxin produces long-term changes in HPA axis activity (Shanks et al., 2000). In particular, early-life exposure to Gram-negative LPS increases corticosterone secretory pulse frequency and amplitude (Vakharia & Hinson, 2005). Moreover, preconditioning with mild stress provides gastroprotection to rats during acute stress (Filaretova et al., 2008). In another study, increasing glucocorticoid receptor expression induced a weaker response to restraint stress (Reichardt et al., 2000). Thus, it can be conjectured that long-term exposure to stressful environmental stimuli may promote the neuroendocrine/neuroimmune response during acute stress events, and that this form of adaptation is lost in the absence of TLR4, thereby decreasing protection against the adverse consequences of acute stress.

In summary, TLR4 deficiency resulted in aggravated gastric ulceration that was associated with a reduction in glucocorticoid release during acute stress, an effect that was alleviated by treatment with exogenous cortisol. TLR4 thus plays a gastroprotective role in stress-induced gastric ulceration that is exerted via modulation of glucocorticoid secretion by impacting the ultrastructure and the synthetic function of the adrenal gland through LPS/TLR4 signaling. In addition, as well as corticosterone, cortisol also plays an important role during acute stress in mice.

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