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Participation of NMDA receptors in the lateral hypothalamus in gastric erosion induced by cold-water restraint

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HIGHLIGHTS

- The lateral hypothalamus (LH) is associated with gastric ulceration.
- NMDA lesion of the LH reduced gastric ulceration induced by cold-water restraint.
- Microinfusion of NMDA antagonist APV into the LH reduced stress-induced ulceration.
- NMDA receptors in the LH play a role in pathophysiological changes in the gut.

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ABSTRACT

The present study investigated whether neurons in the lateral hypothalamus (LH) play a role in the occurrence of gastric ulcerations induced by cold-water restraint. The first experiment indicated that bilateral *N*-methyl-D-aspartate (NMDA) lesions of the LH (20 μg/1 μl per side) reduced the amount of gastric ulceration induced by cold-water restraint. In the second experiment, the NMDA antagonist DL-2-amino-5-phosphonovaleric acid (APV; 2.5 μg/0.5 μl per side) or its vehicle was microinjected bilaterally into the LH prior to the cold-water restraint procedure. APV did not induce gastric ulcerations but reduced the amount of ulceration induced by cold-water restraint. These results indicate that NMDA receptors in the LH play an important role in the occurrence of gastric ulceration induced by cold-water restraint. The participation of the LH and possible neuronal circuitry involved in stress-induced ulceration are discussed.

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1. Introduction

Gastric erosions are lesions in the stomach that result from improper function of the gastrointestinal system. They have long been viewed as a prototypical psychosomatic disorder because of the fact that physical and psychological stress can disrupt gastric activity and consequently induce gastric lesions [1–3]. Since the early work of Selye [4,5], a wide variety of experimental methodologies have been developed to reliably induce gastric ulceration in animals [6–9]. One of these methodologies is cold-water restraint. This procedure consists of restraining the animal in a cylindrical tube and then immersing it vertically in cold water (20 ± 1 °C) to the level of the animal's neck. Cold-water restraint has been shown to produce a high amount of gastric ulceration in a short period of time [3,10].

An elaborate network of neuroanatomical structures and neurochemical events regulates the occurrence of gastric ulceration in response to a stressful stimulus. The lateral hypothalamus (LH) is a large, diffuse, and heterogeneous area within the diencephalon with several distinct nuclear groups associated with different metabolic and autonomic functions [11,12]. Several reports indicated that the LH is closely associated with the gastric dysfunction and the occurrence of gastric ulceration (for review, see [13,14]). For example, electrolytic lesions of the LH lead to the development of gastric ulceration within as little as 3 h [15]. More selective lesioning procedures that use neurotoxic agents, such as the excitatory amino acids, *N*-methyl-D-aspartate (NMDA) and kainic acid, also lead to the occurrence of gastric ulceration within 24 h after the lesioning procedure [16–18].

Surprisingly, the participation of the LH in the occurrence of gastric ulceration induced by stress has not yet been investigated. The present report presents two experiments that addressed this issue. The first experiment investigated whether NMDA lesions of the LH reduce the incidence of gastric ulceration induced by cold-water restraint. The second experiment evaluated the effect of the selective NMDA antagonist DL-2-amino-5-phosphonovaleric acid (APV) microinjected into the LH

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on gastric ulceration induced by the same stress-induced ulceration procedure.

2. Materials and methods

2.1. Subjects

Male Wistar rats, weighing 190–260 g, were used. The animals were housed in pairs and had free access to food and water. The room temperature was controlled, and the lighting was maintained on a 12 h/12 h light/dark cycle. The experiment was conducted during the light phase of the cycle. The experimental protocols used in the present study were in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.2. Cold-water restraint procedure

The rats that were subjected to the stressful condition underwent the cold-water restraint procedure. Each rat was restrained in a polyvinyl chloride tube (17.5 cm length, 5.2 cm inner diameter). After restraining the animal, the tube and animal were vertically immersed to the level of the xiphoid process of the sternum in a 64 l tank of water maintained at 20 ± 1 °C for 3 h. The water level was continuously monitored so that the animal's body was always covered by the water, and the head was invariably above the water surface. The rats that were subjected to the nonstressful condition underwent the same procedure, with the exception that they were not restrained or exposed to cold water. Instead, they were placed in a holding cage (30 × 30 × 28 cm) and left undisturbed for the same period of time.

2.3. NMDA lesion of the LH

The rats were food-deprived but not water-deprived overnight prior to surgery. Under thiopental anesthesia (45 mg/ml), the animals were mounted in a stereotaxic frame with the upper incisor bar set 3.3 mm below the interaural line such that the skull was horizontal between bregma and lambda. Each animal received a bilateral microinjection of 1 μl NMDA (Sigma, St. Louis, MO, USA) dissolved in saline at a dose of 20 μg/μl into each side of the LH. The NMDA dose was based on our previous work [16]. With reference to the Paxinos and Watson atlas [19], the LH coordinates were 2.4 mm posterior to bregma, 1.9 mm lateral to midline, and 7.8 mm ventral to dura. The drug infusion was made using a stainless steel cannula (28 gauge, Plastics One, Roanoke, VA, USA) connected to a 10 μl Hamilton microsyringe via polyethylene tubing. The Hamilton syringe was mounted in an injection pump set to deliver 1 μl of the drug over 15 min. Following the infusion, the cannula was kept in place for an additional 5 min to prevent the drug from diffusing up the cannula track. Before and after each injection, the flow at the tip of the cannula was verified by turning the pump on until a droplet appeared. Sham-lesioned animals underwent the same procedure, with the exception that they were infused with an equal volume of saline vehicle. After surgery, the animals were returned to their home cages and food-deprived for an additional 24 h, at which time the experiment began. This additional postoperative food deprivation period was employed so that the rate of gastric erosion formation would not be influenced by the presence of food in the stomach in some animals but not others. The animals were randomly divided into four independent groups according to a 2 × 2 factorial design. The first factor was the presence or absence of the LH NMDA lesion. The second factor was the presence or absence of cold-water restraint.

2.4. Microinfusion of APV into the LH

The animals were implanted with bilateral guide cannulae (22 gauge, Plastics One, Roanoke, VA, USA) in the LH according to the surgical procedures described above. The coordinates were also the same, with the exception that that bilateral guide cannula was aimed 7.3 mm ventral to dura. The animals were allowed a minimum of 7 days to recover from surgery. APV (Sigma, St. Louis, MO, USA) was dissolved in saline in a volume of 0.5 μl per side of the LH. The dose of APV (2.5 μg/0.5 μl per side) was selected based on a previous study [20]. The microinfusion was made using an internal cannula (28 gauge, Plastics One, Roanoke, VA, USA), which was introduced and lowered 0.5 mm below the guide cannula. The injection cannula was connected to a 10 μl Hamilton syringe via polyethylene tubing. The Hamilton syringe was mounted in an injection pump set to deliver 1 μl of drug over 5 min. The internal cannula remained in place for at least 1 min after the microinfusion before being pulled out. The animals were randomly divided into four independent groups according to a 2 × 2 factorial design. The first factor was the microinjection of APV or saline vehicle. The second factor was the presence or absence of cold-water restraint. The animals had free access to food and water, except for 48 h before beginning the experiment when they were food-deprived but not water-deprived.

2.5. Histology

At the end of the experiment, the animals were sacrificed with an overdose of thionembutal and intracardially perfused with saline followed by 10% formalin solution. The brains of all of the animals were removed and stored in 10% formalin for at least 2 weeks, sectioned at 50–60 μm using a cryostat, mounted on slides, and stained with thionin. The extent of brain damage (i.e., neuronal cell loss) produced by the microinjection of NMDA was evaluated with reference to the Paxinos and Watson [19] rat brain atlas. The cannula locations were evaluated by microinjecting Evans Blue (2%) at the same volume as APV to mark the drug injection sites. Data from animals with misplaced NMDA lesions or APV microinjections were excluded from the statistical analysis.

2.6. Quantification of gastric mucosal damage

The stomach of each animal was also removed. A ligature was placed around the duodenum and esophagus. Three milliliters of 10% formalin was infused into the stomach through the esophagus. Ten minutes later, the stomach was opened along the great curvature, rinsed gently with water, spread on a flat surface, and fixed with 10% formalin. The stomachs were stored in formalin for several weeks, after which the gastric mucosa was examined using a binocular dissection microscope at 8× magnification. One eyepiece was fitted with a reticle that permitted the gastric lesions to be quantified in terms of total area (mm^2). Any discontinuity in the gastric mucosa was considered as a gastric erosion. An independent rater who was blind to the experimental conditions examined all of the stomachs. The total area was estimated by multiplying the length and width of the lesioned area.

2.7. Statistical analysis

The gastric ulceration results are graphically expressed as mean ± standard error of the mean (SEM). A two-way analysis of variance (ANOVA) was used to detect overall differences among groups. Fisher's least significant difference (LSD) *post-hoc* test was used to determine significant differences between groups. The level of statistical significance was $p < 0.05$.

3. Results

3.1. Experiment 1: effect of NMDA lesion in the LH on gastric ulceration induced by cold-water restraint

The bilateral LH microinfusions of NMDA were located in the dorsolateral portion of the LH and centered in the middle portion of the anterior–posterior extent of the ventromedial hypothalamic nucleus. Cell loss was

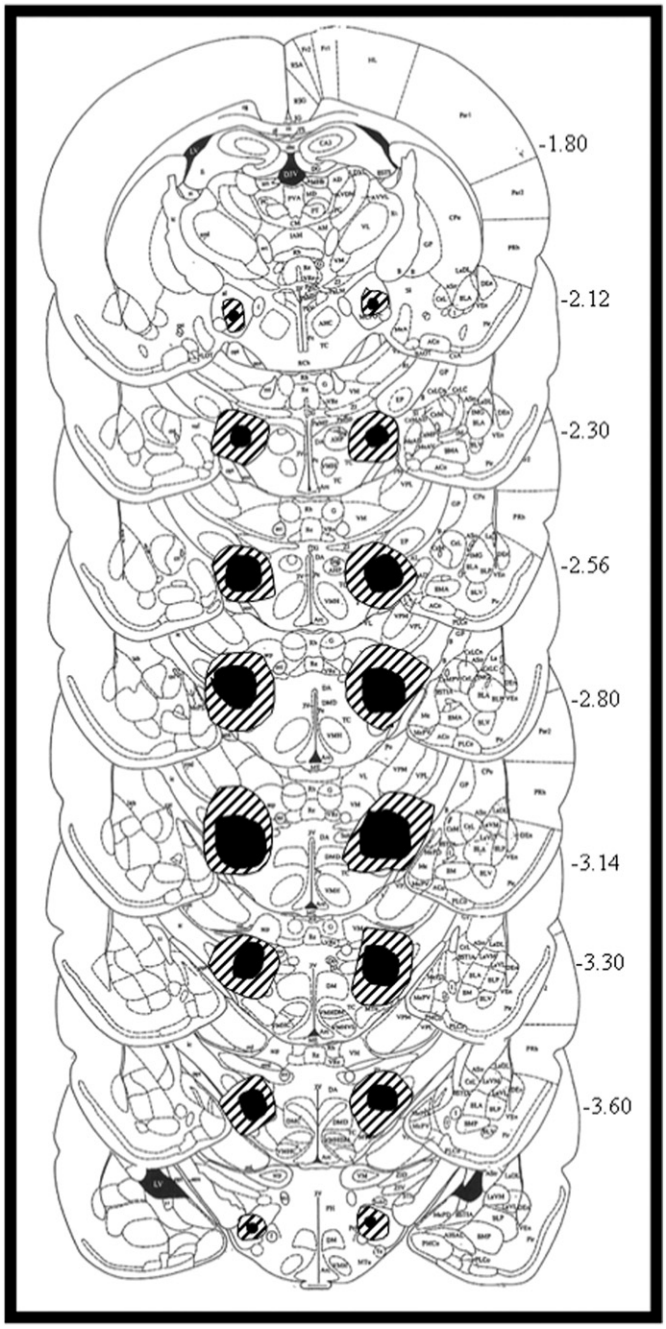

Fig. 1. Composite of coronal sections adapted from the Paxinos and Watson [19] rat brain atlas. Numbers indicate the distance in millimeters from bregma. The figure shows the smallest (black) and largest (striped) areas of damage in the LH.

primarily observed in the LH proper, but some damage was also found in adjacent areas, including the centromedial tip of the internal capsule, fornix, fields of Forel, zona incerta, and lateral borders of the ventromedial nucleus of the hypothalamus. Histological aspects of the bilateral NMDA LH lesions were similar to those described in one of our previous reports (16). Fig. 1 presents a composite of the representative histological section of the smallest and largest lesions in the LH of the present study.

The presence of gastric mucosal injury was observed in the glandular portion of the stomach. The gross appearance was typically spherical or oblong and superficially covered with blood. Fig. 2 presents an illustrative photograph of gastric ulceration induced by cold-water restraint.

Fig. 3 presents the mean (±SEM) gastric mucosal damage among animals with bilateral sham or NMDA lesions of the LH that were exposed or not to the cold-water restraint procedure. The 2 × 2 ANOVA revealed

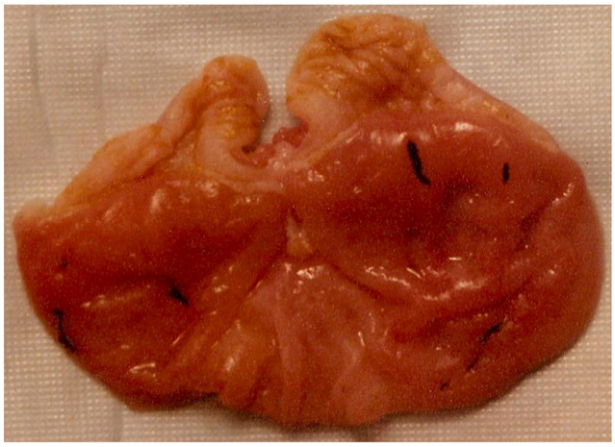

Fig. 2. Representative photograph of gastric ulceration induced by cold-water restraint in the rat stomach.

significant main effects of lesioning ($F_{1,3} = 6.8$, $p < 0.05$) and cold-water restraint ($F_{1,3} = 11.7$, $p < 0.01$) and a lesioning × cold-water restraint interaction ($F_{1,3} = 9.1$, $p < 0.01$). The *post-hoc* comparisons indicated that sham-lesioned animals that were exposed to cold-water restraint exhibited significantly more stomach ulcerations compared with the other groups (all $p < 0.05$). NMDA lesions in the LH reduced gastric ulcerations induced by cold-water restraint. Stressed animals that received lesions in this area exhibited less gastric ulceration compared with sham-lesioned and stressed animals ($p < 0.05$). Non-stressed animals that received NMDA lesions in the LH exhibited more gastric ulcerations compared with sham-lesioned and nonstressed animals ($p < 0.05$).

3.2. Experiment 2: effect of APV microinfusion into the LH on gastric ulceration induced by cold-water restraint

Fig. 4 presents a composite of cannula tip locations among the animals that were microinjected with APV or saline. All of the cannulae were located within the LH.

Fig. 5 shows the mean (±SEM) gastric mucosal damage in rats microinjected with APV or saline and exposed or not to the cold-water restraint procedure. The two-way ANOVA revealed significant main effects of microinjection ($F_{1,3} = 4.5$, $p < 0.05$) and cold-water restraint ($F_{1,3} = 14.6$, $p < 0.01$) and a microinjection × cold-water restraint interaction ($F_{1,3} = 5.1$, $p < 0.05$). The *post-hoc* comparisons indicated that stressed animals that were microinjected with saline into the LH

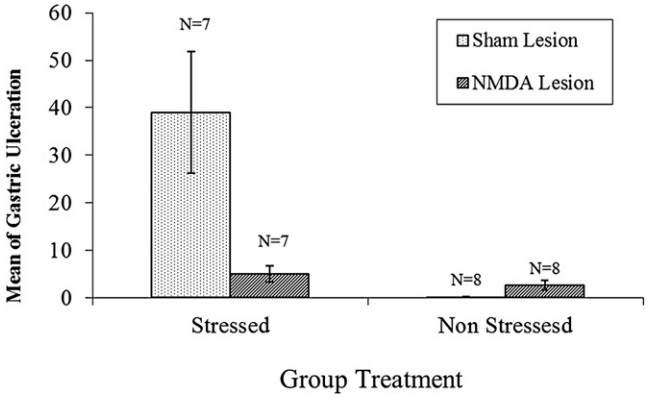

Fig. 3. Mean (±SEM) total area of glandular gastric ulcerations in rats with bilateral sham or NMDA lesions of the LH among animals exposed (stressed) or not exposed (nonstressed) to the cold-water restraint procedure. The number of animals in each group (n) is shown above each column.

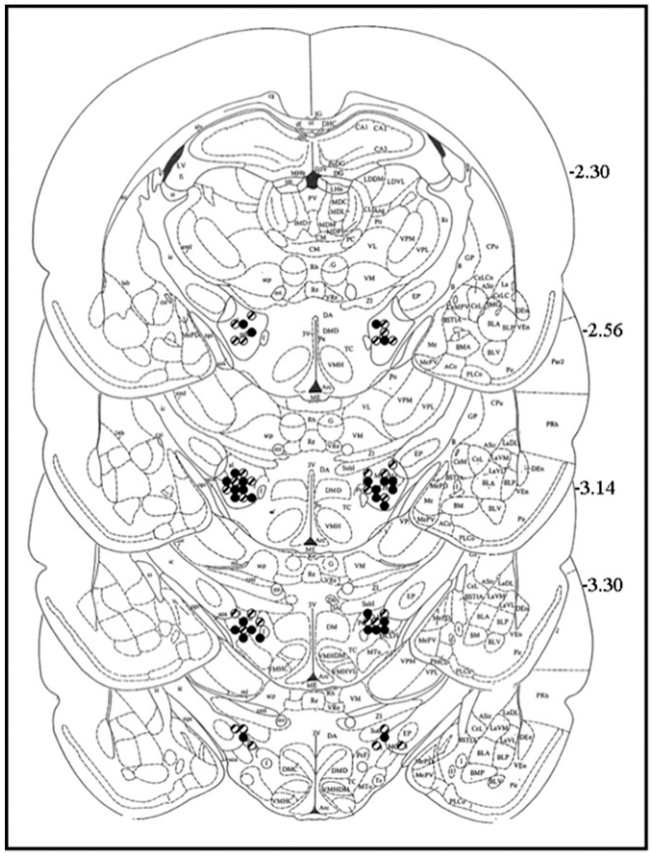

Fig. 4. Composite of cannula locations aimed at the LH. With reference to the Paxinos and Watson atlas [19], the numbers on the right side of each plate indicate the distance from bregma. Black circles represent the APV group, and striped circles represent the saline control group.

exhibited significantly more stomach ulcerations compared with the other groups (all $p < 0.05$). NMDA lesions in the LH reduced gastric ulceration induced by cold-water restraint. Stressed animals that were microinjected with APV exhibited less gastric ulcerations compared with stressed animals that were microinjected with saline vehicle ($p < 0.05$). No significant differences were found between non-stressed animals that were microinjected with APV or saline ($p > 0.2$).

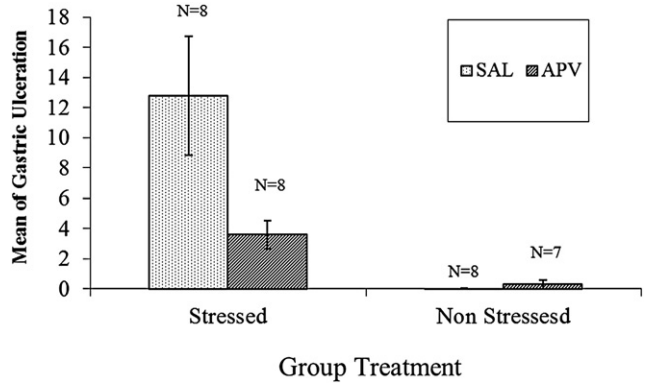

Fig. 5. Mean (±SEM) total area of glandular gastric ulcerations in rats that received APV or saline (SAL) microinjections into the LH among animals exposed (stressed) or not exposed (nonstressed) to the cold-water restraint procedure. The number of animals in each group (n) is shown above each column.

4. Discussion

The results of the present study indicated that NMDA receptors in the LH are implicated in gastric ulceration. NMDA lesions in the LH produced small but reliable gastric mucosal erosions within 24 h after surgery. These results are consistent with previous reports, in which electrolytic or neurochemical LH lesions also produced the formation of gastric erosion [17–19], and suggest that this effect might be mediated by the hyperactivation of LH cells [17]. Previous reports have shown that electrical or chemical stimulation of the LH increased acid secretion [21,22], and electrical stimulation or electrolytic lesions of the LH increased stomach motility [23–25]. Gastric erosion observed 24 h after NMDA lesion appears to be mediated by an acute, abrupt excitatory effect on LH neurons. Therefore, overactivation of the cells that precedes cell death, rather than cell death per se, appears to cause gastric erosions. Supporting this possibility, the present study also found that pharmacological blockade of NMDA receptors in the LH with APV did not, by itself, lead to the formation of gastric erosion.

Important for the present study is the fact that NMDA lesions in the LH or microinfusion of APV in the LH led to resistance to the development of subsequent gastric erosion induced by cold-water restraint. These results are consistent with the view that stress-inducing procedures might produce the excessive activation of LH neurons over a sustained period of time, leading to the development of pathophysiological changes in the gut. Permanent destruction of LH neurons with neurotoxic doses of NMDA or temporary blockade of NMDA receptors with APV in the LH prior to exposure to the stressor reduced the occurrence of gastric erosions induced by cold-water restraint.

Several neural pathways in the LH might participate in stress-induced ulcerations. Some of these neural circuitries are presented in Fig. 6. Direct and indirect descending projections from the LH reach the dorsal vagal complex (DVC), which in turn gives rise to the vagus nerve [26–28]. The DVC consists of the nucleus of the tractus solitarius (NTS) and dorsal motor nucleus of the vagus (DMN) and functions as a final common pathway for the regulation of gastric activity (e.g., gastric secretion and contractility).

Several results indicated that the amygdaloid complex is also implicated in the regulation of gastric function [29]. For example, electrolytic lesions of the central nucleus of the amygdala reduce gastric erosions produced by physical restraint, whereas lesions in the basolateral

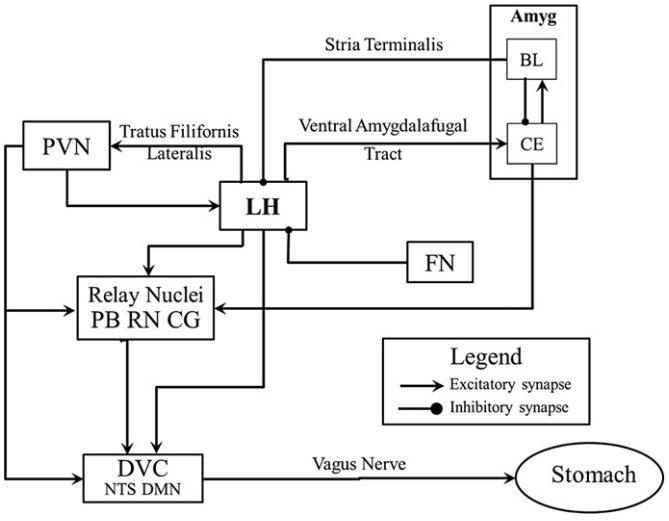

Fig. 6. Flow diagram that illustrates the neural circuitry that underlies the participation of the LH in stress-induced ulcerations. BL, basolateral nucleus of the amygdala; CE, central nucleus of the amygdala; CG, central gray; DMN, dorsal motor nucleus of the vagus; DVC, dorsal vagal complex: FN, fastigial nucleus; LH, lateral hypothalamus; NTS, nucleus of the tractus solitarius; PB, parabrachial nucleus; PVN, paraventricular nucleus of the hypothalamus; RN, raphe nuclei; SN, substantia nigra.

portion of the amygdala increase the severity of gastric ulcerations caused by stressors [30]. These results suggest that the central nucleus of the amygdala has excitatory actions, whereas the basolateral amygdala has inhibitory actions on gastrointestinal function associated with physical stressors. As shown in Fig. 6, both amygdaloid nuclei have reciprocal connections, and the central nucleus has direct and indirect projections to the DMN [31]. Neuroanatomical connections between the LH and amygdaloid complex might also be involved in gastric ulceration. Destruction of the central nucleus of the amygdala has been shown to reduce gastric erosions produced by electrolytic lesions of the LH [32]. There are excitatory projections from the LH to central nucleus of the amygdala via the ventral amygdalofugal pathway, and these excitatory projections are involved in stress-induced ulcerations.

The LH also receives inhibitory projections from the basolateral nucleus of the amygdala through the stria terminalis [33–35]. Coronal incisions anterior to the LH, which likely severed fibers of the stria terminalis, enhanced gastric erosions produced by NMDA lesions of the LH [17]. This finding suggests that bilateral projections between the LH and amygdaloid complex regulate the occurrence of gastric ulcerations through a negative feedback mechanism. Accordingly, the LH may activate the central nucleus of the amygdala, mainly through the ventral amygdalofugal pathway, which in turn activates the DVC either directly or indirectly. The central nucleus of the amygdala also activates the basolateral nucleus of the amygdala, which then sends reciprocal inhibitory projections to the central nucleus of the amygdala. As reported by Henke [30], lesions of the basolateral amygdaloid nucleus may facilitate stomach ulcerations following physical restraint by eliminating inhibitory feedback from the basolateral nucleus to the central nucleus of the amygdala. The basolateral nucleus of the amygdala also projects inhibitory fibers to the LH, mainly through the stria terminalis. The activation of LH neurons during cold-water restraint may activate neurons in the central nucleus of the amygdala. This then triggers inhibitory feedback from the basolateral nucleus of the amygdala to the LH. This inhibitory signal serves to dampen the activity of LH neurons that ultimately contributes to the formation of gastric erosion.

Fig. 6 also shows the connections between the cerebellum and LH [36]. These projections are important because the LH also mediates the participation of the cerebellar fastigial nucleus in gastric ulceration induced by cold-water restraint. Electrical or pharmacological stimulation of the fastigial nucleus with L-glutamic acid [37] or bicuculline, a γ-aminobutyric acid receptor A ($GABA_A$) antagonist attenuated gastric mucosal damage induced by cold-water restraint [38]. This protective effect was prevented by pretreatment with the $GABA_A$ receptor antagonist bicuculline into the LH, indicating that the fastigial nucleus protective effect on LH might be mediated by inhibitory neurotransmitter GABA. Moreover, the inactivation of the fastigial nucleus by local infusion of the $GABA_A$ receptor agonist muscimol [38] or baclofen [39] exacerbated gastric mucosal damage induced by cold-water restraint. This intensifying effect of fastigial nucleus inactivation was abolished by electrical lesions of the decussation of the superior cerebellar peduncle or chemical lesions of the LH with kainic acid [38]. Therefore, the fastigial nucleus appears to play a protective role in stress-induced ulceration through inhibitory ascending projections to the LH.

In conclusion, the present study demonstrated that NMDA lesions of the LH or microinfusions of the NMDA antagonist APV into the LH reduced gastric ulceration induced by cold-water restraint. These results suggest that the LH plays an important role in stress-induced ulceration, representing an important component of neural circuitry that involves other brain structures, such as the amygdaloid complex and fastigial nucleus of the cerebellum.

Author disclosure statement

The author has no financial conflicts of interest.

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