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Research report

Gastric mucosal erosion produced by NMDA microinfusions in the lateral hypothalamus: effect of selective knife cuts

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Abstract

Bilateral infusions of *N*-methyl-D-aspartate (NMDA) into the lateral hypothalamus (LH) produce gastric erosions in rats. The present study attempted to determine the neural pathways that mediate this effect. In order to interrupt axonal transmission, knife cuts (KC) were made in different planes adjacent to the LH. In separate groups of rats, KC were made anterior, posterior or lateral to the LH just prior to bilateral NMDA infusions (20 μg/μl). The incidence of gastric erosions was measured 24 h after NMDA infusions. Animals receiving sham KC and infused with NMDA exhibited significantly more gastric erosions than those infused with vehicle. Lateral parasagittal KC blocked the occurrence of gastric erosions produced by NMDA, whereas anterior coronal KC significantly increased the incidence of erosions produced by NMDA. Posterior coronal KC did not alter the incidence of gastric erosions produced by NMDA infusions into the LH. These results suggest that intrinsic LH neurons with gastric function project axons laterally and probably descend through the internal capsule to brainstem medullary nuclei. The results of the anterior KC suggest that the LH sends and/or receives inhibitory projections from neural structures (possibly the amygdaloid complex) anterior to the plane of the KC.

Keywords: Lateral hypothalamus; NMDA; Ulceration; Gastric activity; Stomach; Knife cuts; Neural circuitry; Fiber tracts

1. Introduction

Several reports indicate that the lateral hypothalamus (LH) is notably associated with gastric activity. For example, bilateral electrolytic LH lesions produce a number of gastric effects such as increase in gastric secretion [59], change in gastric mucosal barrier function [16] and bile reflux [18], increases in stomach contractility [12,20] and the formation of gastric erosions [15,34,53].

It has been shown that microinfusions of neurotoxic doses of a variety of excitatory amino acids, such as kainic acid, ibotenic acid and *N*-methyl-D-aspartate (NMDA), in the LH lead to the formation of gastric mucosal erosions within 24 h of surgery [33,50]. These results indicate that intrinsic LH cell bodies are involved in the occurrence of gastric mucosal ulceration. Moreover, since excitatory amino acid produces excitotoxic effect through a hyperactivation of the cell [51], it is suggested that the occurrence of gastric erosions after the infusion of excitatory amino acid in the LH might be mediated through an hyperactivation of these cells. In support of this 'hyperactivation hypothesis' is the fact that LH electrical or chemical stimulation increases acid secretion [7,36] and stomach motility [10,13]. Moreover, LH electrolytic lesions lead to the development of gastric erosions within as little as 3 h post-lesion [14] and tend to disappear within 1 week after LH lesion with adequate postoperative care and nutrition.

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Likewise, recovered LH rats with NMDA lesions appear to be ulcer-free 3–5 weeks after surgery [62]. It appears, therefore, that the occurrence of gastric erosion observed 24 h after excitatory amino acid neurotoxic infusions in the LH is mediated by an acute abrupt excitatory effect on the LH neurons. Thus, it may not be cell death per se, but the over-activation of the cell that precedes its death, that appears to cause gastric erosions.

Another question regarding the participation of the LH in the occurrence of gastric ulceration is the neural circuitry responsible for the development of gastric erosions produced by excitatory amino acid microinjected in the LH. A useful method generally employed to analyze the input and output pathways involved in the circuitry of a control system is to leave cell bodies intact but to make selective knife cut that severe axonal fibers of passage [6,21,54].

Descending projections from the LH innervate several brainstem structures through different tracts including the periventricular fiber system, the central tegmental tract and the medial forebrain bundle [4]. The periventricular system is mainly responsible for the LH projections with the central gray and superior colliculus [2,4]. The LH also contributes fibers to the central tegmental tract, which projects to the central gray, and the superior layers of the superior colliculus [4] but takes a more medial route than the periventricular system. The caudal portion of the medial forebrain bundle maintains connections between the LH and dorsal, medial and magnus raphe nuclei [3,9,60], dorsal tegmental nuclei [4], parabrachial nucleus [2,52], and locus coeruleus [30]. Descending projections from the LH reach important visceral nuclei, including the nucleus of the solitary tract (NTS) and the dorsal motor nucleus (DMN) of the vagus nerve [4,28,49].

Ascending projections from the LH innervate several cortical areas, including the frontal cortex [27,31,56] the lateral and medial septal nuclei [8,35,58], the lateral and medial portions of the habenula via the stria medullaris [4,26,42], the nucleus of the diagonal band of Broca and the substantia inominata [42]. The LH also sends anterior projections to the amygdaloid complex [1]. The amygdala receives fibers from the LH via the stria terminalis and the ventral amygdalofugal pathway [41,45,46,61]. Fibers from the stria terminalis leave the LH dorsally and dorsomedially, and course through the rostral pole of the thalamus. At a ventral plane, these fibers turn laterally and reach the central and basolateral nucleus of the amygdala [4]. The ventral amygdalofugal system passes laterally between the optic tract and the internal capsule to terminate mainly in the central nucleus of the amygdala [4]. Rostral regions of the LH project primarily to the central nucleus of the amygdala whereas the caudal region of the LH project primarily to the basolateral, basomedial and lateral nuclei of the amygdala [5,39].

The purpose of the present experiment was to investigate which central pathways might mediate the induction of stomach ulceration following a neurotoxic dose of NMDA microinjected in the LH. In order to interrupt axonal transmission, transections were made in different planes adjacent to the LH region. Knife cuts were made anteriorly, posteriorly or laterally to the LH immediately prior to bilateral NMDA microinjections in the LH. Control animals were given sham knife cuts and/or sham NMDA infusions. 24 h following these procedures, stomachs were removed and examined for the presence of erosions.

2. Materials and methods

2.1. Animals

Forty experimentally naive male albino Sprague–Dawley (Bantin Kingman) rats weighing 240 and 330 g were used in this study. They were individually housed in a colony room with a 12:12 h light–dark cycle and had ad lib access to food pellets (Purina Laboratory Chow) and tap water for at least 1 week prior to the experiment.

2.2. Surgery

Rats were food but not water deprived overnight and were then anesthetized with sodium pentobarbital (Nembutal, 65 mg/kg, i.p.) and mounted in a David Kopf model 900 stereotaxic instrument. Bilateral anterior coronal knife cuts were made between the anterior extremity of the LH and the posterior portion of the anteroventral preoptic nucleus. The guide shaft of the knife assembly was placed 0.6 mm anterior to bregma and 2.0 mm lateral to each side of the midline. For the bilateral coronal posterior knife cuts, the guide shaft was placed 5.0 mm posterior to bregma and 2.5 mm lateral to each side of the midline. Lateral knife cuts were made sagittally to the midline. The guide shaft was placed 0.6 mm posterior to bregma and 2.0 mm lateral to each side of the midline. In all three instances the guide shaft was lowered to the ventral surface of the skull. After that, the guide was raised 2.0 mm from the ventral surface of the skull and the wire knife was extended 1.0 mm at an angle of approximately 90°. Cuts were made by lowering the wire knife 2.0 mm to the ventral surface of the skull. In the case of the anterior or posterior knife cuts, the wire knife, when extended, was projected to the midline. In the case of the lateral cuts the wire knife projected posteriorly. Animals with sham knife cuts had the same knife cut procedure with the exception that the wire knife was retracted during the entire procedure.

Microinfusions of NMDA in the LH were performed immediately after the sham cuts or knife cuts. With reference to the Paxinos and Watson atlas [43], LH coordinates were 2.4 mm posterior to bregma, 1.9 mm lateral to each side of midline and 7.8 mm ventral to dura of the brain. Animals received a bilateral infusion of 1 μl of NMDA (Sigma, St. Louis, MO) dissolved in 0.1M phosphate buffer saline (7.4 pH). The NMDA dose was 20 μg/μl and the drug was made fresh. Drug infusion was made by a glass micropipette connected to a 10 μg/μl Hamilton micro syringe via a PE tubing. The Hamilton syringe was mounted on a injection pump set up to deliver 1 μl of the drug over 15 min. Following the infusion, the micropipette was kept in place for an additional 5 min to prevent the drug from diffusing up the micropipette track. Before and after each injection the flow at the tip of the micropipette was verified by turning the pump on until a droplet appeared. Control animals were infused with an equal volume of vehicle PBS alone.

After surgery, animals were returned to their home cages and were food deprived for an additional 24 h. Following the postoperative deprivation period animals were given a lethal injection of sodium pentobarbital and sacrificed by decapitation. A ligature was placed around the duodenum and the esophagus and approximately 3 ml of 10% formalin was infused into the stomach through the esophagus. Approximately 10 min later, the stomach was opened along the great curvature rinsed with water and spread on a flat surface and fixed with 10% formalin. The stomachs were stored in formalin for several weeks and after this time the gastric mucosa was examined with a binocular dissection microscope at $8\times$. One eyepiece was fitted with a reticle permitting gastric lesions to be quantified in terms of total area (mm^2). Any discontinuity in the gastric mucosa was considered a gastric erosion. All stomachs were examined by an independent rater who was blind to the experimental conditions.

Brains of all animals were removed and stored in 10% formalin for about a week, sectioned using the cryostatic method at 50–60 μm, mounted on slides and stained with thionin. The extent of the knife cuts as well as the brain damage produced by the microinjection of the NMDA was evaluated with the reference to the Paxinos and Watson [42] rat brain atlas. Data obtained from animals with misplaced cuts or NMDA injections in the LH were excluded from statistical analysis.

2.3. Procedure

The experimental design of this experiment included five groups. One group of animals (ANT CUT/LH NMDA, $n=11$) was given bilateral coronal knife cuts anterior to the LH. A second group (POST CUT/LH NMDA, $n=8$) received bilateral coronal knife cuts placed posteriorly to the LH and a third group (LAT CUT/LH NMDA, $n=8$) received bilateral parasagittal knife cuts placed lateral to the LH. Animals in these three groups were then given bilateral NMDA infusions into the LH immediately following completion of the knife cuts. Animals in the fourth group (SHAM CUT/LH NMDA) received sham bilateral knife cuts placed anteriorly ($n=3$), posteriorly ($n=2$) or laterally ($n=2$) to the LH. After the sham cuts, animals were given bilateral NMDA infusions in the LH. Animals in the fifth control group (SHAM CUT/LH SHAM) were also given sham bilateral knife cuts (anterior, $n=2$; posterior, $n=2$; or lateral, $n=2$) and then bilaterally infused with PBS vehicle into the LH. The latter two groups served as sham knife-cut controls.

2.4. Data analyses

Since group means and variance tended to covary and the distribution were also positively skewed, a $\log(X+1)$ transformation was conducted on the gastric erosion raw data for each animal. A one-way analysis of variance was used to detect overall differences followed by a student t-test to determine specific differences between groups.

3. Results

3.1. Histology

Five animals were excluded from the experiment due to death during surgery, misplaced cuts or NMDA infusions in the LH. The final group samples were ANT CUT/LH NMDA, $n=9$; LAT CUT/LH NMDA, $n=6$ and POST CUT/LH NMDA, $n=7$. No changes occurred in any of the control groups.

Bilateral LH microinfusions of NMDA were located in the dorsolateral portion of the LH and centered at the middle portion of the anterior–posterior extent of the ventromedial hypothalamic nucleus. Cell loss was primarily observed in the LH proper but some damage was also found in adjacent areas including the ventromedial tip of the internal capsule, fornix, fields of Forel, zone incerta and the lateral borders of the ventromedial nucleus of the hypothalamus. Representative examples of the different types of knife cuts are shown in Fig. 1. The anterior coronal cuts (Fig. 1A) were positioned between the preoptic area and anterior border of the anterior and lateral hypothalamic nuclei. Cuts extended from the lateral border of the LH and the fornix, forming a transection anterior to the midlateral region to anterior hypothalamus. Posterior coronal cuts (Fig. 1B) were positioned along the posterior border of the LH and extended from the medial border of the internal capsule to the region of the fornix and mamillotha-

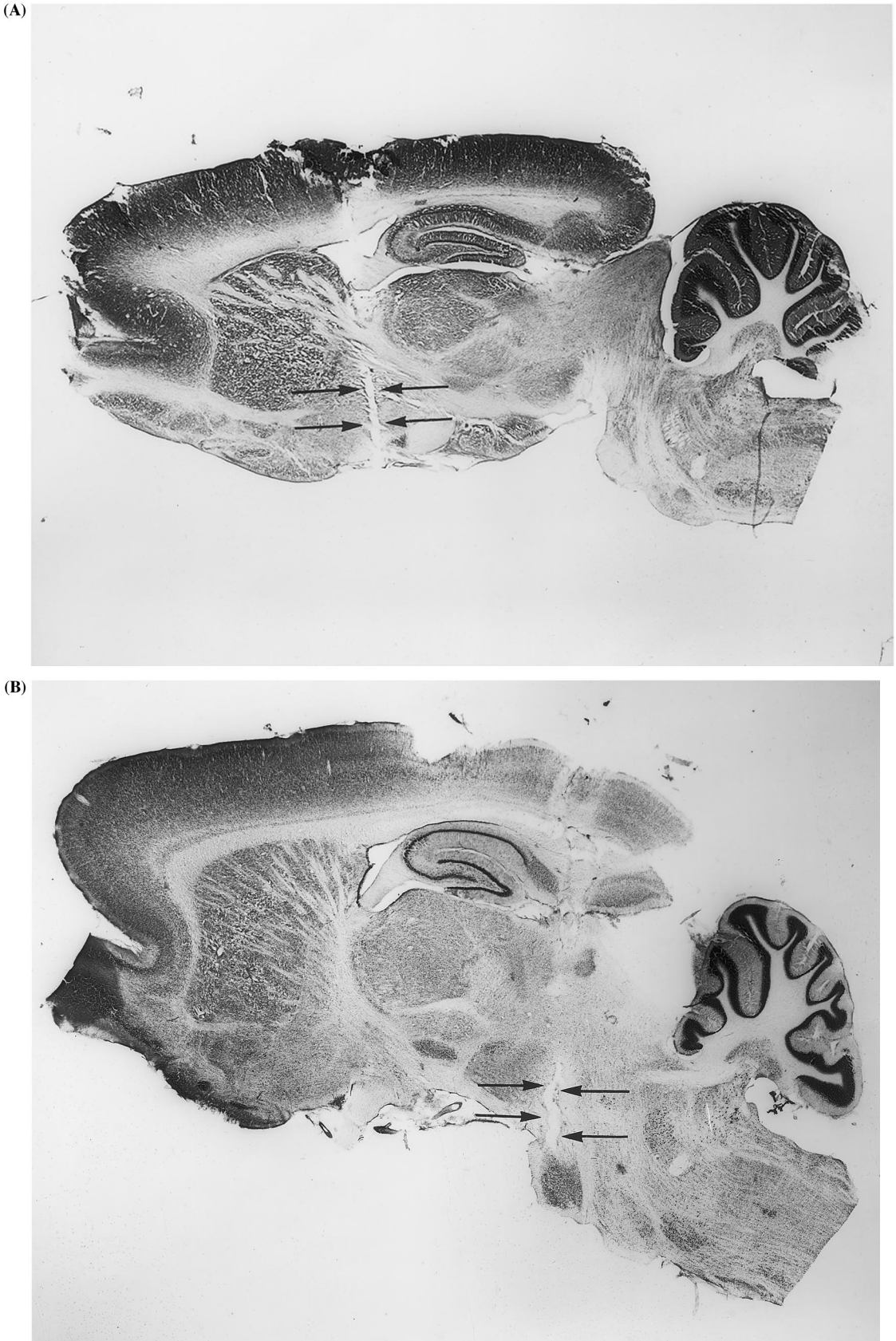

Fig. 1. Representative histological section showing the location of (A) anterior coronal, (B) posterior coronal and (C) lateral parasagittal knife cuts.

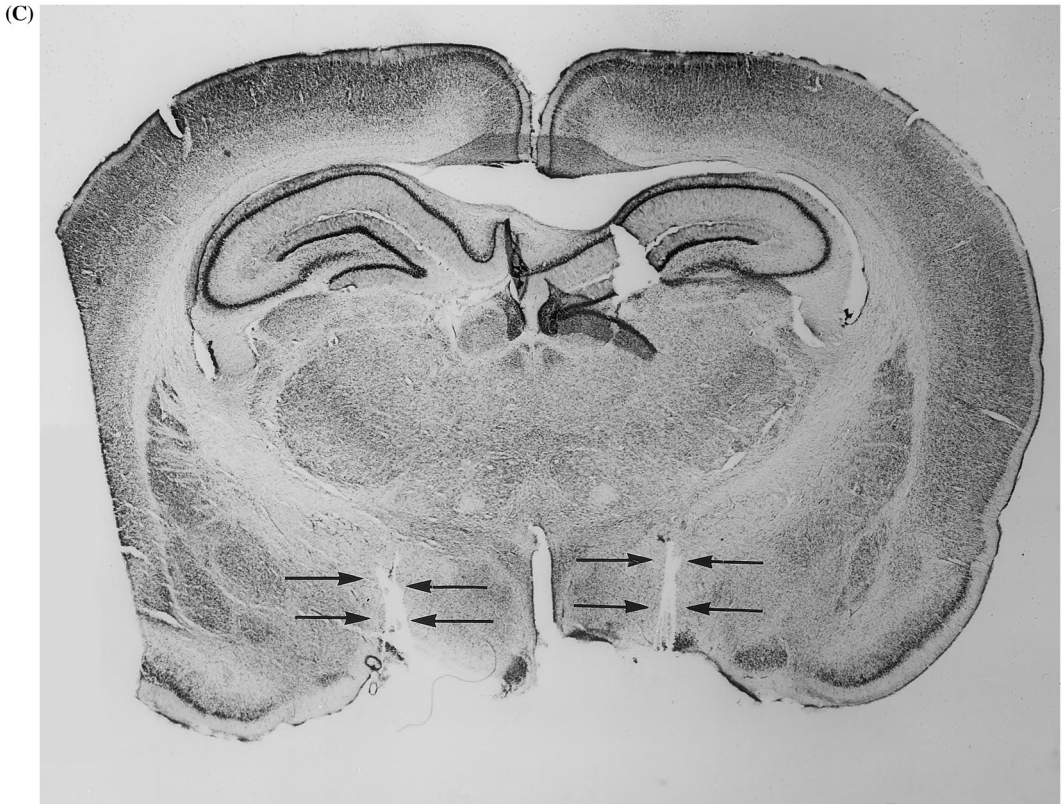

Fig. 1. (*Continued*)

lamic tract. In the ventrodorsal plane, cuts typically extended from the bottom of the brain to the fields of Forel. Lateral cuts (Fig. 1C) coursed along the edge of the internal capsule and the lateral border of the LH and extended from the region of the optic chiasm to the anterior border of the fields of Forel. These cuts extended from the base of the brain to the lateral extent of the zona incerta and occasionally to the ventral border of the thalamus. A schematic representation of the three different knife cuts is shown in Fig. 2.

3.2. Gastric erosions

The stomachs of animals bearing sham anterior, lateral or posterior knife cuts and given vehicle injections in the LH were similar in appearance and did not exhibit any occurrence of gastric mucosal erosions. Therefore the data from these subgroups were pooled for statistical purposes. Animals with sham anterior, lateral or posterior knife cuts but receiving NMDA infusions in the LH displayed similar degree of gastric erosions and were also pooled in a single group.

Mean glandular gastric erosions for each group is presented in Fig. 3. An overall difference among the groups was significant ($F(4,30) = 8.55$; $p = 0.0001$). A reliable difference in the gastric mucosal erosions was found between the sham knife cut groups given PBS vehicle or NMDA infusions in the LH ($p < 0.01$) indicating that microinjections of NMDA in the LH reliably produced stomach erosions. Posterior knife cuts did not significantly alter the incidence of gastric erosions produced by NMDA infusions in the LH (POST CUT/LH NMDA vs. SHAM CUT/LH NMDA, n.s.). However, lateral cuts effectively blocked the occurrence of gastric erosions produced by NMDA infusions in the LH (LAT CUT/LH NMDA vs. SHAM CUT/LH NMDA, $p < 0.03$). An absence of a reliable difference between the LAT CUT/LH NMDA and the SHAM CUT/SHAM NMDA ($p > 0.5$), indicates that lateral knife cuts were effective in blocking the formation of stomach erosions produced by NMDA infusions in the LH. Surprisingly, anterior knife cuts drastically enhanced the production of gastric erosions induced by microinjections of NMDA in the LH (ANT CUT/LH NMDA vs. SHAM CUT/LH NMDA, $p < 0.03$).

4. Discussion

The main purpose of the present study was to begin to explore the potential central pathways that might mediate the gastric erosions produced by excitatory amino acid infusions in the LH. Employing the knife cut method, it was found that bilateral knife cuts placed

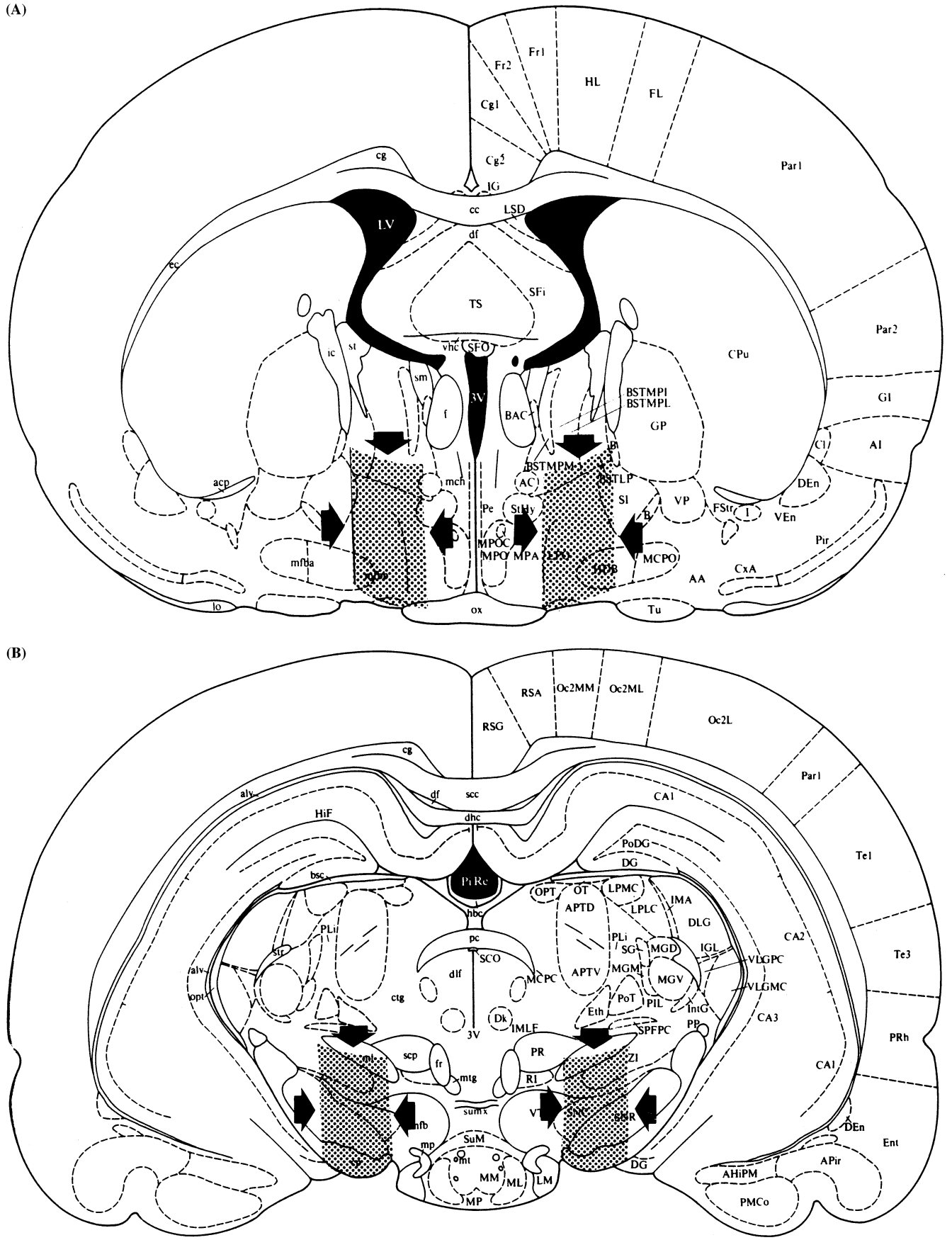

Fig. 2. Schematic representation of the extent of the knife cuts: (A) sagittal representation of the parasagittal cuts lateral to the LH, (B) coronal representation of the coronal cuts anterior to the LH, (C) coronal representation of the coronal cuts posterior to the LH.

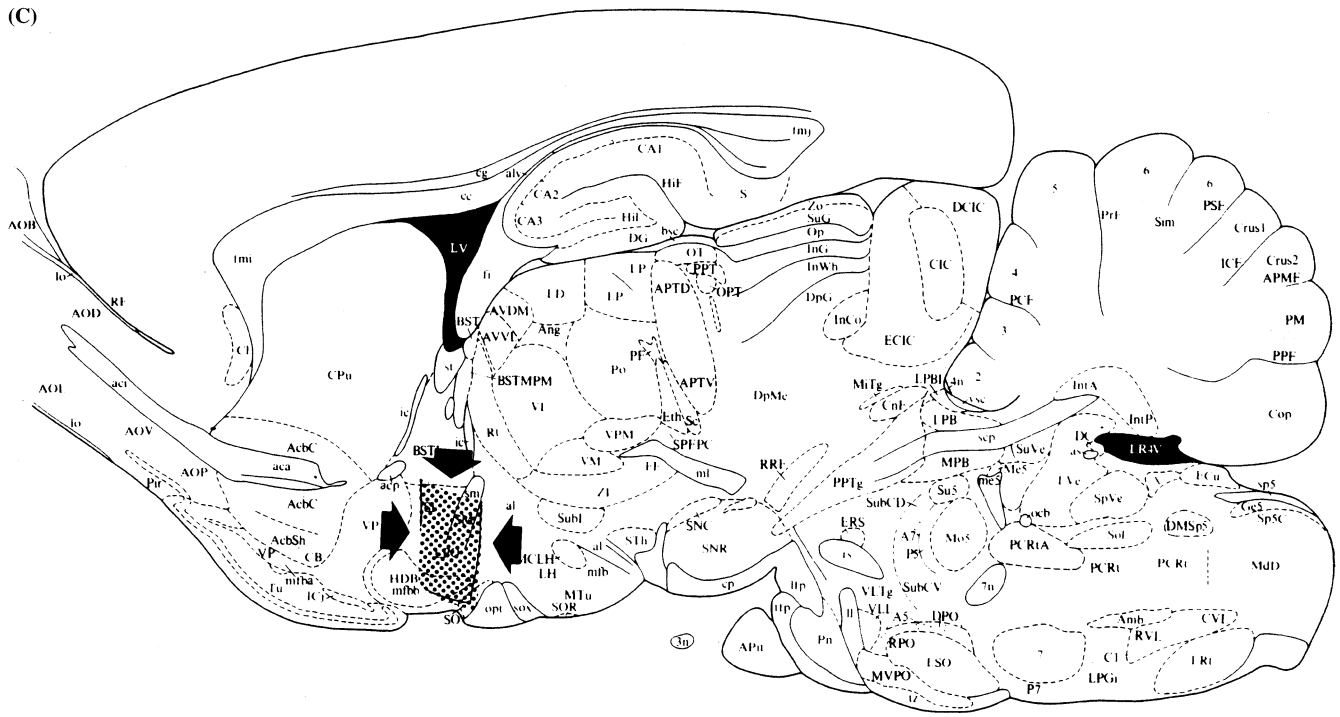

Fig. 2. (*Continued*)

posteriorly to the LH did not affect gastric ulceration induced by a neurotoxic dose of NMDA infused in the LH. However, cuts placed laterally to the LH blocked whereas anterior cuts enhanced gastric ulceration produced by NMDA infusions in the LH.

The fact that lateral knife cuts blocked gastric ulceration produced by NMDA infusions in the LH suggests that LH neurons project fibers through its lateral border and probably descend through the internal capsule. Since posterior knife cuts made in the ventral portion of the border of the substantia nigra and the LH did not affect the gastric erosions produced by microinfusions of NMDA in the LH, it reasonable to assume that the fibers leaving the LH assume a dorsal or a dorsomedial route to the brainstem. An alternative pathway would be an ascending projection from the LH to forebrain structures. However, the present results showing that anterior knife cuts in fact enhances stomach erosions produced by NMDA lesions of the LH, tends to discard this possibility. Therefore, it appears that intrinsic LH neurons with gastric function sends descending axons laterally through the internal capsule and travel through the dorsal or dorsal medial aspect of the brainstem. Unfortunately, results from the present experiment do not permit one to determine the location where the descending fibers originating in the LH terminate. Since there are direct projections from the LH to the NTS and the DMN [4,28,49], it is plausible that these fibers have a direct effect on these visceral structures. However, other structures can not be ruled out, since the LH projects fibers through the MFB in a medial orientation to the raphe complex, parabrachial nucleus, locus coeruleus and dorsal tegmental nucleus, which, in turn, send projections to the NTS and the DMN [44].

The finding that anterior knife cuts enhanced gastric mucosal erosions produced by microinjections of

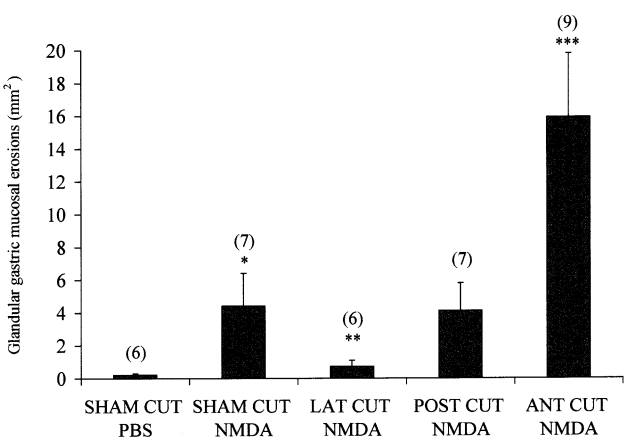

Fig. 3. Mean (±SEM) total area of gastric mucosal erosions in rats given LH infusions of either NMDA (20 μg/μl) or vehicle (SHAM INFUSION) after anterior (ANT CUT),posterior (POST CUT), lateral (LAT CUT) or control (SHAM) knife cuts. Number in parenthesis indicates the number of animals and * $p < 0.01$, SHAM CUT/LH INFUSION(NMDA) compared to SHAM CUT/SHAM INFUSION; ** $p < 0.05$, LAT CUT/LH INFUSION(NMDA) compared to SHAM CUT/LH INFUSION (NMDA); *** $p < 0.005$, ANT CUT/LH INFUSION (NMDA) compared to all other groups.

NMDA in the LH suggests that the LH sends and/or receives inhibitory projections from neural structures anterior to the knife cut. Among the several telencephalic structures anatomically connected to the LH, the amygdala is likely to have been the structure affected by the anterior knife cut. This is because the anterior cuts tended to transect the ventral portion of the brain and portions of the LH-amygdala connections that travel through this area. Therefore, it is possible that the LH and the amygdaloid complex have some sort of inhibitory or negative feedback, such that the gastric erosions produced by NMDA infusions in the LH can be enhanced when this connection is interrupted.

It has been shown that the amygdaloid complex is involved in the regulation of gastric function [22–25]. It has been shown that electrical stimulation of the centromedial nucleus of the amygdala leads to the occurrence of gastric ulceration [22,23,29,55], whereas microinjections of γ-amino butyric acid [57], benzodiazepines [48], and β-endorphins [47] into the centromedial nucleus of the amygdala decrease the occurrence of gastric erosions produced by restraint stress. Moreover, electrolytic lesions of the central nucleus of the amygdala reduces the gastric ulceration associated with various stress-producing procedures such as physical restraint [23,24] and activity stress [37]. Interestingly, lesions of the basolateral portion of the amygdala exacerbate stress-induced gastric mucosal damage [24,37]. These results suggest that the central nucleus of the amygdala has excitatory, whereas the basolateral amygdala has inhibitory properties on gastrointestinal functions associated with physical stressors. The central and basolateral amygdaloid nuclei have reciprocal connections and the central nucleus has direct and indirect projections to the DMN [32]. The occurrence of gastric ulceration can be modulated by connections between the LH the amygdaloid complex. For example, prior lesions of the central nucleus of the amygdala reduce the occurrence of gastric erosions produced by electrolytic LH lesions [19]. Since there are excitatory projections from the LH to the central nucleus of the amygdala, via the ventral amygdalofugal pathway, it appears that some LH cells can control gastric activity through ascending projections to the central nucleus of the amygdala. The LH also receives inhibitory projections from the basolateral nucleus of the amygdala, through the stria terminalis [11,38,40].

Results from the present study showed that coronal knife cuts placed anterior to the LH, which probably transacted fibers of the stria terminalis, enhanced gastric erosions produced by NMDA infusions in the LH. This finding suggests that the anterior cut may have enhanced ulcer production by eliminating a negative feedback system from the amygdala to the LH. Therefore, microinfusions of NMDA in 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 proposed by Henke [24], lesions of the basolateral amygdaloid nucleus may facilitate stomach ulceration following physical restraint by eliminating an 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. It is possible that hyper-excitation of LH neurons by NMDA causes an activation of neurons in the central nucleus of the amygdala. This triggers the inhibitory feedback from the basolateral nucleus to the LH. This inhibitory signal may serve to dampen the activity of LH neurons that ultimately contribute to gastric erosion formation. Thus, gastric ulceration produced by microinjections of NMDA in the LH can be enhanced when this connection is interrupted, as was observed in the present experiment.

Finally, it has previously been shown that parasagittal knife cuts placed lateral to the LH do not produce gastric erosions [17]. This finding, in conjunction with the present results, lends further support to the hypothesis that gastric mucosal injury induced by bilateral LH infusions of NMDA is due to the acute excitatory effects of NMDA on neurons that precede cell death.

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