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Rapid communication

Kainic acid into the parapyramidal region protects against gastric injury by ethanol

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Abstract

Neurons in the parapyramidal region of the ventral medulla project to the dorsal vagal complex and intermediolateral column. Kainic acid (0.5–5.0 ng) microinjected unilaterally into the parapyramidal region reduced 45% ethanol-induced gastric lesions by 50–60% in urethane anesthetized rats. Microinjections at sites nearby, but outside of the parapyramidal region, had no effect. These results provide the first evidence that the activation of parapyramidal region neurons influences gastric function and suggests a possible role of this ventral medulla region in gastric regulation.

Keywords: Kainic acid; Gastric lesion; Parapyramidal region

1. Introduction

The raphe pallidus and raphe obscurus are well documented to be involved in the vagal regulation of gastric function through direct thyrotrophin-releasing hormone (TRH) and serotonin containing efferent projections to the dorsal vagal complex (Taché et al., 1993). In particular, kainic acid microinjected into the raphe pallidus, at doses subthreshold to stimulate gastric acid secretion, partially protects the gastric mucosa against ethanol injury through medullary TRH-vagal pathways (Kaneko et al., 1995, 1998). The parapyramidal region in the medulla consists of neurons close to the ventral surface and lateral to the pyramidal tract. The parapyramidal region displays similar chemical neuroanatomy as the raphe pallidus and raphe obscurus (namely, TRH and monoamine containing neurons projecting to the dorsal vagal complex and the intermediolateral cell column of the spinal cord) (Helke et al., 1989; Lynn et al., 1991). Although these morphological features provide support for a role of the parapyramidal region in the autonomic regulation of gastric function at the medullary level, functional evidence is still lacking. This study examined whether chemical activation of parapyramidal region cell bodies by microinjection of kainic acid into this nucleus influences ethanol-induced gastric injury in urethane-anesthetized rats.

2. Materials and methods

Animal care and use procedures were in accordance with approved protocols of the Veteran Administration Medical Center/West Los Angeles Research Service Animal Committee. All experiments were performed in male Sprague–Dawley rats (Harlan Laboratory, San Diego, CA) weighing 280–320 g, fasted for 24 h and anesthetized with urethane (1.5 g/kg, Sigma, St. Louis, MO). Microinjections of 50 nl of vehicle (0.1 M phosphate buffer used to dissolve kainic acid, Sigma) or kainic acid (0.5, 1, 2 or 5 ng; Sigma, K0250) into the left parapyramidal region were performed essentially as previously described for the raphe pallidus (Kaneko et al., 1995) with the following coordinates (mm): ventral from the surface of the brainstem: 3.7; anterior from the caudal tip of the area postrema: 1.5; lateral from the midline: 1.2. The choice of the doses of kainic acid were based on pilot studies showing the lack of changes in gastric acid secretion. At 20 min post microinjection, 45% ethanol (5 ml/kg) was administered by oral intubation and 1 h later, rats were euthanized by decapitation. Brains were removed for the assessment of microinjection site location as previously described (Kaneko et

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al., 1995). The pylorus and cardia were ligated and 8 ml of 1% formalin was injected into the stomach and after a 30-min period fixation, stomachs were opened and pinned flat. Gastric lesions were assessed by a computerized image analyzer device and expressed as percentage coverage of the whole corpus as previously described (Kaneko et al., 1995). Analysis of variance (ANOVA) followed by Fisher's least significant difference test was used for statistical analyses with the significance level set at $P < 0.05$.

3. Results and discussion

Intragastric administration of 45% ethanol produced macroscopic gastric lesions visualized as long dark-red

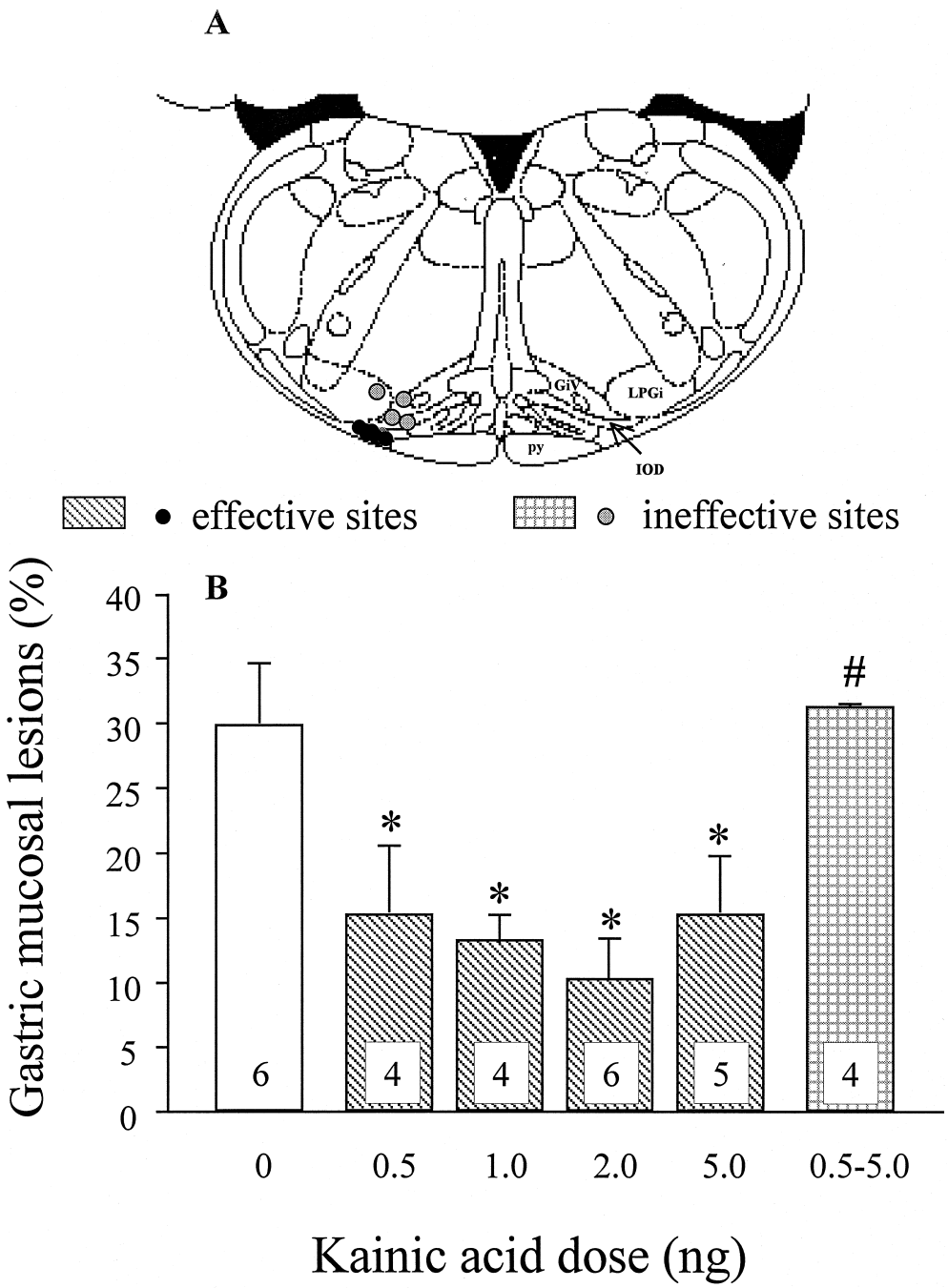

Fig. 1. (A) Coronal brainstem section adapted from the atlas of Paxinos and Watson (1986) (bregma −12.30 mm) showing representative microinjection sites. GiV: ventral gigantocell reticular nucleus; IOD: inferior olive, dorsal nucleus; LPGi: lateral paragigantocellular nucleus; py: pyramidal region. (B) Influence of kainic acid microinjected into the parapyramidal region of the ventral medulla or outside of the parapyramidal region on gastric lesions induced by intragastric administration of 45% ethanol in urethane-anesthetized rats. Each column represents mean ± S.E.M. of number of rats indicated in the bottom of each column. $^{*}P < 0.05$ compared with vehicle microinjected into the parapyramidal region (white column). $\#P < 0.05$ compared with each of the kainic acid/inside parapyramidal region group.

vertical lines covering 30 ± 5% of the corpus mucosa in urethane-anesthetized rats microinjected into the parapyramidal region with vehicle. Kainic acid microinjected unilaterally into the parapyramidal region (0.5, 1.0 and 2.0 ng) reduced significantly the lesion areas to 15 ± 5%, 13 ± 2% and 10 ± 3% of the corpus mucosa, respectively (Fig. 1). At 5.0 ng, kainic microinjected into the parapyramidal region did not show a further decrease in gastric injury (15 ± 4% of the corpus mucosa) compared with 1.0 and 2.0 ng (Fig. 1). Kainic acid (0.5–5.0 ng) microinjected into sites outside of the parapyramidal region, namely into the inferior olive, dorsal nucleus ($n = 2$), ventral gigantocell reticular nucleus ($n = 1$) and lateral paragigantocellular nucleus ($n = 1$), had no effect on ethanol-induced gastric lesions (Fig. 1).

Kainic acid, which was originally introduced as a neuron-specific and axon-sparing lesioning tool, exerts an excitatory action to cell bodies, but not to fibers of passage, at doses below 500 ng (Berger et al., 1989). The present finding revealed that activation of parapyramidal region cell bodies induced by kainic acid at low doses (0.5–5 ng) reduced 45% ethanol-induced gastric erosions by 50–60% in rats. This provides the first demonstration of the modulation of gut function by activation of parapyramidal region neurons. The gastric response is specific to the parapyramidal region as shown by the ineffectiveness of kainic acid microinjected into sites nearby but outside of the parapyramidal region. The activation of raphe pallidus cell bodies by kainic acid at a dose subthreshold to increase acid secretion also reduced ethanol-induced gastric lesions (Kaneko et al., 1995, 1998). In this case, the gastric protection is mediated by the activation of TRH medullary pathways leading to vagal dependent stimulation of prostaglandins and calcitonin-gene related peptide/nitric oxide release thereby increasing the resistance of the gastric mucosa to injury (Kaneko et al., 1995, 1998). Similar mechanisms may underlie the gastric protective effect of activation cell bodies in the parapyramidal region based on the presence of TRH containing neurons projecting from the parapyramidal region to the dorsal vagal complex as established in the raphe pallidus (Lynn et al., 1991). Taken together these neuroanatomical and functional observations support the concept that the parapyramidal region is part of the ventral medullary nuclei which play a role in the medullary regulation of gastric functions.

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