Intracisternal Injection of Basic Fibroblast Growth Factor Reduces the Severity of Gastric Mucosal Lesions Evoked by Ethanol in Rats

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Summary: This study was conducted to examine the hypothesis that basic fibroblast growth factor (bFGF) may have an anti-ulcer action through an acid-independent mechanism. The intracisternal injection of bFGF (1 μ g/10 μ l) significantly attenuated the development of gastric mucosal damage evoked by either subcutaneous indomethacin or intragastric absolute ethanol. On the other hand, intraperitoneally injected bFGF

(1 μ g) failed to inhibit the formation of gastric mucosal injury by indomethacin or ethanol. These results suggest that bFGF acts in the brain to exert a gastroprotective action. Since ethanol-induced gastric lesion formation does not depend upon luminal acid, we speculate that an acid-independent mechanism may mediate the anti-ulcer action of central bFGF. [Japanese Journal of Physiology, 47, 231–233, 1997]

Key words: basic fibroblast growth factor, central nervous system, gastric ulcer.

Increasing evidence suggests that basic fibroblast growth factor (bFGF) has central nervous system actions in addition to its growth-promoting activities of epithelial cells [1–5]. For instance, bFGF and its receptors were identified in the central nervous system and centrally injected bFGF suppressed food intake in rats and mice [2–5]. These results suggest that bFGF may act in the brain to have an action on feeding behavior. Baird *et al.* [1] demonstrated a nonmitogenic pituitary function of FGF, indicating that bFGF may modulate the neuroendocrine system. Along this line, we have demonstrated that intracisternal but not intraperitoneal administration of bFGF inhibits gastric secretion, gastric emptying, and the development of gastric ulceration induced by central injection of thyrotropin-releasing hormone (TRH) or water-immersion restraint stress [6–8]. These results suggest that bFGF may act as a chemical messenger in the brain to regulate gastric function.

A number of gastric factors, such as acid secretion, mucus secretion, mucosal blood flow, and mucosal prostaglandin levels, are related to the development of acute gastric mucosal lesions. Since our previous

studies demonstrated that gastroprotective action was seen after central injection of bFGF in antisecretory doses [6, 8] and the above two gastric ulcer models (TRH and water immersion stress) are dependent upon, at least in part, gastric acid secretion [9–11], it was speculated that the inhibition of acid likely contributed to the anti-ulcer action of central bFGF. However, we cannot exclude the possibility that factors other than acid may be involved in the gastroprotective action of bFGF. To address the problem, we examined, in this study, the effects of central bFGF on the development of ethanol-induced gastric injury, a gastric ulcer model that is independent of gastric acid secretion [12].

Male Sprague-Dawley rats weighing 250–300 g were housed under controlled light /dark conditions (lights on: 07:00–19:00) with room temperature regulated to 23–25°C. Rats were allowed free access to food (solid rat chow, Purina, Richmond, IN, USA) and tap water. All the experiments were performed on conscious animals deprived of food for 24 h but with free access to water up to the initiation of the experiment.

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Indomethacin was obtained from Sigma Chemical (St. Louis, MO, USA) and dissolved in 7.5% sodium bicarbonate immediately before the experiment. The bFGF preparation used in this study was recombinant human bFGF (Funakoshi Co., Tokyo). This chemical was dissolved in physiological saline before being injected.

We examined the effect of intracisternal injection of bFGF on the development of experimentally-induced gastric mucosal lesions. Gastric mucosal damage was induced by intragastric ethanol or subcutaneous injection of indomethacin as described previously [13]. Rats were given an intracisternal injection (10 μ l) of saline or bFGF at a dose of 1 μ g just prior to being injected with absolute ethanol (1 ml) or indomethacin (30 mg/kg). Intracisternal injection was performed under brief ether anesthesia with a 10- μ l Hamilton microsyringe after rats were mounted in a stereotaxic apparatus (David Kopf Instruments, Tijuana, CA, USA). To exclude the possibility that the intracisternally injected bFGF exerted its action through peripheral leakage, intraperitoneal injection of bFGF was also performed prior to the injection of the ulcer-producing agents. The animals were returned to their cage. Then, 1 h after injection of ethanol or 4 h after administration of indomethacin, the animals were sacrificed under deep ether anesthesia and their stomachs removed.

The removed stomachs were opened along the greater curvature, and the gastric mucosa was observed macroscopically to evaluate the severity of gastric mucosal lesions. The severity of gastric mucosal lesions, expressed at the ulcer index (mm), was evaluated by the total length of all mucosal lesions observed.

All results are represented as means $\pm$ SEM. Comparisons between two groups were calculated by Student's *t*-test. $p < 0.05$ was considered as statistically significant.

Experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Committees at the Asahikawa Medical College was obtained for all studies.

Table 1 illustrates the effect of centrally injected bFGF on the development of gastric mucosal damage induced by indomethacin. Intracisternal injection of bFGF significantly inhibited the severity of the gastric mucosal lesion.

Absolute ethanol-evoked gastric mucosal injury was significantly suppressed by intracisternal injection of bFGF as shown in Table 2.

Intraperitoneal administration of bFGF (1 μ g) failed to reduce the severity of gastric lesions by in-

Table 1. Effect of intracisternal injection of bFGF on the severity of gastric mucosal damage induced by indomethacin.

	N	Ulcer index (mm)	
Intracisternal injection			
Control	11	10.1 $\pm$ 2.8	
bFGF	10	2.5 $\pm$ 1.3	* $p = 0.031$
Intraperitoneal injection			
Control	5	11.6 $\pm$ 1.9	
bFGF	5	10.2 $\pm$ 2.7	

Rats received intracisternal injection of bFGF at a dose of 1 μ g/10 μ l or saline (control) and subcutaneous administration of indomethacin (30 mg/kg). The severity of gastric mucosal damage was evaluated 4 h after treatment. * Compared with control.

Table 2. Effect of intracisternal injection of bFGF on the severity of gastric mucosal damage induced by absolute ethanol.

	N	Ulcer index (mm)	
Intracisternal injection			
Control	18	10.2 $\pm$ 2.5	
bFGF	20	3.9 $\pm$ 1.4	* $p = 0.029$
Intraperitoneal injection			
Control	4	11.6 $\pm$ 2.8	
bFGF	5	12.2 $\pm$ 3.2	

Rats received intracisternal injection of bFGF at a dose of 1 μ g/10 μ l or saline (control) and intragastric administration of absolute ethanol (1.0 ml). The severity of gastric mucosal damage was evaluated 1 h after treatment. * Compared with control.

domethacin or absolute ethanol (Tables 1 and 2).

Previous studies have demonstrated that centrally but not peripherally administered bFGF in anti-secretory doses inhibit gastric lesion formation by intracisternal TRH or water-immersion restraint stress [6]. These two models are known to be inhibited by anti-secretory treatments [9–11]. This evidence suggests that the suppression of acid by central bFGF may contribute to the gastroprotective action of bFGF. However, the studies do not necessarily exclude the possibility that factors other than acid inhibition may be involved in the anti-ulcer action of central bFGF.

This study first shows that centrally administered bFGF reduced the severity of the gastric mucosal lesions by indomethacin, a cyclooxygenase inhibitor. These results further support our hypothesis that bFGF acts centrally to have a gastroprotective action. Since indomethacin-induced gastric damage is inhib-

ited by anti-secretory drugs [14], the reduction in the development of gastric lesions by indomethacin in this study may be due to the inhibitory effect of bFGF on acid secretion. It is well known that prostaglandins mediate some gastroprotective effects [15]. The dose (30 mg/kg) of indomethacin used in this experiment almost completely suppresses the biosynthesis of prostaglandins in the gastric mucosa [16]. The present result that centrally administered bFGF still exerted an anti-ulcer action in indomethacin-treated rats led us to speculate that the gastroprotective action of bFGF may not be mediated by prostaglandins.

The major finding of this study was the reduction of severity of ethanol-induced gastric mucosal injury by centrally injected bFGF. Since the development of ethanol-evoked gastric mucosal lesions is not suppressed by anti-acid agents [12], this ulcer model is acid-independent. These results suggest that bFGF may act in the brain to have an anti-ulcer action through a mechanism that does not depend upon acid secretion. Together with our previous observations [6, 8], we suggest that the gastroprotective action of central bFGF may be exerted not only by way of anti-acid but also acid-independent mechanisms. We do not know, at this moment, the precise mechanism that is independent on gastric acid, but a change in gastric mucosal blood flow might be involved in the mechanism because ischemic change is known to be an important factor in ethanol-induced gastric mucosal lesions [17]. This speculation requires further investigations.

In summary, this study suggests that bFGF acts centrally in the brain to have an anti-ulcer action through acid-independent mechanisms.

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