Induction of Gastric Lesions by 2-Deoxy-D-Glucose in Rats Following Chemical Ablation of Capsaicin-Sensitive Sensory Neurons

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ABSTRACT—Effects of chemical ablation of capsaicin-sensitive sensory nerves on functional and mucosal ulcerogenic responses to 2-deoxy-D-glucose (2DG) were investigated in the rat stomach, in comparison with those of indomethacin, a prostaglandin (PG) biosynthesis inhibitor. Intravenous injection of 2DG (200 mg/kg) followed by infusion of this agent (100 mg/kg/hr, i.v.) significantly increased gastric acid secretion and motility, but rarely induced macroscopic damage in the gastric mucosa of normal conscious rats. Chemical ablation of capsaicin-sensitive sensory nerves or pretreatment with indomethacin (5 mg/kg, s.c.) did not significantly affect the acid secretory and motility responses to 2DG, but induced severe hemorrhagic lesions in the stomach within 4 hr. Gastric mucosal blood flow (GMBF) determined by laser Doppler flowmetry under anesthetized conditions did not consistently change during 2DG treatment in any of these three groups, but the rise in GMBF in response to mucosal acidification (0.2 N HCl) was significantly inhibited in the animals pretreated with indomethacin or following chemical deafferentation. We conclude that functional ablation of capsaicin-sensitive sensory nerves, similar to the PG deficiency, increases the gastric mucosal vulnerability during 2DG infusion (acid hypersecretion and hypermotility due to vagal excitation), resulting in hemorrhagic lesions, and that the mechanism may be accounted for at least partly by the impairment of gastric mucosal blood flow response to mucosal acidification.

Keywords: 2-Deoxy-D-glucose, Capsaicin-sensitive sensory neuron, Gastric lesion

Capsaicin-sensitive afferent neurons densely innervate the stomach of various species of animals including the rat and have been shown to play an important role in the defensive mechanism of the stomach (1–5). Functional ablation of these neurons leads to aggravation of various types of gastric lesions (3, 4), while stimulation of these nerves by intragastric capsaicin alters various gastric functions such as gastric mucosal blood flow (GMBF), motility, acid and HCO₃⁻ secretion (6–10) and protects the gastric mucosa against damage (3–7, 11).

It is known that 2-deoxy-D-glucose (2DG) stimulates the glycoprivic receptors in the lateral hypothalamic area, which in turn initiate and sustain the vagally-mediated gastric functional excitation (12). We previously reported that intravenous infusion of 2DG caused hemorrhagic lesions in the rat stomach when a prostaglandin (PG) deficiency was concomitantly induced by indomethacin, although 2DG alone induced non-hemorrhagic lesions only (13). Since several studies showed the interaction of endogenous PGs and capsaicin-sensitive sensory nerves (6, 9, 10, 14), it may be expected that sensory deafferentation exacerbates the 2DG-induced gastric damage to hemorrhagic damage, similar to PG deficiency.

In the present study, we thus examined the effects of chemical ablation of capsaicin-sensitive sensory nerves on the mucosal functional and ulcerogenic responses induced by 2DG in the rat stomach and compared such effects with those of indomethacin, a PG biosynthesis inhibitor.

MATERIALS AND METHODS

Male Sprague Dawley rats weighing 230–260 g (Charles River, Shizuoka, Japan) were used. The ani-
mals kept in individual cages with raised mesh bottoms to prevent coprophagy were deprived of food but allowed free access to tap water for 18 hr before the experiments. All studies were performed using 5–6 rats per group.

Experimental protocol
The experiments were performed in the following three groups of rats: A, control group; B, sensory deafferented group; C, indomethacin-treated group. Chemical deafferentation was done by s.c.-injection of capsaicin once daily for 3 consecutive days (20, 30, 50 mg/kg) 2 weeks before the experiments (9). All capsaicin injections were performed under ether anesthesia, and the rats were pretreated with terbutaline (0.1 mg/kg, i.m.) and aminophylline (10 mg/kg, i.m.) before capsaicin injection to counteract the respiratory impairment associated with capsaicin injections. To check for the effectiveness of the treatment, a drop of 0.1 mg/ml solution of capsaicin was instilled into one eye of each rat, and the wiping movements were counted as previously reported (15). Indomethacin (5 mg/kg) was given s.c. 30 min before treatment with 2DG. Control animals received the vehicle alone. In some cases, the combined effects of indomethacin and sensory deafferentation were examined.

Induction of gastric lesions
The animals were kept in Bollman cages and given 2DG (200 mg/kg) i.v. as a bolus injection followed by intravenous infusion of 2DG (100 mg/kg/hr). Four hours later, the animals were killed under ether anesthesia, and the stomachs were then removed, inflated by injecting 8 ml of 2% formalin, immersed in 2% formalin for 10 min to fix the gastric wall, and opened along the greater curvature. The length (mm) of each hemorrhagic lesion was measured under a dissecting microscope with square grids (×10), summed per stomach and used as a lesion score. The person measuring the lesions did not know the treatment given to the animals.

Measurement of gastric acid secretion
Under light ether anesthesia the abdomen was incised, and both the stomach and duodenum were exposed. An acute fistula prepared with a polyethylene tube was provided in the forestomach. Another tube was inserted in the stomach through a slit in the duodenum and held in place by a ligature around the pylorus. Both tubes were withdrawn through the lateral body walls. Then, the animals were kept in Bollman cages, and the stomachs were perfused at a flow rate of 1 ml/min with saline (154 mM NaCl) warmed at 37°C. Acid secretion was measured at pH 7.0 using a pH-stat method (Hiranuma Comtite-7, Tokyo, Japan) and by adding 100 mM NaOH. The animals were treated with 2DG-i.v. after basal acid secretion had well stabilized.

Determination of gastric motility
Gastric motility was determined with a miniature balloon according to a previous paper (13). Briefly, under ether anesthesia, a balloon and the catheter was placed in the glandular stomach through an incision of the forestomach. The catheter was pulled out through the abdominal incision and held in place by a ligature. The animals were then kept in Bollman cages, and the gastric motility was measured as intraluminal pressure recordings and monitored on a recorder (Nippon Densi Kagaku Co., Unicorder U-228, Tokyo, Japan) using a pressure transducer and polygraph device (San-Ei, Model 6M-72, Tokyo, Japan). Quantitation of motility was performed by measuring the amplitude of each contraction (clear spike) over a 10-min period, determining the mean for these periods of each rat and by calculating the mean ± S.E. for each period from 5 different rats. The animals were treated with 2DG, i.v. after basal motility had stabilized.

Measurement of gastric mucosal blood flow
Under urethane anesthesia, the abdomen was incised, and the pylorus ligated. The stomach was then mounted in a lucite chamber and perfused at the flow rate of 1 ml/min with saline according to a previous paper (9). GMBF was continuously measured by laser Doppler flowmetry (Advance Ltd., Model-2100, Tokyo, Japan) by softly touching the probe (1 mm in diameter) on the surface of the corpus mucosa with the aid of a balancer (Medical Agent, Kyoto, Japan). After basal GMBF had stabilized, 2DG was given intravenously as described above, and GMBF was measured for 2 hr thereafter. In some cases, changes in GMBF were also examined when the mucosa was acidified by intraluminal application of 0.2 N HCl (2 ml) for 10 min.

Preparation of drugs
Drugs used were 2-deoxy-D-glucose, capsaicin (Wako, Osaka, Japan), urethane (Tokyo Kasei, Tokyo, Japan), indomethacin, atropine (Sigma Chemicals, St. Louis, MO, U.S.A.), terbutaline (Bricanyl®: Fujisawa, Osaka, Japan), and aminophylline (Neophyline®: Eisai, Tokyo, Japan). 2DG and atropine were dissolved in saline, while indomethacin was suspended in saline with a drop of Tween 80 (Nacalai Tesque, Kyoto, Japan). Capsaicin was dissolved in Tween 80–ethanol solution (10% ethanol, 10% Tween 80, 80% saline). Each agent was prepared immediately before use and was given in
a volume of 0.5 ml/100 g of body wt. in the case of s.c.-
and i.p.-administration or in a volume of 0.1 ml/100 g
of body wt. in the case of i.v.- and i.m.-injection. Con-
trol animals received the vehicle alone.

Statistics
Data are presented as the mean ± S.E. from 5–6
rats per group. Statistical analyses were performed us-
ing a two-tailed Dunnett's multiple comparison test,
and values of P < 0.05 were regarded as significant.

RESULTS

Induction of gastric lesions following 2DG infusion

Intravenous administration of 2DG in the control
animals caused only slight damages in the gastric mu-
cosa 4 hr later; they were mostly non-hemorrhagic le-
sions and appeared in the corpus along the mucosal
foldings, the score of hemorrhagic damage being 4.8 ±
2.3 mm (Fig. 1). The treatment with 2DG, however, in-
duced much severe damages in the stomachs of animals
following chemical ablation of capsaicin-sensitive sen-
sory neurons. These lesions were localized in the corpus
mucosa, and they were similar to those observed in
control rats but became in most parts hemorrhagic, the
lesion score being 24.6 ± 5.6 mm. Pretreatment of the
animals with indomethacin (5 mg/kg, s.c.) also signifi-
cantly worsened the development of gastric lesions in
response to 2DG; the lesion score was 43.2 ± 7.2 mm.
Additional treatment of sensory deafferented animals
with indomethacin significantly aggravated 2DG-
induced gastric lesions as compared with the control,
but the lesion score (34.1 ± 4.2 mm) was not signifi-
cantly different when compared with those observed in
the animals with either treatment alone.

Gastric functional responses to 2DG

Acid secretion: Gastric acid secretion was stabilized in
the range of 6–14 μEq/15 min without much fluctua-
tion during a 3-hr test period. Intravenous administra-
tion of 2DG in the control group caused a progressive
increase of acid secretion from 9.7 ± 2.4 μEq/15 min to
30.8 ± 4.8 μEq/15 min within 90 min, which remained
elevated thereafter (Fig. 2). Functional ablation of
capsaicin-sensitive sensory nerves did not significantly
alter acid secretion under either basal or 2DG-stimu-
lated conditions; and in the latter, the acid output was
increased from 7.3 ± 1.6 μEq/15 min to the maximal
values of 31.2 ± 6.1 μEq/15 min. Pretreatment with in-
domethacin also had no effect on both the basal (6.9 ±
1.2 μEq/15 min) and 2DG-stimulated acid secretion;
the maximal acid output after 2DG treatment was 36.3
± 8.1 μEq/15 min.

Gastric motility: In control rats, clear gastric contra-
tions were observed at the frequency of 1–2/min under
basal conditions. Intravenous treatment with 2DG aug-

![Fig. 1](image-url)  
**Fig. 1.** Effects of sensory deafferentation and indomethacin, either alone or in combination, on the development of gas-
tric lesions after 2DG treatment in rats. The animals were given 2DG, i.v. by a single bolus injection followed by infusion
for 4 hr. Sensory deafferentation (capsaicin pretreatment) was performed by s.c.-injection of capsaicin 2 weeks before the
experiment, while indomethacin (5 mg/kg) was given s.c. 30 min before 2DG treatment. Data are presented as the mean
± S.E. from 6 rats. *Statistically significant difference from the control group, at P < 0.05.
Fig. 2. Effects of sensory deafferentation and indomethacin on the acid secretory responses to 2DG treatment in anesthetized rats. 2DG was given i.v. as a bolus injection (200 mg/kg) followed by infusion (100 mg/kg/hr) for 2 hr. Sensory deafferentation (capsaicin pretreatment) was performed by s.c.-injections of capsaicin 2 weeks before the experiment, while indomethacin (5 mg/kg) was given s.c. 30 min before 2DG treatment. Data are presented as the mean ± S.E. of values determined every 15 min from 6 rats. ●: Control, ■: Capsaicin pretreatment, ▲: Indomethacin pretreatment.

Fig. 3. Effects of sensory deafferentation and indomethacin on the gastric motility responses to 2DG treatment in rats. 2DG was given i.v. by a bolus injection (200 mg/kg) followed by infusion (100 mg/kg/hr). Sensory deafferentation (capsaicin pretreatment) was performed by s.c.-injections of capsaicin 2 weeks before the experiment, while indomethacin (5 mg/kg) was given s.c. 30 min before 2DG treatment. Data are expressed as % of basal values (amplitude) and represent the mean ± S.E. of values determined every 10 min from 5 rats. ●: Control, ■: Capsaicin pretreatment, ▲: Indomethacin pretreatment.
mented gastric motility significantly; the amplitude of contractions reached the maximal levels (2 times greater than basal values) within 40 min, and it remained elevated for 2 hr thereafter (Fig. 3). The increased gastric motility responses to 2DG were not significantly altered by either sensory deafferentation or indomethacin pretreatment, although overall, the amplitude of contraction was greater in the indomethacin-pretreated group as compared to that in control rats. Neither deafferentation nor indomethacin by itself had any effect on basal gastric motility.

*Gastric mucosal blood flow:* Gastric mucosal blood flow determined by laser Doppler flowmetry in the chambered stomach varied in the range of 10–15 ml/min/100 g tissue, and it remained relatively constant during a test period. After i.v.-treatment with 2DG, GMBF showed oscillatory changes depending on the relaxation-contraction of the stomach and failed to produce consistent changes in any group of rats. On the other hand, GMBF in the control group increased significantly in response to mucosal acidification (0.2 N HCl) when compared with the pre-exposure values, reaching the maximal value of 136.3 ± 9.5% (Fig. 4). The GMBF responses induced by acid were almost completely attenuated by chemical ablation of capsaicin-sensitive sensory neurons, and the maximal increase in GMBF was only 1.6 ± 8.7%, which was significantly different from that (36.3 ± 9.5%) observed in the control group. The increased GMBF response to 0.2 N HCl was also significantly mitigated by pretreatment with indomethacin, but this effect was less marked when compared with sensory deafferentation.

**DISCUSSION**

Many studies have shown that functional ablation of capsaicin-sensitive afferent neurons aggravated gastric lesions induced by stress or chemical agents (4, 5). These studies indicate that chemical deafferentation significantly worsens the severity of gastric lesions which can be induced by noxious stimuli even in the animals with intact sensory neurons. The present study, however, showed the prerequisite of sensory deafferentation in the induction of gastric lesions in response to 2DG stimulation, which by itself does not cause any macroscopic damage in the stomach, suggesting that capsaicin-sensitive sensory neurons may play an important role in maintaining the homeostasis of the gastric mucosa under adverse conditions.

We previously showed that 2DG treatment alone did not cause visible damage in the gastric mucosa but provoked hemorrhagic lesions in the presence of PG deficiency induced by indomethacin (13). The present study confirmed this finding and further showed that sensory deafferentation similarly increased the mucosal susceptibility to 2DG, resulting in hemorrhagic lesions in the stomach. The pathogenesis of 2DG-induced gastric lesions may be related to the increase of gastric acid secretion and motility resulting from excitation of the vagus nerves. Other agents such as thyrotropin-releasing hormone (TRH) and insulin are also known to produce vagally-mediated acid secretion and hypermotility and result in gastric lesions in rats (16, 17). Thus, the mechanism by which sensory deafferentation or PG deficiency worsens such lesions may be associated with alterations of vagal-dependent gastric functions. However, the acid secretory and motility responses induced by 2DG were not significantly altered
by either indomethacin or functional ablation of capsaicin-sensitive sensory nerves. Many studies showed that high-amplitude stomach contractions may be the important pathogenetic element in development of gastric damage along the mucosal folds as seen in the animals after administration of 2DG (13, 17, 18). Since the motility response to 2DG was augmented considerably in the presence of indomethacin, the worsening effect of this agent may be attributable in part to changes in the mucosal fold sensitivity due to abnormal contractions (17). Yet, the same cannot account for aggravation of 2DG-induced gastric lesions by sensory denervation, as this treatment did not significantly affect the gastric motility response to 2DG.

On the other hand, the influences of capsaicin pretreatment on vagally-induced acid secretion remained controversial. Evangelista et al. (19) reported a significant decrease in the acid secretory response to 2DG by capsaicin pretreatment in rats and suggested that capsaicin-sensitive fibers are involved in the afferent branch of the reflex response activated by 2DG to stimulate acid secretion. Similar findings were reported by Raybould et al. (20), who showed that peri-vagal application of capsaicin significantly reduced the acid secretion elicited by TRH. In contrast, Esplagues et al. (8) showed that sensory deafferentation did not significantly affect the acid secretory response to insulin in rats. We found no change in the acid secretory response to 2DG following ablation of these sensory neurons. At present, the reason for these different data remains unknown, but the overall results suggest that ablation of capsaicin-sensitive sensory neurons does not increase the acid secretion induced by 2DG. Thus, acid secretory changes may be excluded in the mechanism for aggravation to hemorrhagic lesions in sensory deafferented rats following capsaicin pretreatment.

Unexpectedly, 2DG failed to produce a significant change in GMBF, despite causing an increase in acid secretion. It has been reported that vagal excitation by TRH and its analog increased both acid secretion and GMBF (20, 21). At present, the reason why a definite rise in GMBF was not obtained after 2DG treatment remains unknown. In general, GMBF is considered to be important in protecting the acidic stomach by translocating H⁺ away from the mucosa. Since 2DG makes the stomach more acidic by increasing acid secretion and makes the mucosa more vulnerable to acid by increasing the fold sensitivity, the GMBF response to mucosal acidification may play a critical role in the development of hemorrhagic lesions. As evidenced in this study, capsaicin pretreatment almost completely blocked the increase of GMBF in response to mucosal acidification. Holzer et al. (22) recently reported that sensory neurons monitor H⁺ back-diffusion in the superficial mucosa and signal for a protective increase in GMBF. The present results further suggest that the impairment of this response makes the mucosa more susceptible to acid and induces aggravation to hemorrhagic lesions. Indomethacin also mitigated the acid-induced GMBF response significantly, but this effect was much less than that of sensory deafferentation. However, the severity of 2DG-induced gastric lesions was much greater in the animals pretreated with indomethacin than in sensory deafferentation. Thus, the aggravating mechanism of such lesions may be associated with the impairment of acid-induced GMBF responses, although other factors related to PG deficiency, such as mucus secretion and epithelial renewal, need to be considered as well.

Uchida et al. (23) examined the effect of capsaicin pretreatment on the development of gastric lesions after combined treatment with 2DG, aspirin and ammonia, and found that this treatment selectively worsened gastric lesions in the antrum but not in the corpus, suggesting a protective role of these sensory neurons in the antral mucosa. However, we found that 2DG treatment did cause hemorrhagic damage in the corpus but not in the antrum following sensory deafferentation. This discrepancy may be explained by different experimental conditions; they examined gastric lesions 2 days after the ulcerogenic treatment, while we evaluated gastric lesions 4 hr after 2DG treatment. These results may suggest that capsaicin-sensitive sensory neurons may be important in maintaining the protective ability of the stomach, both in the corpus and antral mucosa.

Taken together, the present study showed that 2DG induced hemorrhagic lesions in the stomach of rats following ablation of capsaicin-sensitive sensory neurons, although this agent alone did not cause any macroscopic damage in normal rats with intact sensory neurons. Capsaicin-sensitive sensory neurons, in addition to endogenous PGs, may play an important role in the defensive mechanism of the stomach. Although the detailed mechanisms still remain speculative, the impairment of GMBF responses in the acidic stomach may be one of the pathophysiologic elements responsible for aggravation of 2DG-induced gastric damage following sensory deafferentation or PG deficiency.

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