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RAPID COMMUNICATION

INHIBITION OF GASTRIC SECRETION IN GUINEA PIG BY RELATIVELY LOW DOSE IONIZING RADIATION

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ABSTRACT. We evaluated the effect of a single dose of ionizing radiation on gastric secretion in awake guinea pigs equipped with a permanent gastric cannula. Changes in gastric secretion were measured using a dye dilution technique. Infusion of histamine increased acid and fluid output and there was a positive correlation ($r = 0.93$) between the two. Total body irradiation with 400 cGy, like cimetidine, suppressed acid and fluid secretion under basal conditions and during histamine stimulation by 50-90%. Recovery from the radiation damage was only partial after one week. Irradiation inhibited the rise in gastric juice volume during histamine stimulation and also reduced the normal gain in body weight of the guinea pig. These results demonstrate that ionizing radiations have an immediate and long lasting effects on the gastric mucosal function of the guinea pig.

INTRODUCTION. Exposure to high levels of ionizing radiation produces major changes throughout the GI tract. The onset, duration and intensity of these changes depend on the species involved, the radiation dose and rate (1,2). The effects caused by low total body irradiation (~100cGy) may be temporary (e.g., nausea, vomiting) or may be more permanent and severe such as the GI syndrome characterized by diarrhea and melena (600 cGy). The pathophysiology of these effects on gastric function are still relatively unknown.

Recent studies on the acute effects of ionizing radiation were performed in the monkey. Exposure of these highly trained, chair adapted monkeys to a single dose of 800cGy altered gastric emptying, gastric secretion and the secretion of soluble mucus glycoproteins (3,4). However, these changes in gastric functions returned to normal within two days after irradiation. It is not known yet what is the mechanism by which ionizing radiation alters gastric function and whether these observations are unique for the monkey. To explore this in more detail, we developed a chronic model for studying gastric secretion *in vivo* in which guinea pigs are equipped with a permanent gastric cannula enabling access to their stomach (5). The animal can be studied awake and repeatedly and this also offers the advantage that studies of radiation injury and gastric secretory functions *in vivo* can be compared to *in vitro* gastric glands/cells studies (6,7).

In the present studies we used the chronic guinea pig model to evaluate the effect of low dose ionizing radiation on gastric secretory functions *in vivo*. We first correlated acid to fluid output under basal conditions and during histamine stimulation and then determined the changes in gastric secretion after radiation exposure.

METHODS. Permanent gastric cannulae were surgically implanted in the stomachs of guinea pigs (5). Fasted guinea pigs were studied in a Bowman restrainer. Acid and fluid secretion as well as intragastric fluid

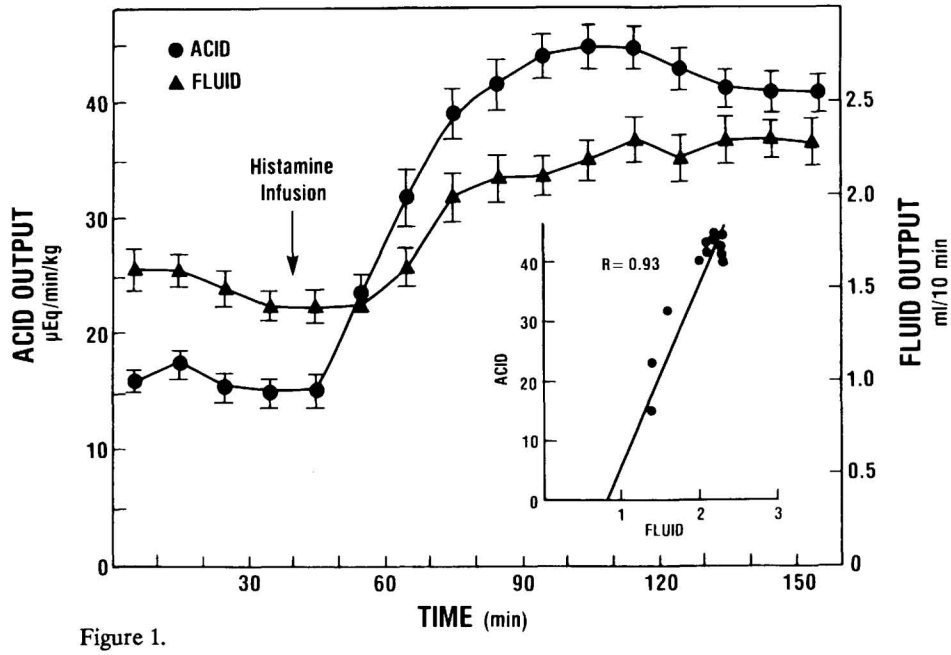

Figure 1.

Time course of histamine-stimulated increase in acid and fluid output in guinea pig *in vivo*. Animals were studied awake and gastric samples were collected every 10 min for acid and dye determinations. Histamine infusion (30 µg/kg/h) was started at the arrow and continued throughout the experiments. Gastric output was normalized for the weight of the animal. Values are mean ±1 SEM (vertical bars) from 48 experiments in which histamine significantly increased both fluid and acid secretion. *Insert,* fluid output in the presence of histamine was plotted against the corresponding acid output. There was a positive correlation between these two processes, R = 0.93.

volume (i.e., gastric juice) were determined by a marker dilution technique (5,8).

Gastric sampling was carried out via the gastric cannula using a No.10 French, double lumen polyvinyl nasogastric Levin tube which was introduced into the stomach. Phenol red was used as a marker and sampling was at 10 min intervals (5). Histamine (Sigma Chemical Co.) in aqueous solution was infused subcutaneously (sc) at the rate of 0.9 ml/h to yield a dose of 30 µg/kg/h. Cimetidine (Smith, Kline & French Laboratories) was given in a bolus sc injection at 3 µmole/kg. Each sample of gastric juice and phenol red solution was adjusted to pH 10.0 with 0.25% Na_3PO_4 and the color intensity was determined at 560 nm. Hydrogen ion concentration was determined by endpoint titration to pH 7.0 with 0.01N NaOH using an Auto burette/pH-stat system.

Studies were performed 1-2 h after sham irradiation on controls or after radiation exposure. Control animals underwent the entire procedure as irradiated animals (transferred to the exposure room, closed doors, noise level, etc.) except for the radiation exposure. Each animal was exposed unilaterally to 400 cGy of total body ^{60}Cobalt radiation delivered at 100 cGy/min. Animals were tested on the irradiation day and again one week later. Each animal was visually monitored for at least 5 h on the irradiation days. Acid and fluid output were calculated as the mean ± 1 SEM for each group of animals. Differences between means were analyzed by analysis of variance or by Student's t-test, as appropriate, at probability of $P < 0.05$.

RESULTS. Gastric secretion in sham irradiated animals was the same as in untreated animals. In these animals basal acid output was 15.8 ± 1.2 µEq/kg/min and gradually increased with histamine infusion to a plateau of 43.4 ± 2.2 µEq/kg/min (Fig 1). In 62 experi-

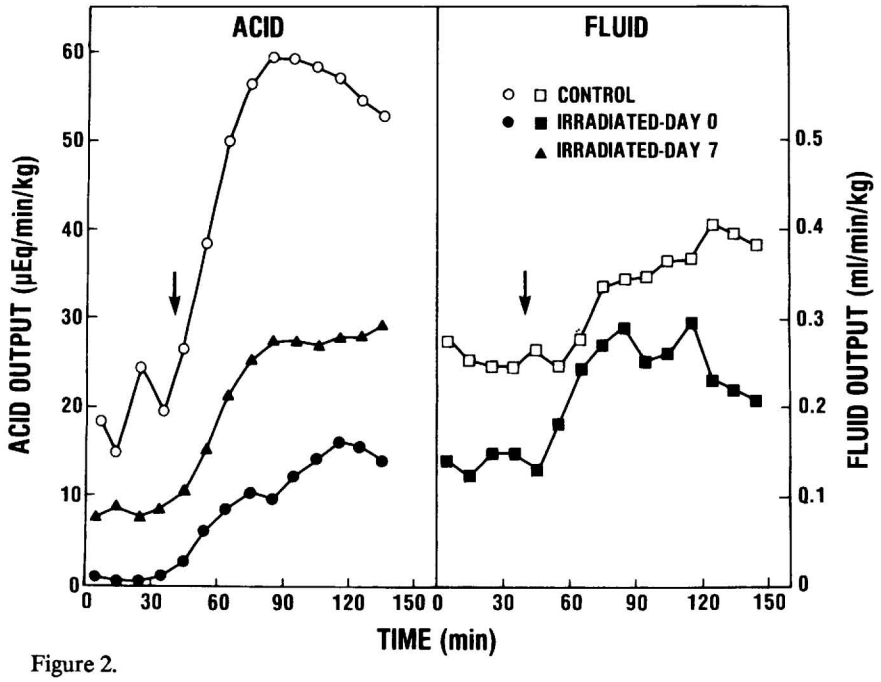

Figure 2.

Effect of ionizing radiation on acid and fluid output in guinea pig *in vivo*. Histamine infusion (30 μg/kg/h) was started at the arrow. Control represents values from sham irradiated animals, while day 0 and day 7 represent animals tested on the irradiation day and one week later. For clarity we omitted the fluid output values on day 7 because the line lies between the two presented lines and was not significantly different from either control or radiated values at day zero. Values are the mean of 8 animals tested before and after radiation exposure.

ments histamine always caused a significant increase in acid output. The increase in acid output was also dependent on the dose of histamine infused (5). Similarly, in control or sham irradiated animals, basal fluid output was 1.6 $\pm$ 0.25 ml/10 min (n = 24), and increased upon infusion of histamine to about twofold over basal conditions (Fig 1). However, histamine significantly increased fluid output over basal conditions in only 80% of the experiments (n = 61). There was a positive correlation between the histamine-stimulated fluid output and acid output (R = 0.93, Fig 1).

We compared these parameters in guinea pigs exposed to 400 cGy of total body radiation and in animals treated with the histamine H_2-antagonist, cimetidine. Ionizing radiation affected all gastric secretory parameters on the irradiation day. Basal acid output was suppressed by over 90% after irradiation and histamine-stimulated acid output by 65-70% (Fig 2A and Table 1). Fluid output was also reduced in irradiated animals by 40-60% under basal conditions and during histamine stimulation.

Exposure to ionizing radiation also reduced the volume of gastric juice during histamine stimulation. Under basal conditions the stomach of the guinea pig contains approximately 6 ml of fluid (Table 1). Gastric juice volume is a balance of two simultaneous processes. One is the secretion of fluid and the other is gastric emptying, the exit of fluid from the stomach into the duodenum. Upon stimulation with histamine there was a doubling of the gastric juice volume. Since there was no significant change in gastric emptying (results not shown), the increase in gastric juice volume probably reflects the increase in fluid output.

Cimetidine had similar effects on gastric secretion. Guinea pigs received a continuous infusion of histamine and after 1h, cimetidine

TABLE 1. Effect of ionizing radiation and cimetidine on gastric secretory parameters in guinea pig *in vivo*

Function\ Animal Condition	Sham radiated Control	Ionizing radiation 400 cGy	Cimetidine 3 μmol/kg
Acid Output (μEq/min/kg)			
Basal	12.8 ± 5.7(14)	0.1 ± 0.2 (8)*	2.8 ± 0.4 (6)*
Histamine	48.9 ±12.9(24)	13.5 ± 1.3 (8)*	19.5 ± 2.3 (6)*
Fluid Output (ml/10 min/kg)			
Basal	1.6 ± 0.1(26)	1.0 ± 0.2 (8)	0.6 ± 0.2 (6)*
Histamine	2.4 ± 0.4(26)	1.3 ± 0.2 (8)*	1.6 ± 0.3 (6)*
Intragastric Volume (ml)			
Basal	6.3 ± 1.6(14)	5.2 ± 3.5 (8)	5.1 ± 1.5 (6)
Histamine	13.4 ± 4.1(24)	7.1 ± 5.8 (8)*	8.1 ± 1.8 (6)

Guinea pigs were continuously infused with histamine (30 μg/kg/h) for at least 2h. Basal values represent measurement during 40 min prior to the start of histamine infusion. Histamine represents values during 40-80 min after histamine infusion. Values with cimetidine represent those in the absence of histamine (Basal) and those with histamine taken 40-60 min after bolus sc injection of cimetidine. Values are the mean ± 1SD of the number of experiments indicated in parentheses.

*Significantly different ($P < 0.05$) from control value.

was administered. Within 30-40 min, cimetidine significantly inhibited both basal (by 80%) and histamine-stimulated (by 60%) acid output (Table 1). Cimetidine also reduced fluid output and reduced the rise in gastric juice volume caused by histamine (from 13.4 ± 4.1 ml to 8.1 ± 1.8 ml).

To evaluate the duration of the effect we re-examined the gastric secretory parameters in the same animals one week after exposure. Acid output under both basal conditions and during histamine stimulation was still suppressed (Fig 2) and recovery was only 40% of the preirradiation response. Similarly, fluid output values did not return to the preirradiation level. However, due to the relatively small decline in fluid output under radiation exposure, fluid output one week later was not significantly different from either control values or the values on the irradiation day. The cimetidine effect lasted only during the experimental day.

Kinetic analysis revealed that radiation exposure did not change the time course of histamine increased gastric output. That is, in control and in irradiated animals the rise in acid output occurred within 30 min after infusion of histamine and plateaued by 50-60 min. As expected, exposure of the guinea pig to ionizing radiation has dramatic effects on other physiological functions. Sham irradiated and control animals (200-1000 g) increased their body weight by 5.29 ± 0.29 g per day ($n = 24$). During the first 3 weeks after exposure to 400 cGy ionizing radiation the gain in body weight was reduced from 5.29 ± 0.29 g/day to 0.4 g/day ($n = 8$).

DISCUSSION. Exposure of guinea pigs to a sublethal dose of ionizing radiation inhibited both basal and histamine stimulated acid and fluid secretion and reduced the rise in gastric juice volume. These effects persisted for at least one week after the irradiation. Inhibition of acid output could be due to a direct damage of histamine receptors on the parietal cells. Functioning histamine receptors are essential for mediating acid output even under basal conditions as evidenced by the inhibi-

tion of basal acid secretion by cimetidine. Prostaglandins could be released peripherally and act directly on the gastric mucosa. Various prostaglandins were shown to inhibit acid secretion in several species (9). An increase in small bowl prostaglandins following irradiation has been reported in the rat (10), but plasma PGE_2 and PGI_2 were unchanged in the monkey (11). It is possible that a transient increase in plasma prostaglandins or a local release of prostaglandins may occur during or immediately after radiation exposure. Alternatively, ionizing radiation may directly or indirectly (via prostaglandins) alter the blood flow to the gastric mucosa thereby causing reduction in acid output (9). Finally, the suppression of acid output could also be due to ultrastructural changes of the parietal cells similar to those observed in the mouse (12).

We found that radiation inhibited acid output and fluid output from the parietal cells, but inhibited fluid output to a lesser extent. While acid output during histamine stimulation declined by 75-80%, fluid output declined by only 40% (Table 1). This smaller decline in fluid relative to acid output probably reflects unchanged fluid output from non-parietal cells. In contrast, data on the monkey showed that basal fluid output was elevated after radiation exposure and that after water load fluid output declined below the pre-stimulation level (3).

Radiation exposure significantly reduced gastric juice volume during histamine stimulation. Since radiation did not significantly alter gastric emptying, the reduction in gastric juice volume during histamine stimulation must be due to the reduction in fluid secretion.

Finally, ionizing radiation had a prolonged duration of effects suggesting that radiation injury affects not only parietal cell functions but also has some other systemic damage which has a slow recovery process. These results are in contrast to those in the monkey in which 2 days after irradiation all the gastric secretory parameters return to normal (3). These differences between the monkey and the guinea pig may be due to differences in species or in radiation exposure conditions (400 cGy at 100 cGy/min in guinea pig vs 800 cGy at 500 cGy/min in the monkey).

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