EFFECTS OF GASTRIC ANTIBODIES ON GASTRIC SECRETION

II. EFFECTS OF RABBIT ANTIBODIES AGAINST RAT GASTRIC MUCOSA AND GASTRIC JUICE, ON GASTRIC SECRETION IN THE RAT

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The etiology of atrophic gastritis has not been established. Although the circulating antibody to a constituent of the gastric parietal cell has been demonstrated in a large number of patients with pernicious anemia and atrophic gastritis (1-5), the significance of the parietal cell antibody in causing or perpetuating any type of chronic gastritis is unknown. Jacob and Glass (6) have presented direct evidence that the parietal cell antibody is a complement fixing antibody, and have supported the concept that the autoimmune mechanism participates in the development of the gastric atrophic lesion in a proportion of patients with pernicious anemia and atrophic gastritis. Fiasse et al. (7) failed to show inhibition of gastric secretion after a single injection of human parietal cell antibody in the rat. On the other hand, Tanaka and Glass (8) have reported that rats injected with human parietal cell antibody for 6 to 8 weeks showed a profound decrease of hydrochloric acid output, and had mild atrophic lesions in the gastric mucosa. Hausamen et al. (9) have shown that the injection of rabbit antisera against antigens from guinea pig gastric mucosa into guinea pigs, resulted in an acute inflammation confined to the stomach. In the present study, short- and long-term effects of rabbit antibodies against rat gastric mucosa and gastric juice on gastric secretion in the rat, were investigated.

MATERIALS AND METHODS

Animals
Male Donryu strain rats weighing 170-252 g, were used.

Antisera
Rabbit antisera, the production and characteristics of which were reported in the preceding paper (10), were used. Three groups of antisera were available and were directed against extract from rat gastric mucosa of the oxyntic area (GM), rat gastric juice (GJ) and extract from rat uterus (Ut). Lyophilized γ-globulin fractions, prepared from these antisera and normal rabbit serum, were dissolved in saline and used for animal experiments, after absorption with normal rat serum and a lyophilized homogenate of rat esophagus.
Animal experiments

The following three experimental groups (A, B and C) were employed:

A) In order to study the duration of the effect of antibodies on gastric secretory function, gastric secretion was investigated at various periods of time (0, 1, 2, 4 and 7 days) after the injection of 25 mg of the γ-globulin preparations into the femoral vein. Saline was similarly administered as a control. Rats were fasted overnight and the pylorus was ligated under light anesthesia with ether, according to the method of Shay et al. (11). Three hr after the operation, rats were sacrificed by a blow on the head, the cardia was ligated and the stomach removed.

B) In order to study the effects of antibodies on gastric secretion stimulated with secretagogues, γ-globulin preparations were injected intravenously, and a dose either of 4.5 mg/kg of histamine dihydrochloride or 500 μg/kg of gastrin-like tetrapeptide, t-AMyloxy carbonyl Try. Met. Asp. Phe. NH₂ (AOC-TP), was administered intramuscularly immediately after the pyloric ligation. These doses of histamine and AOC-TP have been demonstrated to produce a maximal and submaximal acid response, respectively (12).

C) In the study of long-term effects, 5 mg of γ-globulin preparations from rabbit antisera and normal serum in 0.25 ml saline were injected daily for 3 weeks, into the tail vein. Saline was similarly administered as a control. At the end of the experimental period, rats were fasted overnight, the pylorus was ligated under light ether anesthesia, and a dose of 4.5 mg/kg of histamine dihydrochloride was administered intramuscularly at the time of operation. The single injection of this dose of γ-globulin preparation did not show any effect on gastric secretion.

Studies of gastric juice

The volume of gastric juice in the stomach was measured. Free and total acidities of gastric juice were determined by titrating with 0.1 N NaOH using Töpper's reagent and phenolphthalein as indicators. The acid output was calculated from the total acid and the volume of gastric juice.

Pepsin activity was determined by the modified Bock's method (13) using bovine serum albumin (The Armour Laboratories) as substrate and expressed as mg tyrosine released per 30 min incubation.

As an indicator of mucus secretion, hexosamine output was measured by the modified Masamune's method (14), and expressed in mg per 3 hr of gastric secretion.

Histological studies

Tissue specimens of the stomach were fixed in 10% formal saline. Histological sections were made after paraffin embedding and stained by the hematoxylin-eosin method.

RESULTS

A) The duration of the effect of rabbit antibodies on gastric secretory function of the rat

A-1 In 50 rats of body wt 174–203 (mean 187) g, the gastric secretory responses for the first 3 hr after administration of γ-globulin preparations were investigated. Results are summarized in Table 1.
TABLE 1. Gastric secretory responses in 3 hr pylorus ligated rats immediately after administration of saline (Sal), rabbit antibodies against rat uterus (Ut), against rat gastric mucosa (GM) and against rat gastric juice (GJ).

<table>
<thead>
<tr>
<th>Ab</th>
<th>No. of animals</th>
<th>Volume ml/3 hr</th>
<th>Acidity mEq/l</th>
<th>Acid output μEq/3 hr</th>
<th>Peptic activity mg/3 hr as tyrosine</th>
<th>Hexosamine output μg/3 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sal</td>
<td>10</td>
<td>5.2±0.3</td>
<td>78±3</td>
<td>95±3</td>
<td>500±40</td>
<td>78±3</td>
</tr>
<tr>
<td>Ut</td>
<td>20</td>
<td>5.0±0.2</td>
<td>82±3</td>
<td>99±3</td>
<td>503±32</td>
<td>80±4</td>
</tr>
<tr>
<td>GM</td>
<td>10</td>
<td>3.5±0.4**</td>
<td>65±5*</td>
<td>87±4*</td>
<td>306±34**</td>
<td>53±5**</td>
</tr>
<tr>
<td>GJ</td>
<td>10</td>
<td>3.7±0.4**</td>
<td>69±4*</td>
<td>89±3*</td>
<td>330±37**</td>
<td>58±5**</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.

* Significantly different from Ut at P=0.05
** Significantly different from Ut at P=0.01

TABLE 2. Gastric secretory responses in 3 hr pylorus ligated rats 1 day after administration of rabbit antibodies against rat uterus (Ut), against rat gastric mucosa (GM) and against rat gastric juice (GJ).

<table>
<thead>
<tr>
<th>Ab</th>
<th>No. of animals</th>
<th>Volume ml/3 hr</th>
<th>Acidity mEq/l</th>
<th>Acid output μEq/3 hr</th>
<th>Peptic activity mg/3 hr as tyrosine</th>
<th>Hexosamine output μg/3 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ut</td>
<td>9</td>
<td>5.6±0.3</td>
<td>93±2</td>
<td>109±3</td>
<td>615±34</td>
<td>87±7</td>
</tr>
<tr>
<td>GM</td>
<td>9</td>
<td>5.1±0.4</td>
<td>82±6</td>
<td>98±5</td>
<td>463±69*</td>
<td>67±6*</td>
</tr>
<tr>
<td>GJ</td>
<td>9</td>
<td>5.2±0.5</td>
<td>89±5</td>
<td>104±5</td>
<td>571±61</td>
<td>77±11</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.

* Significantly different from Ut at P=0.05

Ut antibodies exerted no inhibitory effect on gastric secretion compared with saline.

GM antibodies reduced the volume of gastric juice by 30%, free acid by 20%, total acid by 13%, acid output by 39%, pepsin activity by 34% and hexosamine output by 30%. These were statistically significant at P=0.01 or 0.05, as compared with Ut antibodies.

GJ antibodies also reduced the volume of gastric juice by 26%, free acid by 16%, total acid by 11%, acid output by 34%, pepsin activity by 28% and hexosamine output by 16%, compared with Ut antibodies. These were statistically significant at P=0.01 or 0.05.

The reduction of all the parameters of gastric secretion after administration of GM antibodies was greater than that after administration of GJ antibodies.

A-2 One day after administration of γ-globulin preparations, rats weighing 180–227 (mean 202) g, were studied for gastric secretory function (Table 2).

GM antibodies reduced acid output by 24% and pepsin activity by 23%, figures were statistically significant reductions at P=0.05, compared with Ut antibodies. The volume of gastric juice, free acid and total acid in rats injected with GM antibodies decreased by about 10%, but values were not statistically significant.

GJ antibodies slightly reduced all the parameters of gastric secretion, except that of hexosamine output.

A-3 Table 3 shows the gastric secretory responses 2 days after administration of γ-globulin
TABLE 3. Gastric secretory responses in 3 hr pylorus ligated rats 2 days after administration of rabbit antibodies against rat uterus (Ut), against rat gastric mucosa (GM) and against rat gastric juice (GJ).

<table>
<thead>
<tr>
<th>Ab</th>
<th>No. of animals</th>
<th>Volume ml/3 hr</th>
<th>Acidity mL/4 Total acid</th>
<th>Acid output pEq/3 hr</th>
<th>Peptic activity mg/3 hr as tyrosine</th>
<th>Hexosamine output pEq/3 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ut</td>
<td>9</td>
<td>6.6 ± 0.3</td>
<td>88 ± 5</td>
<td>100 ± 1</td>
<td>665 ± 46</td>
<td>101 ± 7</td>
</tr>
<tr>
<td>GM</td>
<td>10</td>
<td>5.5 ± 0.6</td>
<td>86 ± 6</td>
<td>103 ± 4</td>
<td>584 ± 75</td>
<td>90 ± 10</td>
</tr>
<tr>
<td>GJ</td>
<td>10</td>
<td>5.7 ± 0.3</td>
<td>86 ± 4</td>
<td>99 ± 6</td>
<td>573 ± 61</td>
<td>89 ± 9</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.

TABLE 4. Gastric secretory responses in 3 hr pylorus ligated rats 4 days after administration of rabbit antibodies against rat uterus (Ut), against rat gastric mucosa (GM) and against rat gastric juice (GJ).

<table>
<thead>
<tr>
<th>Ab</th>
<th>No. of animals</th>
<th>Volume ml/3 hr</th>
<th>Acidity mL/4 Total acid</th>
<th>Acid output pEq/3 hr</th>
<th>Peptic activity mg/3 hr as tyrosine</th>
<th>Hexosamine output pEq/3 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ut</td>
<td>9</td>
<td>5.8 ± 0.4</td>
<td>97 ± 4</td>
<td>112 ± 4</td>
<td>647 ± 55</td>
<td>104 ± 11</td>
</tr>
<tr>
<td>GM</td>
<td>10</td>
<td>5.9 ± 0.4</td>
<td>98 ± 4</td>
<td>111 ± 1</td>
<td>655 ± 58</td>
<td>102 ± 9</td>
</tr>
<tr>
<td>GJ</td>
<td>10</td>
<td>5.8 ± 0.3</td>
<td>100 ± 3</td>
<td>116 ± 3</td>
<td>670 ± 38</td>
<td>101 ± 9</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.

TABLE 5. Gastric secretory responses in 3 hr pylorus ligated rats 7 days after administration of rabbit antibodies against rat uterus (Ut), against rat gastric mucosa (GM) and against rat gastric juice (GJ).

<table>
<thead>
<tr>
<th>Ab</th>
<th>No. of animals</th>
<th>Volume ml/3 hr</th>
<th>Acidity mL/4 Total acid</th>
<th>Acid output pEq/3 hr</th>
<th>Peptic activity mg/3 hr as tyrosine</th>
<th>Hexosamine output pEq/3 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ut</td>
<td>10</td>
<td>6.3 ± 0.3</td>
<td>103 ± 3</td>
<td>113 ± 3</td>
<td>723 ± 69</td>
<td>116 ± 8</td>
</tr>
<tr>
<td>GM</td>
<td>10</td>
<td>6.1 ± 0.5</td>
<td>106 ± 9</td>
<td>116 ± 2</td>
<td>715 ± 61</td>
<td>103 ± 6</td>
</tr>
<tr>
<td>GJ</td>
<td>10</td>
<td>6.3 ± 0.4</td>
<td>103 ± 5</td>
<td>116 ± 5</td>
<td>740 ± 71</td>
<td>104 ± 9</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.

preparations, in rats weighing 182-211 (mean 194) g.

GM antibodies and GJ antibodies reduced the volume of gastric juice, acid output and pepsin activity by about 10%, as compared with Ut antibodies, but did not affect either free or total acid, or hexosamine output.

A-4 The data on gastric secretory responses, determined 4 days after injection of γ-globulin preparations, are summarized in Table 4. Twenty-nine rats, weighing 185-214 (mean 199) g, were used.

None of the parameters of gastric secretion in rats injected with GM antibodies and GJ antibodies differed from those of rats injected with Ut antibodies.

A-5 Seven days after administration of γ-globulin preparations, gastric secretory function was studied in rats weighing 174-213 (mean 193) g. Results are shown in Table 5.

There were no differences in gastric secretory responses among rats injected with GM
antibodies, GJ antibodies and Ut antibodies.

Administration of 25 mg of either GM antibodies or GJ antibodies resulted in a marked decrease in all the parameters of gastric secretion studied. The most profound inhibition of these parameters was observed in the study performed immediately after administration. Of the parameters reduced, reduction of acid output was highest in rats injected with either GM antibodies or GJ antibodies. Significant inhibition of acid output lasted for as long as 24 hr, and the inhibition disappeared 4 days after administration.

B) Effects of γ-globulin preparations on gastric secretion, stimulated by either histamine or AOC-TP, were investigated immediately after administration when the inhibitory activity of these antibodies on gastric secretion appeared most clearly.

B-1 Effects of γ-globulin preparations on histamine-stimulated gastric secretion were studied in 39 rats weighing 174-206 (mean 187) g. Results are summarized in Table 6.

Ut antibodies had no effect on gastric responses stimulated by 4.5 mg/kg of histamine dihydrochloride.

GM antibodies reduced the volume of gastric juice by 28%, free acid by 17%, total acid by 12%, acid output by 42%, and pepsin activity by 34%. Values were statistically significant at P=0.01 or 0.05, compared with Ut antibodies.

Table 6. Histamine-stimulated gastric secretory responses in 3 hr pylorus ligated rats immediately after administration of saline (Sal), rabbit antibodies against rat uterus (Ut), against rat gastric mucosa (GM) and against rat gastric juice (GJ).

<table>
<thead>
<tr>
<th>Ab</th>
<th>No. of animals</th>
<th>Volume ml/3 hr</th>
<th>Acidity mEq/l</th>
<th>Acid output μEq/3 hr</th>
<th>Peptic activity mg/3 hr as tyrosine</th>
<th>Hexosamine output μg/3 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sal</td>
<td>10</td>
<td>5.9 ± 0.3</td>
<td>97 ± 4</td>
<td>113 ± 3</td>
<td>667 ± 51</td>
<td>86 ± 7</td>
</tr>
<tr>
<td>Ut</td>
<td>10</td>
<td>5.4 ± 0.3</td>
<td>95 ± 4</td>
<td>111 ± 3</td>
<td>600 ± 28</td>
<td>80 ± 6</td>
</tr>
<tr>
<td>GM</td>
<td>9</td>
<td>3.5 ± 0.3**</td>
<td>79 ± 5*</td>
<td>98 ± 5*</td>
<td>349 ± 47**</td>
<td>53 ± 5**</td>
</tr>
<tr>
<td>GJ</td>
<td>10</td>
<td>4.5 ± 0.3*</td>
<td>87 ± 4</td>
<td>103 ± 4</td>
<td>462 ± 53**</td>
<td>60 ± 7*</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.
* Significantly different from Ut at P < 0.05
** Significantly different from Ut at P < 0.01

Table 7. AOC-TP-stimulated gastric secretory responses in 3 hr pylorus ligated rats immediately after administration of saline (Sal), rabbit antibodies against rat uterus (Ut), against rat gastric mucosa (GM) and against rat gastric juice (GJ).

<table>
<thead>
<tr>
<th>Ab</th>
<th>No. of animals</th>
<th>Volume ml/3 hr</th>
<th>Acidity mEq/l</th>
<th>Acid output μEq/3 hr</th>
<th>Peptic activity mg/3 hr as tyrosine</th>
<th>Hexosamine output μg/3 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sal</td>
<td>10</td>
<td>5.4 ± 0.4</td>
<td>89 ± 5</td>
<td>105 ± 3</td>
<td>575 ± 62</td>
<td>88 ± 9</td>
</tr>
<tr>
<td>Ut</td>
<td>10</td>
<td>5.4 ± 0.3</td>
<td>85 ± 3</td>
<td>100 ± 3</td>
<td>547 ± 38</td>
<td>90 ± 8</td>
</tr>
<tr>
<td>GM</td>
<td>10</td>
<td>4.0 ± 0.4**</td>
<td>73 ± 5*</td>
<td>92 ± 3</td>
<td>377 ± 43**</td>
<td>71 ± 6</td>
</tr>
<tr>
<td>GJ</td>
<td>10</td>
<td>4.4 ± 0.4*</td>
<td>81 ± 4</td>
<td>98 ± 3</td>
<td>437 ± 48*</td>
<td>69 ± 6*</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.
* Significantly different from Ut at P < 0.05
** Significantly different from Ut at P < 0.01
GJ antibodies reduced the volume of gastric juice by 17%, acid output by 23%, and pepsin activity by 25%, compared with Ut antibodies. These values were statistically significant at $P=0.05$.

**B-2 Effects of γ-globulin preparations on gastric secretory responses**, stimulated by 500 μg/kg of AOC-TP, were studied in rats weighing 183–208 (mean 192) g. Results are shown in Table 7.

Gastric secretion in rats, injected with Ut antibodies, did not differ from that of the saline injected control.

In rats injected with GM antibodies, the volume of gastric juice, free acid and acid output were reduced by 26%, 14%, and 31%, respectively. These differences were statistically significant when compared to data of rats injected with Ut antibodies ($P=0.01$ or 0.05). Pepsin activity was also inhibited by 21%, but this is not statistically significant.

The volume of gastric juice, acid output and pepsin activity, in rats administered with GJ antibodies, was reduced by about 20%, which was statistically significant at $P=0.05$, compared to rats injected with Ut antibodies. Free and total acidity in rats treated with GJ antibodies, was almost at the same level as in rats treated with Ut antibodies.

When gastric secretion was stimulated by either histamine or AOC-TP, the reduction of acid output was most pronounced in rats injected with GM antibodies. In contrast, GJ antibodies produced the most remarkable reduction of pepsin activity. In rats injected with GM antibodies and GJ antibodies, the reduction of free and total acid was not so great as in the studies of non-stimulated secretion.

**C) Long-term effects**

Five mg of γ-globulin preparations were administered for 3 weeks. At the end of the experiment, gastric secretory responses stimulated by 4.5 mg/kg of histamine dihydrochloride were determined. Results are shown in Table 8.

Gastric secretory responses, in rats treated with normal rabbit γ-globulin preparation and Ut antibodies, were not different from those of saline injected controls.

GM antibodies reduced the volume of gastric juice by 17%, free acid by 13%, total acid by 10%, acid output by 22%, pepsin activity by 16% and hexosamine output by 10%.

<table>
<thead>
<tr>
<th>Ab</th>
<th>No. of animals</th>
<th>Volume ml/3 hr</th>
<th>Acidity Free acid</th>
<th>mEq/l Total acid</th>
<th>Acid output μEq/3 hr</th>
<th>Pepsin activity mg 3 hr as tyrosine</th>
<th>Hexosamine output μg/3 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sal</td>
<td>10</td>
<td>4.8 ± 0.5</td>
<td>87 ± 4</td>
<td>107 ± 4</td>
<td>526 ± 52</td>
<td>71 ± 8</td>
<td>1149 ± 50</td>
</tr>
<tr>
<td>Nor</td>
<td>8</td>
<td>4.7 ± 0.7</td>
<td>87 ± 11</td>
<td>106 ± 12</td>
<td>513 ± 70</td>
<td>69 ± 7</td>
<td>1252 ± 71</td>
</tr>
<tr>
<td>Ut</td>
<td>9</td>
<td>4.6 ± 0.3</td>
<td>86 ± 5</td>
<td>107 ± 2</td>
<td>497 ± 37</td>
<td>67 ± 5</td>
<td>1189 ± 59</td>
</tr>
<tr>
<td>GM</td>
<td>9</td>
<td>3.8 ± 0.5</td>
<td>75 ± 10</td>
<td>96 ± 8</td>
<td>386 ± 68</td>
<td>56 ± 7</td>
<td>1074 ± 48</td>
</tr>
<tr>
<td>GJ</td>
<td>9</td>
<td>4.1 ± 0.4</td>
<td>84 ± 7</td>
<td>104 ± 5</td>
<td>442 ± 57</td>
<td>59 ± 8</td>
<td>1025 ± 68</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.
These values, however, were not significant when compared with those of Ut antibodies.

GJ antibodies reduced the volume of gastric juice, acid output, pepsin activity and hexosamine output by about 10% of Ut antibodies. Values were not statistically significant.

All rats maintained growth during the experimental period, with no differences seen in weight gain among the five groups.

Fig. 1. Sections of rat gastric mucosa obtained 3 hr after administration of saline (A), rabbit antibodies against rat uterus (B), against rat gastric mucosa (C) and against rat gastric juice (D), H-E, ×100.
**Histological studies**

No macroscopic change in the stomach was observed following the administration of \( \gamma \)-globulin preparations.

Sections of rat gastric mucosa, prepared 3 hr after injection of \( \gamma \)-globulin preparations, are shown in Fig. 1.

Rats injected with GM antibodies showed a reduction in staining of the parietal cell with eosin, and of the peptic cell with hematoxylin. A slightly denatured profile of the parietal cell and some changes in foveolae were also observed.

Reduction of staining of the peptic cell with hematoxylin and a slight reduction of staining of the parietal cell with eosin, were observed in rats injected with GJ antibodies.

In rats injected with Ut antibodies, lumen of the gastric gland was slightly widened and foveolae were slightly changed.

In the long-term study, the widening of the gastric gland mainly at the upper half of the mucosa, was apparent. Also, some histologic changes of the peptic cell were observed in rats treated with GM antibodies and GJ antibodies. In addition, some atrophic features of the parietal cell and a slight cell infiltration were observed in rats treated with GM antibodies.

**DISCUSSION**

The result of this study demonstrates that either a single or prolonged administration of heterologous antibodies, against rat gastric mucosa and gastric juice, inhibited gastric secretion in rats with pyloric ligation. Inhibition of gastric secretion is characterized by reduction of the volume of gastric juice, free and total acid, acid output, pepsin activity and hexosamine output.

Reports concerning effects of gastric antibodies on gastric secretion are few. Walder (15) reported the production of experimental achlorhydria in dogs administered with heterologous antiserum against the canine parietal cell, for 4 weeks. Fiasse et al. (7) failed to show inhibitory effects on gastric secretion in the rat after a single injection of parietal cell antibody-containing immunoglobulin G fraction processed from sera of patients with pernicious anemia and atrophic gastritis. Tanaka and Glass (8) demonstrated that prolonged administration of the same material to rats resulted in the reduction of gastric acid secretion.

A single injection of 25 mg of \( \gamma \)-globulin preparations, obtained from GM sera and GJ sera, inhibited gastric secretion. The most pronounced inhibition of gastric secretion observed in this study was obtained immediately after the administration of \( \gamma \)-globulin preparations. The duration of the inhibition was not long, and disappeared 4 days after the administration.

Among the parameters reduced, the reduction of acid output was the greatest. This reduction is ascribable to the reduction of both the volume of gastric juice and total acid. Reduction of the volume of gastric juice and gastric acidity is more likely due to a decrease in acid output of the individual parietal cells resulting from temporary impairment of the
function of the cell by antibodies, than to the reduction of the parietal cell mass, as the reduction of these parameters disappeared 4 days after administration of the antibodies. A decrease of HCl output of the individual parietal cells may be due to the formation of an antigen-antibody complement complex at the cellular membrane site, which would form an impediment to the discharge of HCl outside of the cell by impairing the oxidative and enzymatic processes necessary for HCl secretion (8).

Reduction of free acid was greater than that of total acid. This may be attributed to 1) back diffusion of hydrogen ion into the gastric mucosa, as suggested by Davenport (16), 2) increase in secretion of some acid-neutralizing substances.

Pepsin activity was inhibited both in vitro and in vivo by GM antibodies and GJ antibodies. This result could be expected from previous findings of the characteristics of these antibodies (10). Giron and Ramos (17) reported that injection of rabbit antibodies against swine pepsinogen into rats reduced the volume of gastric juice and concentration of acid and pepsin.

Reduction of hexosamine output, as indicator of inhibition of mucus secretion, was observed only immediately after the administration of GM antibodies and GJ antibodies, and was no longer seen one day after administration. This may be attributed to the rapid turnover rate of mucus-producing epithelial cells (18).

Histologic alterations in the gastric mucosa, observed after a single injection of GM antibodies and GJ antibodies, such as impairment of the eosinophilic property of the parietal cell and the basophilic property of the peptic cell, were slight. These changes were different from the finding of Hausamen et al. (9) in which a single injection of γ-globulin, obtained from rabbit antiserum against extract of adult guinea pig stomach, into guinea pig resulted in an acute inflammation confined to the stomach, characterized by extreme capillary dilatation, hemorrhage and neutrophilia.

In the study of histamine- and AOC-TP-stimulated gastric secretion (Tables 6, 7) in rats treated with GM antibodies, the degree of reduction of the parameters of gastric secretion, except for gastric acidity and hexosamine output, was almost similar to that observed in the study of non-stimulated secretion (Table 1). In rats treated with GJ antibodies reduction of pepsin activity was the greatest among the parameters, the next being acid output. When compared with non-stimulated secretion, gastric acidity in rats treated with GJ antibodies returned almost to the control level, while the reduction in rats treated with GM antibodies was slight. These results indicate that GM antibodies and GJ antibodies may either impair the secretory functions of the parietal cell or lower sensitivity of the parietal cell to stimuli. It seems plausible that strong stimuli could overcome the effect of GJ antibodies and partially overcome that of GM antibodies.

Prolonged 3 wk administration of GM antibodies and GJ antibodies reduced gastric secretion. Reduction of acid output was most pronounced, although pepsin activity was also reduced. This pattern of gastric secretion was similar to that observed in patients with superficial gastritis (19). As described above, Tanaka and Glass (8) observed mucosal change in the stomachs of rats administered heterologous parietal cell antibody for 6 to
Specificity for the inhibition of gastric secretion by GM antibodies and GJ antibodies is demonstrated by the facts that 1) GM sera and GJ sera reacted with the gastric mucosa but did not react with the colonic mucosa, 2) GM antibodies and GJ antibodies, however, were directed against various components of the gastric mucosa, the pattern of the inhibition of gastric secretion by these antibodies being consistent with the findings of the immunofluorescence test (10), 3) Ut sera neither reacted with the gastric mucosa nor with the colonic mucosa, and 4) gastric secretory responses in rats treated with Ut antibodies, used as control, were the same as those in rats treated with physiologic saline.

The role of circulating parietal cell antibody in the natural history of atrophic gastritis has long been a matter of dispute (18, 20–22). Jacob and Glass (6) suggested an autoimmune mechanism in the development of the gastric atrophic lesion by demonstrating that parietal cell antibody is a complement-fixing antibody. Tanaka and Glass (8) reported that parietal cell antibody might play a contributory role in the natural history of gastric atrophic lesions in man as a result of the reduction of the parietal cell mass and acid output. In this study, it was demonstrated that GM antibodies and GJ antibodies which contain antibodies against the parietal cell, pepsin and pepsinogen, and mucous substances, inhibit gastric secretory function of their target cells. Should such antibodies actually exist in human circulation, they may actively contribute to the development of gastric atrophic lesions.

SUMMARY

Effects of γ-globulin preparations obtained from rabbit antisera against rat gastric mucosa, gastric juice and uterus on gastric secretion were studied in the rat with pyloric ligation. A single injection of antibodies against gastric mucosa and gastric juice caused an inhibition of gastric secretion, while antibodies against uterus, used as control, had no effect. The inhibition of gastric secretion was characterized by the reduction of the volume of gastric juice, free and total acid, acid output, pepsin activity and hexosamine output. Among the parameters reduced, the reduction of acid output was most pronounced. In rats treated with antibodies against gastric mucosa, the reduction of acid output was greatest when gastric secretion was stimulated with histamine or gastrin tetrapeptide, while in rats treated with antibodies against gastric juice, the reduction of pepsin activity was greatest. Prolonged administration of antibodies against gastric mucosa and gastric juice also reduced gastric secretion. The pattern of this reduction of gastric secretion was similar to that of a single injection. No macroscopic change in the stomach was observed following administration of the antibodies, but slight histologic changes in the gastric mucosa were observed by light microscopic examination. A possible role of gastric antibodies in the natural history of atrophic gastric lesions was discussed.

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