

THE RELATION BETWEEN HISTAMINE AND ATROPINE ON GASTRIC SECRETION.

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Popielski (3) in Poland and Kock, Luckhardt and Keeton (2) in America separately first demonstrated that histamine is a strong stimulant of gastric gland. Since that time numerous investigators have continued to study the action of histamine on gastric secretion. But the relation between the action of histamine and that of atropine which latter is known generally to inhibited the gastric secretion has not been completely set forth in the literature. It is known that the lethal dose of atropine antagonized with the action of histamine on gastric secretion but Keeton, Luckhardt and Koch (2) stated that atropine 1 mg. dose not antagonize with the submaximal dose of histamine. Vinverg and Babkin (4) stated that atropine 2 mg. slightly affected the volume of gastric secretion stimulated by a dose of 1 mg. histamine in case of Heidenhain pouch dog as well as on gastric fistula dogs. Data of Ivy and Barry (1) show that the action of histamine on gastric secretion in a dose of 0.5 mg. was markedly depressed by the injection of atropine 1 mg. The volume and acidity of gastric juice was reduced. The relation with atropine and histamine is still an unfinished problem. Moreover the relation between the sublethal dose of atropine and the minimal dose of histamine is still unclarified. In this experiment we tried to show this relation.

PROCEDURE.

Two kinds of experimental dogs were used- a dog prepared according to the method of Heidenhain pouch which is vagi sectioned and a dog prepared by gastrostomy with vagi intact. The experiments were performed on the animal at least 6 months after operation and 15 hours after last feeding so as to avoid the gastric as well as the intestinal phase of gastric secretion; at this time of basic secretion free HCl shows zero or nearly zero.

Histamine prepared from Grüber company was used. The threshold dose of histamine on gastric secretion is not the same in different animals also it slightly changes day by day in the same animal. Therefore these experiments were done only after positive results on gastric secretion by

the subcutaneous injection of minimal dose of histamine had been established. Then the relation between atropine and histamine (when the influence of first injection of histamine on gastric secretion had disappeared) was continuously tested. The experiments were divided into three groups: viz:

1. Histamine and atropine injected subcutaneously at the same time.
2. Atropine injected 30 min before histamine injection.
3. Atropine injected 60 min before histamine injection.

The doses of the two substance show as per data.

Gastric juice was collected every 30 min. period and the volume and acidity determined by the usual methods, i. e. Topfer's reagent was used for free HCl and phenolphthalein for the total acidity and titrated by N/40 NaOH solution. The acidity calculated in mg. is shown on each table.

RESULT.

1. HISTAMINE AND ATROPINE INJECTED SUBCUTANEOUSLY AT THE SAME TIME.

Histamine 0.03 mg. was injected to the Heidenhain pouch dog and 0.1 or 0.2 mg. was injected to the gastrostomy dog for the control at the time when the free HCl of the gastric juice showed zero or nearly zero. Later when the free HCl caused by the first injection of histamine had disappeared, histamine in doses as before (0.03 mg. to the Heidenhain pouch dogs and 0.1 or 0.2 mg. to the gastrostomy dogs) together with atropine 1 mg. was injected.

Table I.

Period	Time	Volume c.c.	Free HCl %	Total HCl %	Output HCl mg.
(Heidenhain pouch dog)					
Control	10:30				
	11:30	1.0	—	0.018	0.180
	12:30	0.5	—	0.018	0.090
Histamine 0.03 mg. subcut.					
After eff.	1:00	0.6	0.054	0.100	0.600
	1:30	0.6	0.054	0.100	0.600
	2:00	0.5	0.045	0.091	0.455
	2:30	0.2	0.036	0.073	0.146
	3:00	0.4	0.018	0.082	0.328
	3:30	0.4	0.009	0.054	0.216
	4:00	0.1	—	0.009	0.009
Atropine 1 mg. & histamine 0.03 mg. subcut. at the same time					
After eff.	4:30	0.4	—	0.036	0.144
	5:00	0.5	—	0.027	0.135
	5:30	0.4	—	0.018	0.072
	6:00	0.4	—	0.018	0.072
(Gastrostomy dog)					
Control	10:30				
	11:30	4.0	—	0.009	0.360
	12:30	5.0	—	0.018	0.900

Histamine 0.1 mg. subcut.					
After eff.	1:00	1.0	—	0.027	0.270
	1:30	1.8	0.036	0.073	1.314
	2:00	7.0	0.081	0.127	8.890
	2:30	1.0	0.063	0.100	1.000
	3:00	0.8	—	0.036	0.288
	3:30	1.4	—	0.018	0.252
Atropine 1 mg. & histamine 0.1 mg. subcut. at the same time					
After eff.	4:00	1.4	—	0.018	0.252
	4:30	1.2	—	0.018	0.216
	5:00	1.0	—	0.018	0.180
	5:30	1.0	—	0.009	0.090
Control					
Control	10:00				
	11:00	1.0	—	0.009	0.090
	12:00	1.4	—	0.054	0.756
Histamine 0.2 mg. subcut.					
After eff.	12:30	1.8	—	0.054	0.972
	1:00	1.8	0.054	0.119	2.142
	1:30	1.0	0.045	0.110	1.100
	2:00	0.8	0.018	0.036	0.288
	2:30	1.2	—	0.018	0.216
Atropine 1 mg. & histamine 0.2 mg. subcut. at the same time					
After eff.	3:00	1.1	—	0.018	0.198
	3:30	0.9	—	0.018	0.162
	4:00	1.2	—	0.018	0.216
	4:30	1.0	—	0.018	0.180

The table I st show that the atropine 1 mg. completely inhibits the action of the histamine 0.03 mg. in Heidenhain pouch dog and the histamine 0.1 or 0.2 mg. in gastrostomy dog.

This experiment was repeated 10 times on each dog.

2. HISTAMINE INJECTED 30 MIN. AFTER ATROPINE INJECTION SUBCUTANEOUSLY.

The control was the same as former experiment. In the case of the Heidenhain pouch dogs histamine 0.03 mg. was injected 30 min. after atropine 1 mg. and in case of gastrostomy dogs histamine 0.1 mg. was injected 30 min. after atropine 0.5 mg. and histamine 0.1 or 0.2 mg. was injected 30 min. after atropine 1 mg.

Table II.

Period	Time	Volume c.c.	Free HCl %	Total HCl %	Output HCl mg.
(Heidenhain pouch dog)					
Control	10:30				
	11:30	1.0	—	0.018	0.180
	12:30	1.2	—	0.018	0.218
Histamine 0.03 mg. subcut.					
After eff.	1:00	3.0	0.091	0.119	3.570
	1:30	1.0	0.100	0.136	1.360
	2:00	0.8	0.027	0.054	0.432
	2:30	1.2	—	0.036	0.432
	3:00	1.0	—	0.018	0.180
Atropine 1 mg. subcut.					
After eff.	3:30	0.5	—	0.018	0.090

Histamine 0.03 mg. subcut.					
After eff.	4:00	0.4	—	0.018	0.072
	4:30	0.4	—	0.018	0.072
	5:00	0.5	—	0.018	0.090
	5:30	0.4	—	0.018	0.072
(Gastrostomy dog)					
Control	10:30				
	11:30	1.4	—	0.018	0.252
	12:30	0.6	—	0.027	0.162
Histamine 0.1 mg. subcut.					
After eff.	1:00	2.0	0.073	0.127	2.540
	1:30	0.6	0.054	0.110	0.660
	2:00	0.5	0.018	0.054	0.270
	2:30	0.5	—	0.045	0.225
Atropine 0.5 mg. subcut.					
After eff.	3:00	0.6	—	0.018	0.108
Histamine 0.1 mg. subcut.					
After eff.	3:30	0.4	—	0.018	0.072
	4:00	0.6	—	0.036	0.216
	4:30	0.5	—	0.036	0.180
	5:00	0.5	—	0.027	0.135
Control	10:30				
	11:30	0.6	—	0.009	0.054
	12:30	0.5	—	0.009	0.054
Histamine 0.1 mg. subcut.					
After eff.	1:00	0.6	0.045	0.100	0.600
	1:30	0.8	0.054	0.119	0.952
	2:00	0.7	0.045	0.100	0.700
	2:30	1.0	0.018	0.045	0.450
	3:00	1.4	—	0.036	0.504
Atropine 1 mg. subcut.					
After eff.	3:30	0.6	—	0.018	0.108
Histamine 0.1 mg. subcut.					
After eff.	4:00	0.8	—	0.018	0.144
	4:30	2.3	—	0.018	0.414
	5:00	0.5	—	0.018	0.090
	5:30	0.3	—	0.018	0.054
	6:00	0.5	—	0.018	0.090
Control	10:00				
	11:00	3.0	—	0.018	0.540
	12:00	0.4	—	0.018	0.072
Histamine 0.2 mg. subcut.					
After eff.	12:30	1.6	0.018	0.073	1.168
	1:00	2.5	0.100	0.164	4.100
	1:30	0.5	0.045	0.063	0.315
	2:00	0.6	0.027	0.073	0.438
	2:30	0.4	—	0.036	0.144
Atropine 1 mg. subcut.					
After eff.	3:00	0.5	—	0.036	0.180
Histamine 0.2 mg. subcut.					
After eff.	3:30	1.0	—	0.036	0.360
	4:00	0.6	—	0.027	0.162
	4:30	0.6	—	0.027	0.162
	5:00	1.0	—	0.018	0.180

The table 2 show that atropine 1 mg. completely inhibits the action of histamine 0.03 mg. on the gastric secretion in case of Heidenhain pouch

dog. Likewise in case of gastrostomy dogs histamine 0.1 mg. antagonized with atropine 0.5 mg. and histamine 0.1 or 0.2 mg. with atropine 1 mg.

3. HISTAMINE INJECTED 60 MIN. AFTER ATROPINE INJECTION SUBCUTANOUSLY.

The control was done as in former experiments. Then in the case of the Heidenhain pouch dog histamine 0.03 mg. or 0.05 mg. was injected subcutaneously, and in the case of the gastrostomy dogs histamine 0.1 mg. was injected 60 min. after atropine 1 mg.

Table III.

Period	Time	Volume c.c.	Free HCl %	Total HCl %	Output HCl mg.
(Heidenhain pouch dog)					
Control	12:30				
	1:30	1.8	—	0.018	0.324
	2:30	1.2	—	0.018	0.216
Histamine 0.03 mg. subcut.					
After eff.	3:00	1.0	0.027	0.073	0.730
	3:30	0.3	0.027	0.045	0.135
	4:00	1.0	0.027	0.054	0.540
	4:30	0.6	0.018	0.045	0.270
	5:00	0.3	—	0.027	0.081
Control	12:30				
	1:30	4.2	—	0.045	1.890
	2:30	2.2	—	0.009	0.198
Atropine 1 mg. subcut.					
After eff.	3:00	0.6	—	0.009	0.054
	3:30	0.9	—	0.009	0.081
Histamine 0.03 mg. subcut.					
After eff.	4:00	1.0	—	0.018	0.180
	4:30	1.0	—	0.009	0.090
	5:00	1.1	—	0.009	0.099
	5:30	0.8	—	0.009	0.072
Control	10:30				
	11:30	2.6	—	0.045	1.170
	12:30	0.3	—	0.027	0.081
Histamine 0.05 mg. subcut.					
After eff.	1:00	1.2	0.018	0.063	0.756
	1:30	1.0	0.073	0.127	1.270
	2:00	1.0	0.073	0.127	1.270
	2:30	0.8	0.009	0.036	0.288
	3:00	0.8	0.018	0.063	0.504
	3:30	0.4	—	0.045	0.180
Atropine 1 mg. subcut.					
After eff.	4:00	0.4	—	0.018	0.072
	4:30	0.3	—	0.018	0.054
Histamine 0.05 mg. subcut.					
After eff.	5:00	0.2	—	0.018	0.036
	5:30	0.4	—	0.027	0.108
	6:00	0.4	—	0.018	0.072
	6:30	0.2	—	0.091	0.182
(Gastrostomy dog)					
Control	10:30				
	11:30	0.6	—	0.018	0.108
	12:30	0.2	—	0.027	0.054

Histamine 0.1 mg. subcut.					
After eff.	1:00	1.6	—	0.018	0.288
	1:30	1.3	0.036	0.119	1.547
	2:00	1.2	0.054	0.145	1.740
	2:30	1.0	0.018	0.127	1.270
	3:00	0.8	0.009	0.073	0.584
	3:30	0.8	—	0.036	0.288
Atropine 1 mg. subcut.					
After eff.	4:00	2.0	—	0.082	1.640
	4:30	1.2	—	0.063	0.756
Histamine 0.1 mg. subcut.					
After eff.	5:00	1.0	—	0.009	0.090
	5:30	0.8	—	0.018	0.144
	6:00	0.8	—	0.009	0.072
	6:30	0.8	—	0.009	0.072

Table 3 show that atropine 1 mg. completely inhibits the action of histamine in a dose of 0.03 mg. or 0.05 mg. on Heidenhain pouch dog and 0.1 mg. on gastrostomy dog.

These experiments were repeated 5 times on each dog.

DISCUSSION.

The above results were self explanatory. The action of histamine in a dose of 0.03 mg. on Heidenhain pouch dog was completely inhibited by the atropine 1 mg. in all instances, whether the atropine was given with the histamine, 30 min. or 60 min. previously. In the case of gastrostomy dogs the action of histamine in a dose of 0.1 or 0.2 mg. was completely inhibited by the atropine 1 mg. in all experiments. Also the action of histamine in a dose of 0.1 mg. was inhibited by the atropine 0.5 mg. injected 30 min. previously. Thus it is shown that atropine in a sublethal dose completely inhibits the action of histamine in a minimal or double minimal dose on gastric secretion.

The previous investigators statement that the action of atropine in sublethal dose did not inhibited the action of histamine may have arisen because experiments did not consider the dose of histamine. It is suggested that the mutual antagony between two substances in their physiological as well as pharmacological effects might depend upon the dose of each substance.

The results of our experiment were similar in Heidenhain pouch dog (which is vagi-sected) and in gastrostomy dog (which is vagi intact). This indicated that the inhibitory action of atropine in sublethal dose on gastric secretion stimulated by histamine in a minimal dose (but not super-minimal dose) is caused not by the paralysis of the ends of the secretory fibers of vagus but it might be due to the lowered susceptibility to the histamine of secretory cells of gastric gland.

CONCLUSION.

Atropine in a dose of 1 mg. antagonized mutually with histamine in a dose of 0.03 mg. in Heidenhain pouch dogs and 0.1 or 0.2 mg. in gastrostomy dogs. The antagonising result is shown in the effect upon acidity of gastric secretion.

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