Department of Pathology, "Markusovszky" Hospital, Szombathely

EFFECT OF ACETAZOLAMIDE ON THE ARGENTAFFINECELLS OF THE INTESTINES

L. KÁDAS

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The argentaffine cells of the intestinal tract are known to produce 5-hydroxytryptamine (5-HT) [1, 2, 3, 4], a regulator of peristalsis [1, 2, 5, 6]. Its secretion depends on the pH in the upper portion of the intestinal tract. If the duodenum is perfused with 0.1 n HCl, the level of 5-HT rises in the intestine and the argentaffine cells undergo degranulation [7, 8]. These cells lose their affinity for silver salts if sections of small intestine or intestinal fragments are treated with diluted hydrochloric acid [9, 10].

By antagonizing carbonic anhydrase in the cover cells of the gastric mucosa, acetazolamide reduces the secretion of hydrochloric acid [11, 12, 13, 14]. Since there seemed to exist a functional correlation between the two kinds of cell, the present experiments were undertaken in order to establish study of the argentaffine cells on chronic inhibition by acetazolamide of gastric hydrochloric acid secretion.

Material and method

White rats (15 males and 15 females), with body weights from 200 to 250 g, were treated with 5 mg acetazolamide subcutaneously b. i. d. but were left under the accustomed conditions and fed a normal diet. The animals died spontaneously between the 15th and 102nd day. (The average time of survival was 50 to 56 days during which 20 rats died. Three died between the 15th and 50th, seven between the 87th and 102nd day).

The organs were fixed in 10 per cent formalin, Bouin's fluid and 70 per cent alcohol. The stomachs were stained with haematoxylin-eosin, azan, methylgreenpyronine and Schiff's periodic acid, the intestines also by means of ammonium silver nitrate according to Erős—Hasegawa.

Results

This study is concerned only with gastric and intestinal manifestations; those observed in other organs will be reported elsewhere [15, 16].

Stomach. Gross inspection revealed that the stomach, especially its mucous membrane, had grown very thin, atonic, smooth, dilated balloonwise. Histology showed the gastric glands to be dissociated and grouped in islands; they exhibited a lacelike pattern. Glands in the denser packed portions had

a normal structure, contained a normal amount of nucleic acid and their mucus production was unimpaired. The major part of the glands had, however, a distended lumen, their epithelium was flat, the nuclei were pycnotic. The atrophied cells were poor in nucleic acid, stained with mucus-stains slightly, some were completely devoid of mucus. The cover cells displayed the most pronounced atrophy in certain areas. In 7 to 10 days their nuclei shrank, the cytoplasm became uniformly rose-coloured. Their atrophy was marked at a time when the other mucous membrane cells were still normal in appearance. In the third week the lumen of the glands began to distend and show the said histochemical changes.

Intestines. The intestines, the ileocaecal portion in particular, were dilated and thin. Histology showed a normal structure of the mucous membrane but Brunner's glands were dilated like the gastric glands. The argentaffine cells were swollen and their granulation increased after, or together with, the disintegration of the cover cells. After this period of 7 to 14 days they condensed into a tarlike mass. This second phase lasted 14 to 25 days. The cells disintegrated thereafter, and no argentaffine cells could be found in the intestines of animals that had survived for 50 days.

The above changes were followed by marasmus. The pancreas showed the pattern of cystic fibrosis. A correlation was first supposed to exist between the destruction of the argentaffine cells and the development of pancreatic lesions [15]; recent investigations of the cover cells showed that these lesions are connected, since, once the production of hydrochloric acid is inhibited, the synthesis of secretion, an essential factor of exocrine pancreatic activity, suffers irreversible damage. Besides acetazolamide exerts a direct inhibitory effect on the secretion of pancreatic enzymes. It is thought to be of some aetiological significance that we have succeeded in inducing the characteristic pancreatic lesion; this subject will be discussed elsewhere. The pancreatic injury was followed by marasmus and the other sequelae of cystic fibrosis, such as fatty liver, anaemia, bronchiectasis, bronchitis, pneumonia, etc.

Discussion

In agreement with the literary data [11—14] in our experiments acetazolamide inhibited secretory activity of the gastric cover cells and caused their atrophy. While, however, all the quoted reports refer to acute experiments, we have applied chronic acetazolamide treatment. Since it is not to the

Fig. 1. Stomach of animal died on 20th day of acetazolamide treatment. Dissociated structure, pycnotic nuclei, dissolved cytoplasm. Haematox.-eos. ×400

Fig. 2. Stomach of animal died on 56th day of acetazolamide treatment. Cystic glandular lumina, flat epithelium. Haematox.-eos. ×400

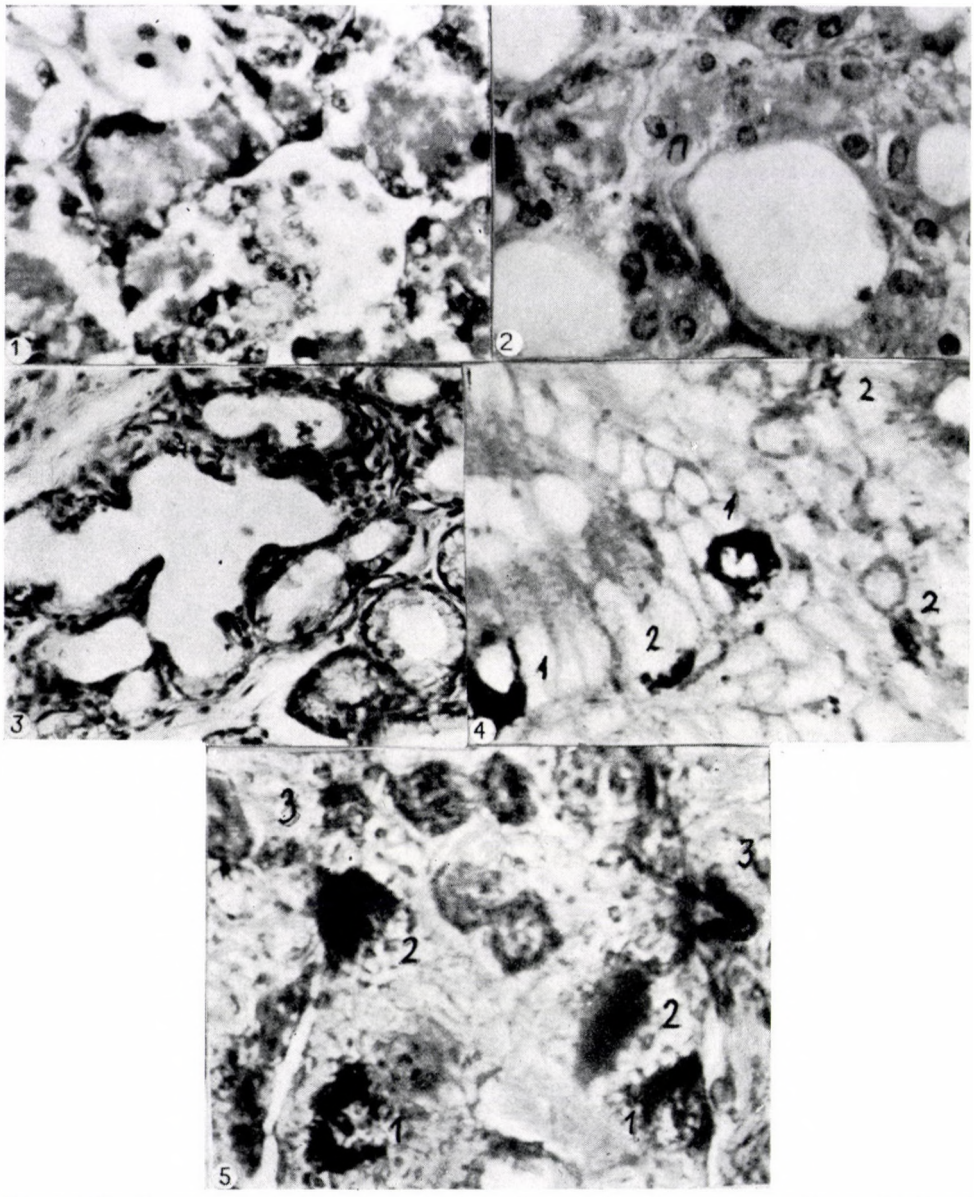

Fig. 3. Duodenum of animal died on 56th day of acetazolamide treatment. Cystic duodenal glands. Haematox.-eos. ×400

Fig. 4. Duodenum.
1 — Swollen, granulated, comparatively intact argentaffine cells
2 — Clumped, granulated argentaffine cells
3 — Disintegrating argentaffine cells
15th day of acetazolamide treatment. Silver impregnation. ×400

Fig. 5. Duodenum.
1 — Argentaffine cell filled with tarlike mass
2 — Disintegrating argentaffine cells
21st day of acetazolamide treatment. Silver impregnation. ×400

direct action of acetazolamide but to the absorption disturbance caused by the pancreatic lesion that we attribute the other changes observed in the gastric glands, it is not intended to expatiate upon them in this paper.

On the other hand, a close correlation seemed to exist between the destruction of the cover cells and the changes observed in the argentaffine cells. The disintegration of the two cell systems went parallel but the damage to the cover cells always preceded that of the argentaffine cells. The histological picture suggested that, unable to release 5-HT, the argentaffine cells become oversaturated, their granules increase in number and then coagulate to form a black mass filling the body of the cells which finally disintegrates into separate clumps.

The present experiments have proved that morphological changes in the cover cells are followed by similar phenomena in the argentaffine cells. A functional interconnection of the two systems is further indicated by the observation that gastric resection is followed by a significant decrease in the blood 5-HT serotonin [17]. This interconnection has been confirmed by our observation that the number of argentaffine cells significantly decreases and grave pancreatic changes, similar to cystic fibrosis, appear in cases of extensive gastric cancer, subtotal or total gastrectomy, atrophic gastritis and gastric achylia, in other words whenever that part of the gastric mucosa which secretes hydrochloric acid is partly or completely destroyed [10].

Another phenomenon, observed in the course of the present experiments, was the pronounced dilatation and thinning of the stomach and intestines. Changes of this kind are usually found in animals suffering from partial lack of protein (absence of methionine) [18, 19]. We suggest that the action of 5-HT becomes weaker or stops altogether along with the destruction of the argentaffine cells, so that with the inhibition of intestinal peristalsis the intestines become thin, distended and permeable. Voluminous steatorrhoea further a shortage of protein due to the absorption disturbance of pancreatic origin, may likewise play a role in this connection.

Summary

Atrophy and desctruction of the gastric cover cells secreting hydrochloric acid have been observed to ensue on chronic acetazolamide treatment in rats. The intestinal argentaffine cells secreting serotonin were likewise damaged by the treatment. It has been concluded that gastric hydrochloric acid enhances the function of the argentaffine cells.

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ÜBER DIE WIRKUNG VON ACETAZOLAMID AUF DIE ARGENTAFFINEN ZELLEN DES DARMTRAKTES

L. KÁDAS

Mit chronischer Acetazolamid Verabreichung wurde bei Ratten eine Atrophie der Deckzellen der Magenschleimhaut hervorgerufen. Gleichzeitig wurden auch die serotoninproduzierenden argentaffinen Zellen des Darmes geschädigt. Die Befunde ließen die Folgerung zu, daß die Magensalzsäure ein Stimulator der argentaffinen Zellen ist.

ДЕЙСТВИЕ ДИАМОКСА НА ОБЛАДАЮЩИЕ СРОДСТВОМ К СЕРЕБРУ КЛЕТКИ КИШЕЧНОГО ТРАКТА

Л. КАДАШ

Автор добился продолжительной дачей диамокса крысам атрофии и гибели образующих соляную кислоту клеток слизистой оболочки желудка. Параллельно с этим поражаются также и вырабатывающие серотонин, имеющие сродство к серебру, клетки кишечника. Сравнивая вышеуказанные наблюдения с литературными данными автор предполагает, что вырабатываемая слизистой оболочкой желудка соляная кислота является стимулятором клеток, имеющих сродство к серебру.

DR. L. KÁDAS: Szombathely, "Markusovszky" Kórház Kórbonctani Osztály Hungary