in Fig. 5, the hexamer packing simulates close packing of spheres. The molecules make direct contacts with one another yet leaving between them solvent channels, 10 Å or more across, through which other smaller molecules and ions may diffuse (Fig. 6). And with the crystal structure as a whole we return once more to the pancreas. Many past observers have noticed small crystals in the β granules of the pancreas of different animals and particularly of the dog. With the electron microscope one can now see roughly spherical units packed within them. A particularly good example, taken of rat islet cells at the University of Sussex, shows lines across the granules representing the packing of particles 50 Å across (Fig. 7) (Greider et al., 1969). Almost certainly these are insulin hexamers formed around the zinc ions in the pancreas, since 50 Å is very nearly the diameter of the hexamers.

Clues in Amino-acid Distribution

It seems most likely that the formation of hexamers around zinc ions is a way of storing insulin which is found in many creatures, though not in all. From the islet cells the hormone is released for action; at the dilutions at which it occurs in the body fluids it is very probably present as the dimer or monomer. We can already see certain clues in the amino-acid distribution in these structures that are suggestive in relation to the biological activity of insulin.

First there are several observations made during the syntheses of insulin carried out in Aachen, Pittsburgh, Shanghai, and Peking. In each case the syntheses were carried out by making separately the A and B chains, reducing them to the sulphydryl form, and leaving them in solution to unite in the correct order and shape. The A chain alone was observed to have some little activity, the B chain none. The reaction to produce insulin was rather inefficient; clearly the organization of separate chains into the correct conformations, to make the correct internal links, is not at all automatic. In nature, indeed, a quite different course, via the single-chain precursor proinsulin, is adopted.

On the other hand, some biologically active insulin is formed by the chemical route; it seems most likely that the B chain tends to fold in the specific form now observed and this may then support the A chain in a biologically active shape through the interaction of certain specific residues.

The nature of these specific residues is suggested by the study of different insulins and the changes that occur with separation. The residues that so far are observed as unchanged include all the cystine residues, three glycines, and a number of leucine and isoleucine residues. These are concentrated in the core of the molecule and seem to be largely concerned with maintaining its correct three-dimensional form. Other residues, such as B 24 phenylalanine along the dimer twofold axis or the A chain residues, glycine A 1, glutamine A 5, tyrosine A 19, and asparagine A 21, might, on the other hand, constitute, in some part or other, an active surface; removal of A 21 or the A 1 amino group largely destroys activity. B 24 might well be opened for interaction with a membrane receptor by opening the dimer.

These clues do not yet tell us what it is that insulin does at the molecular level that affects glucose utilization and transport and protein synthesis and so our own continued well-being. But they may help us to devise new experiments so that in time we may understand how this remarkable molecule operates.

References


---

Serum Gastrin and the Antral Mucosa in Atrophic Gastritis

R. G. STRICKLAND, P. S. BHATHAL, M. G. KORMAN, J. HANSKY

British Medical Journal, 1971, 4, 451-453

Summary

The gastric antral mucosa was studied histologically in 22 patients with atrophic gastritis, of whom 11 had high levels and 11 had normal levels of serum gastrin. The antrum was graded histologically from normal to grade 3 gastritis. All patients with hypergastrinaemia (nine seropositive and two seronegative for parietal cell antibody) had either a normal antrum or minimal (grade 1) antral gastritis. In contrast all but one patient without raised serum gastrin (nine seronegative and two seropositive for parietal cell antibody) had severe (grades 2-3) antral gastritis. Thus circulating gastrin levels observed in patients with gastritis and achlorhydra can be directly related to the presence or absence of antral mucosal damage.

Introduction

The hypergastrinaemia of pernicious anaemia has been explained on the basis of achlorhydra with consequent interruption of the normal inhibition by acid of gastrin release...
from the antral mucosa (McGuigan and Trudeau, 1970). In many patients with atrophic gastritis and achlorhydria, however, gastrin levels are not raised, particularly in those without gastric autoantibodies (Ganguli et al., 1971; Korman et al., 1971). Hence other factors must determine levels of serum gastrin in atrophic gastritis. As gastrin-secreting cells are confined to the antrum in the normal stomach (McGuigan, 1968) it was suggested that variation in the distribution of gastritis, and in particular whether or not the antral mucosa was diseased, could be important (Korman et al., 1971).

In this study the antral mucosa has been compared histologically in two groups of patients with atrophic gastritis, those with hypergastrinaemia and those without raised serum gastrin. Serum gastrin levels in patients with postgastrectomy gastritis were also investigated.

Patients and Methods

Chronic Atrophic Gastritis.—Twenty-two patients from a larger group with atrophic gastritis studied by Korman et al. (1971) were investigated. The groups were equally divided, 11 having hypergastrinaemia and 11 having no rise in serum gastrin. Hypergastrinaemia: Eleven patients had hypergastrinaemia (mean 710 pg/ml, range 430-1,140 pg/ml) and their mean age was 62 years. All had total achlorhydria (Kay, 1953). Nine of them (five with pernicious anaemia) gave a positive test for antibody to gastric parietal cells by immunofluorescence, as described by Whittingham and Mackay (1969) but using human stomach as antigen. Normogastrinaemia: Eleven patients did not have raised basal gastrin levels (mean 44 pg/ml, range 5-110 pg/ml) and their mean age was 64 years. Seven had total achlorhydria and four had basal achlorhydria but secreted 0,1, 1-2, and 5 mEq of acid per hour after injection of Histalog (ametazole hydrochloride) 1.5 mg/kg body weight. Two (one with pernicious anaemia) gave a positive test for parietal cell antibody.

Postgastrectomy Gastritis.—Twenty patients with atrophic gastritis after gastric surgery were also studied. Their mean age was 60 years. Surgery had been performed 3-19 years previously, for a gastric ulcer in five and a duodenal ulcer in 15. Three had a Billroth I gastrectomy, 10 a Polya gastrectomy, and six an antroduodenectomy; one had a sleeve resection for a gastric ulcer, the antrum being left in situ. Fourteen had total achlorhydria and six secreted less than 5 mEq of acid per hour after ametazole. All gave a negative test for parietal cell antibody.

Histological Studies.—One or two biopsy specimens were obtained from the antrum of the stomach in the 22 patients with atrophic gastritis. In eight they were taken under vision with a fiberoptic gastroscope (Olympus Model GFB). In 14 patients biopsy specimens were obtained by fluoroscopic positioning of the peroral gastric biopsy tube of Wood et al. (1949). Sections were stained with haematoxylin and eosin and slides were coded and examined by one of us (P.S.B.) without knowledge of their origin. Biopsy specimens were classified as showing "normal" (N) or showing one of three grades of gastritis: grade 1, superficial gastritis or gastritis with focal glandular atrophy; grade 2, gastritis with diffuse but partial glandular atrophy; and grade 3, gastritis with total or subtotal glandular atrophy. The density of inflammatory cell infiltration and the extent of intestinal metaplasia varied within each of these grades.

Serum Gastrin Determinations.—Fasting serum gastrin was measured by radioimmunoassay (Hansky and Cain, 1969; Hansky et al., 1971). The range for age-and-sex-matched hospitalized controls was 0-120 pg/ml.

Statistics.—The histological appearances of the antral mucosa, parietal cell antibody status, and serum gastrin levels were compared and associations between them sought by using \( \chi^2 \) analysis. For the purposes of this analysis the four antral histological grades were contracted to two—namely, grades N and 1 versus grades 2 and 3.

Results

ANTRAL HISTOLOGY IN ATROPHIC GASTRITIS

The histological appearances of the antral mucosa varied from normal (Fig. 1 A) to those of advanced gastritis (Fig. 1 B) in the 22 patients studied. Seven had a normal antrum, five had grade 1 gastritis, five had grade 2 gastritis, and five had grade 3 changes in the antral mucosa.

Relationship to Serum Gastrin (Fig. 2).—The 11 patients with hypergastrinaemia had either a normal antrum or grade 1 antral gastritis, whereas 10 of the 11 without raised serum gastrin had either grade 2 or 3 antral gastritis, the one exception being a man aged 20 with pernicious anaemia, a normal gastrin level of 80 pg/ml, yet a normal antrum histologically. Significant associations existed between normal antral mucosa (histological grades N and 1) and high serum gastrin (P<0.001) and between antral gastritis (histological grades 2 and 3) and normal serum gastrin levels (P<0.001).

FIG. 1.—Antral mucosa: (A) normal, grade N, and (B) grade 3 gastritis. Reduction in mucosal depth, subtotal atrophy of pyloric glands, patchy intestinal metaplasia, and an inflammatory cell infiltrate can be seen in B. (H. and E. \( \times \) 100.)
SERUM GASTRIN IN POSTGASTRECTOMY GASTRITIS

The mean serum gastrin in the 20 patients with postgastrectomy gastritis was 24 pg/ml (range 0-250 pg/ml). In 19 patients the values were <30 pg/ml and the only high level (250 pg/ml) occurred in the patient who had undergone a sleeve resection, the antrum having been left in situ.

Discussion

Previous studies have shown that hypergastrinaemia is not universally present in patients with atrophic gastritis and achlorhydria, and neither the presence of achlorhydria nor the in-vivo action of parietal cell antibody entirely accounts for the hypergastrinaemia (Korman et al., 1971).

The present study indicates that patients with atrophic gastritis and hypergastrinaemia have a normal or near normal antral mucosa while those without raised gastrin have advanced antral gastritis. Thus serum gastrin levels accurately reflect the histological state of the antral mucosa in atrophic gastritis.

The patients with advanced antral gastritis are comparable with the postgastrectomy patients in whom the gastric antrum had been surgically removed and chronic gastritis with achlorhydria subsequently developed in the gastric remnant. Gastrin levels in such patients were in the lower normal range and the only patient with hypergastrinaemia had the antrum still in situ.

Sparing of the antral mucosa in atrophic gastritis associated with pernicious anaemia was originally found in necropsy studies by Magnus and Ungley (1938). te Velde et al. (1966) showed that histological appearances of the fundus in chronic gastritis associated with parietal cell antibody differ morphologically from those seen in chronic gastritis without gastric autoantibodies. The present study shows that the histological appearances of the antral mucosa too differ in these two forms of chronic gastritis. Thus comparison of the histological appearances of the antral mucosa with serum gastrin and parietal cell antibody status has provided a further basis for the separation of two distinct forms of atrophic gastritis.

This work was supported by the National Health and Medical Research Council of Australia (R.G.S., M.G.K., and J.H.).

We wish to thank Dr. S. Whittingham for performing the serological tests, Miss C. Soveny for technical help with the gastrin immunoassay, Sister I. Langford for assistance in the biopsy procedures, and Dr. I. R. Mackay for his advice and help in preparing this manuscript.

Requests for reprints should be addressed to: Dr. R. G. Strickland, Clinical Research Unit, The Walter and Eliza Hall Institute of Medical Research, P.O. Royal Melbourne Hospital, Victoria, 3050, Australia.

References

Kay, A. W. (1953), British Medical Journal, 2, 77.