CHEMICAL MODIFICATION OF A PEPSIN INHIBITOR FROM THE ACTIVATION PEPTIDES OF PEPSINOGEN

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A pepsin inhibiting substance formed during the activation of porcine pepsinogen has been known for many years (1). Based on the finding that in solutions more acid than pH 4, the loss of pepsinogen was not immediately accompanied by an equivalent increase in pepsin. Herriott postulated the scheme shown in Figure 1 for the autocatalytic activation of pepsinogen. The pepsin inhibitor was separated and partially characterized by Herriott (2) and by Van Vunakis and Herriott (3,4). At that time, the techniques of peptide purification and amino acid analysis had not been perfected, and their analysis does not agree with any part of the amino-terminal sequence later elucidated by Ong and Perlmann (5). In 1973, however, Anderson and Harthill (6) prepared an inhibitor almost corresponding in composition to the amino-terminal 16 amino acids of porcine pepsinogen. A homologous 17-amino acid peptide from bovine pepsinogen was reported jointly by Foltmann's group and by Kay and Kassell (7), while Kassell et al. (8) found a peptide from canine pepsinogen of similar composition to the first 14 amino acids of bovine pepsinogen. The high degree of homology of the amino-terminal portions of the pepsinogens of the three species, shown in Figure 2, makes it likely that the activation peptides are not simply "throw aways", but have a physiological role. We have therefore returned to the porcine activation peptides for further investigation, since porcine pepsinogen is readily available.

To study the basis for inhibiting activity, we have modified peptide 1-16 by guanidination of the lysine residues, carried out Edman degradation of the guanidinated inhibitor, and studied the activity of the resulting peptides.
Figure 1. The scheme proposed by Herriott (1) to explain the delay in the formation of active pepsin upon activation of pepsinogen.

![Diagram](image_url)

Figure 2. Homology in the structure of the amino-terminal portions of porcine, bovine, and canine pepsinogens.

- **Porcine**: LEU-VAL-LYS-VAL-PRO-LEU-VAL-ARG-LYS-LYS-SER-LEU-ARG-GLN-ASN-LEU
- **Bovine**: SER-VAL-LYS-ILE-PRO-LEU-VAL-LYS-LYS-SER-LEU-ARG-GLN-ASN-LEU
- **Canine**: ALA-ILE, VAL, LYS, VAL, PRO, LEU, VAL, ARG, LYS, LYS, SER, LEU, ARG