PROTEASES OF HUMAN BRAIN*

ALFRED POPE AND RALPH A. NIXON
Ralph Lowell Laboratories
McLean Hospital
Belmont, Massachusetts

and

Departments of Neurology-Neuropathology, and Psychiatry
Harvard Medical School
Boston, Massachusetts

Accepted December 2, 1983

Growing appreciation of the multiple functions of proteolytic enzymes in intracellular protein degradation and post-translational modification, in the release of biologically active macromolecules and peptides from precursors and in cellular protein regulation and quality control has stimulated interest in proteases in neurobiology and neuropathology. In this article, the proteinases and peptidases thus far studied in the human central nervous system are reviewed with respect to their enzymology, anatomical and cytological distributions and contributions to neurological and psychiatric disease states. Though information concerning brain proteases in man is fragmentary, it suffices to establish the importance of these complex systems for advancing knowledge of human cerebral function in health and disease.

INTRODUCTION

Approximately half a century has passed since the importance of intracellular proteolysis for living systems began to be recognized (1). Until then, the systematic study of proteolytic enzymes had largely developed from their self-evident role in digesting dietary proteins and led to the identification, classification and analysis of alimentary tract enzymes ca-
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Pable of hydrolyzing the peptide bonds of ingested proteins and their oligopeptide cleavage products.

Proteolytic enzymology achieved a high level of sophistication during the 1930's, particularly with the work of Max Bergmann and his colleagues at the Rockefeller Institute. This group introduced the use of synthetic substrates having varying amino acid sequences to determine the specific peptide bonds that were attacked by acidic (pepsin) and alkaline proteinases (trypsin, chymotrypsin) (2). Such analyses were extended to C- and N-terminal peptidases and di- and tripeptide hydrolases that further degrade the products of proteinase action (3). Out of this grew the concept that proteolytic enzymes could be classified into two primary groups, endopeptidases that can attack internal bonds in a peptide chain with or without an adjacent free amino or carboxyl residue, and exopeptidases that cleave only C- and N-terminal peptidyl or dipeptidyl residues from polypeptide chains or fragments thereof including dipeptides (2).

Meanwhile, studies on the phenomenology of post-mortem autolysis had shown that animal organs and tissues undergo catalytic degradation of structural components and must contain enzymes (termed cathepsins by Willstätter) capable of hydrolyzing proteins and peptides (1). A major step forward in the understanding of this system was recognition, again by the Bergmann school (2, 4) that certain intracellular proteases are homospecific with those of the gastrointestinal tract with respect to preferred synthetic substrates and activator-inhibitor properties. During the same era, the pioneer work of Rudolph Schoenheimer was also establishing the principle that throughout life there is a vigorous and continuous turnover of body constituents including proteins (5). Since certain proteolytic enzymes under some circumstances can catalyze transamidation and transpeptidation reactions and, by reversing their normal degradative roles, form peptide bonds, the possibility that intracellular proteases might somehow be involved in protein synthesis was also postulated (2, 6). This hypothesis stimulated further interest in such enzymes but was, of course, short-lived. However, the postulate that proteases are of significance for protein turnover remained and has been repeatedly validated. Moreover, other roles for tissue proteases have received increasing attention including their participation in unmasking the active sites of enzymes from zymogens (7), in the regulation of intracellular protein concentrations (8–10), and in the posttranslational modification (11, 12) and quality control of newly synthesized proteins (13, 14). Added impetus for intensive study of proteases in the nervous and endocrine systems has stemmed from their important role in releasing active neuropeptides from macromolecular precursors and probably inactivating such peptides at effector sites (15–17). As a result of these manifold putative functions and the inferred