Exploring mechanisms of insulin-degrading enzyme activation and localization in the degradation of amyloid beta and insulin.

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The amyloid beta peptide is central to the etiology of Alzheimer's disease, and the small number of proteolytic enzymes that degrade it are therefore of considerable interest. Insulin-degrading enzyme (IDE) is a zinc metallopeptidase that, in additional to metabolizing amyloid beta, is responsible for degrading insulin and likely other bioactive peptides. Efforts are underway to target IDE for the treatment of Alzheimer's disease and diabetes, primarily by developing substrate specific activators or inhibitors. We have characterized IDE activation by both small peptides and anions, particularly polyanions, and obtained crystal structures that define both allosteric binding sites. In addition, a key question is how IDE produced in the cytosol gains access to amyloid beta and insulin, which are taken up by the cell into endocytic compartments. We present recent evidence that IDE may partially localize to endosomes by binding the head groups of phosphatidylinositol phosphates located on the organelle outer membranes. Crystal structures with bound phosphatidylinositol phosphate and inositol phosphate illuminate aspects of the localization mechanism as well as activation by anions.