

**Highlights of Publishes Articles by Dr. Vivian Hook
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A. Novel cathepsin L protease pathway in secretory vesicles for biosynthesis of active opioid and related peptide neurotransmitters and hormones.

The review article summarizes our many recent articles demonstrating function of the novel cathepsin L protease pathway in secretory vesicles for production of opioid and related peptide neurotransmitters and hormones. The cathepsin L protease pathway has more prominent function to generate these cell-cell signaling neuropeptides compared to the previously known prohormone convertase proneuropeptide processing proteases. Pharmacologic features of the dual protease pathways are being investigated for potential therapeutic applications in health and disease.

1. Hook, V., Funkelstein, L., Lu, D., Bark, S., Wegrzyn, J., and Hwang, S.R. (2008) Proteases for processing proneuropeptides into peptide neurotransmitters and hormones. *Annu. Rev. Pharmacol. Toxicol.* 48, 393-423.
2. Funkelstein, L., Toneff, T., Hwang, S.R., Beuschlein, F., Lichtenauer, U.D., Reinheckel, T., Peters, C., and Hook, V. (2008) Major role of cathepsin L for producing the peptide hormones ACTH, β -endorphin, and α -MSH, illustrated by protease gene knockout and expression. *J. Biol. Chem.* 83, 35652-35659.

B. Cathepsin B is a novel protease target for Alzheimer's disease therapeutics.

We identified cathepsin B as a novel protease for production of neurotoxic beta-amyloid that is a major factor causing memory loss in Alzheimer's disease. Inhibitors of cathepsin B reduce beta-amyloid and improve memory in genetic mouse models of AD. Notably, pharmacogenetic differences in drug response were found in different genetic mouse models.

3. Hook, V., Kindy, M., and Hook, G. (2008) Inhibitors of cathepsin B improve memory and reduce β -Amyloid in transgenic Alzheimer's disease mice expressing the wild type, but not the Swedish mutant, β -secretase site of the amyloid precursor protein. *J. Biol. Chem.* 283, 7745-7753.
4. Hook, V., Kindy, M., Reinheckel, T., Peters, C., and Hook, G. (2009) Genetic cathepsin B deficiency reduces beta-amyloid in transgenic mice expressing human wild-type amyloid precursor protein. *Biochem. Biophys. Res. Commun.* 386, 284-288.

C. Proteomics and peptidomic technology for investigation of peptides functioning as neurotransmitters, hormones, and neurotoxic peptides in health and disease.

Studies of bioactive peptides and proteases that generate them require implementation of current mass spectrometry technology and bioinformatics. Establishment of mass spectrometry expertise for proteomics/peptidomics is illustrated by the article below, among several recently published articles from the Hook lab. These approaches include relevance to peptide biomarkers for monitoring disease progression and drug response.

5. Wegrzyn, J., Lee, J., Neveu, J.M., Lane, W.S., and Hook, V. (2007) Proteomics of neuroendocrine secretory vesicles reveal distinct functional systems for biosynthesis and exocytosis of peptide hormones and neurotransmitters. *J. Proteome Research* 6, 1652-1665.