Organisms use protein hormones even when smaller molecules can trigger identical transduction paths. Why? Could residual peptides from hormone proteolysis extend the mechanisms of action of these hormones? Protein hormones are endocytosed by target cells and digested by cathepsins (A, B, C, D, F, H, L, O, X) acting sequentially as endosomes/lysosomes move centripetally. *In silico* prediction of multiple cathepsin action on each of 92 hormones usually leaves 3–24 residual peptides of 6–25 amino acids; post-translational modification maps suggest some predicted cleavages may be blocked *in vivo* so residual peptides may be even longer (the 30-residue hCGβ C-terminus may remain nearly intact). Stepwise application of cathepsins to hormones known to contain independently active peptides also suggests etiologies (cathepsins S and K release obestatin from GHrelin). Complete endosomal digestion of most protein hormones is unlikely so more secondary hormones (vasoinhibin from prolactin, preptin from IGFII) or peptides active in metabolically modulating cytoplasmic proteins in target cells are expected. To find transducer or modulator peptides and their cytoplasmic targets (peptide-motif-matched-proteins, PMMPs) BLASTp (1D matches) and LabelHash (3D matches) are applied; 1D matches with E<0.05 and 3D matches with $P<0.01$ for LRMSD for non-parent homologs are common with many located on PMMP surfaces. PMMPs used to seed network software (CytoScape, STRING) identify PMMP partners; peptide motif involvement in PMMP-partner binding is ascertained from known complex structures or docking software. Complexes that use peptide motifs dictate future bench tests for peptide actions. Present results suggest proteolytic peptides do extend protein hormone action mechanisms.
Protein hormone proteolysis in target cell endosomes and lysosomes and release of previously unrecognized signaling information (<1 min ago)
However, targeting the pathways that regulate autophagy and the biogenesis of lysosomes may present approaches that can rescue cells from the deleterious effects of amyloidogenic proteins. The principal sites for protein degradation in cells are lysosomes and proteasomes. Both are involved in the constitutive turnover of cellular proteins; typically, short-lived proteins are degraded by proteasomes, whereas lysosomes are responsible for the degradation of long-lived proteins. Misfolded proteins also represent an important class of substrate for lysosomes and proteasomes. These may include proteins that require degradation because they fail to fold after translation, such as those encoded by mutated sequences.