Intrinsic mechanisms of the neuropeptide Y hormone aggregation process into functional amyloids as a strategy for storage and release in secretory granules

Souza, Murilo de Oliveira [1] Mendes, Luis Felipe Santos [2]

Vol 1, 2025 - 328728
Abstract Prion 2025

Abstract

While amyloid fibril formation is associated with neurodegenerative diseases, it also serves essential biological functions including protein storage and secretion. This process controls peptide release into the bloodstream, facilitating normal physiological activity. However, the cellular mechanisms that enable harmless intracellular amyloid formation remain unknown. We hypothesize that functional amyloids assemble more rapidly than pathological forms, though the basis for this kinetic difference is unclear. We expressed neuropeptide Y (NPY), an anxiety-regulating hormone, heterologously and induced fibril formation under controlled conditions. Amyloid detection employed atomic force microscopy, transmission electron microscopy, and SDS-resistance assays. Circular dichroism (CD) tracked secondary structure changes, while Thioflavin T (ThT) fluorescence kinetics at varying monomer concentrations enabled global fitting to differentiate aggregation pathways. Heterologously expressed NPY formed amyloid fibrils under secretory granule pH conditions (~5.5). CD spectroscopy revealed a conformational shift from α-helical (208 nm, 222 nm minima) to β-sheet-rich amyloid structures, confirmed by microscopy. ThT kinetics demonstrated aggregation proceeding through primary nucleation (monomer association), elongation (monomer addition), and fragmentation producing secondary nucleation sites. This autocatalytic cycle exponentially increased fibril numbers until system equilibrium. The interplay of nucleation, elongation, and fragmentation mechanisms drives efficient NPY amyloidogenesis, culminating in stable amyloid fibrils. NPY aggregation produces β-sheet-rich, ThT-positive, SDS-resistant fibrils optimally at 37°C and acidic pH (matching secretory granule conditions). Kinetic analysis indicates fragmentation and secondary nucleation, both concentration-dependent, accelerated amyloid formation, representing a common feature of functional amyloids. These findings support a secretion-coupled mechanism consistent with granule maturation dynamics and physiological hormone concentrations.

Programme

16:45 to 17:30 on 11/05/2025

Geribá/João Fernand…

Institutions

[1] University of São Paulo

[2] Universidade de São Paulo

Track

- Functional protein aggregation in yeast and mammalian systems

Keywords

Functional Amyloid

Neuropeptide Y

Secretion Granules