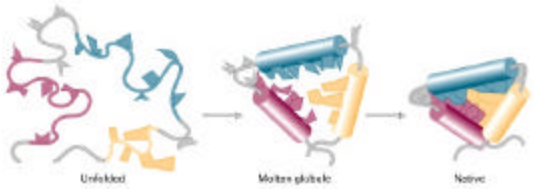
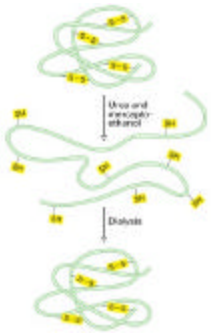
Protein Folding

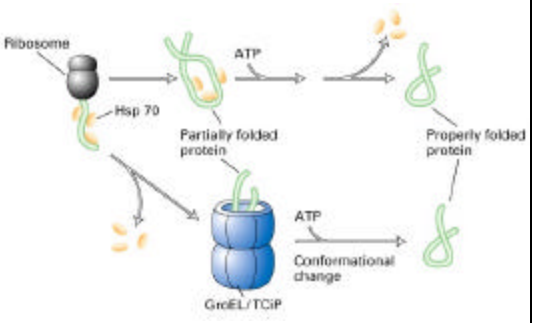
- Most polypeptides spontaneously assume a defined three-dimensional structure during translation
- chaotropic agents and heat break weak bonds that stabilize secondary and tertiary structures = **denaturation**
- under certain circumstances denaturation is reversible = **renaturation**





Chaperones

- Many eukaryotic proteins require assistance of accessory proteins during folding
- **chaperones** bind to partially folded proteins and stabilize transition states that lead to appropriate structures
- many "heat shock" proteins are chaperones
- **chaperonins** mediate the transport of polypeptides across lipidbilayers



Degenerative diseases of the nervous system associated with amyloid formation are frequently caused by misfolded peptides

Neuronal degeneration associated with amyloid plaque formation

- Alzheimer's disease
- Prion diseases

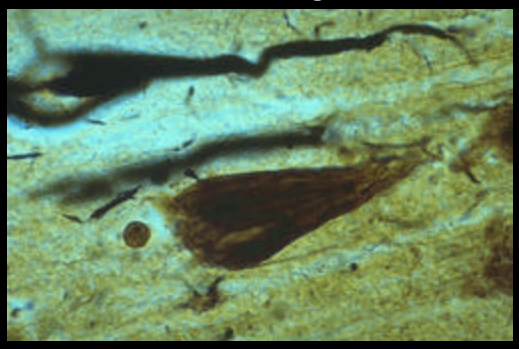
Neuronal degeneration associated with amyloid plaque formation

- accumulation of insoluble protein aggregates
- symptoms result from cellular death in selected regions of the CNS
- the spread of the disease within tissues probably follows axonal tracts

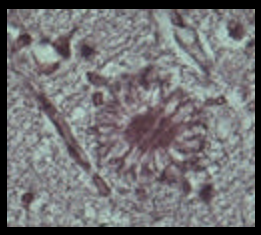
Alzheimer's disease

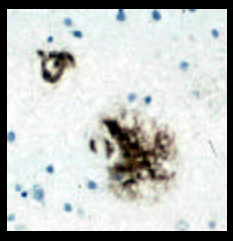
- Formation of "**amyloid plaques**" in brain tissue **predominantly consisting of a single peptide: b-*amyloid* (beta A4)**
- Neuronal **cell death** induced by the cell's inability to remove peptide aggregates
- large-scale memory loss, dementia and personality changes as a result of **degeneration**

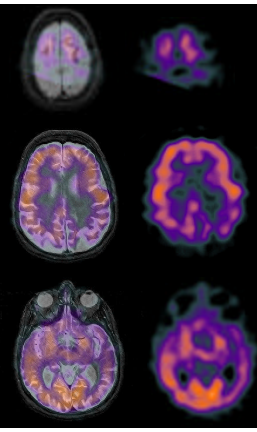
Alzheimer's filamentous tangles in brain tissue



Amyloid Plaque in Neuronal Tissue

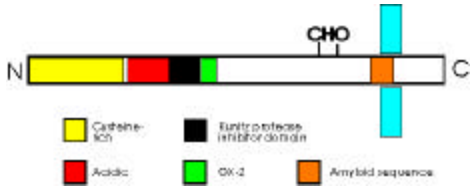






Tissue shrinkage and large-scale degeneration as a result of Alzheimer's disease

Amyloid precursor protein (APP)



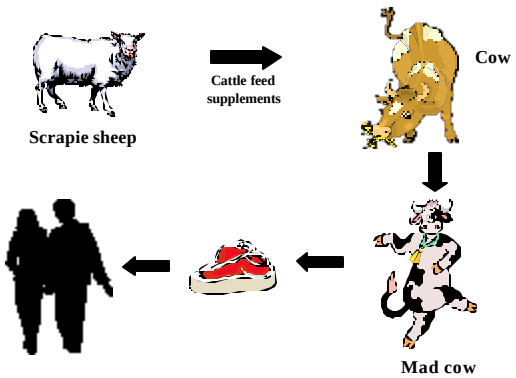
The main component of amyloid plaques is a proteolytic breakdown product of APP

Prion diseases

- Formation of "**amyloid plaques**" in brain tissue
- appearance of large **filamentous tangles consisting of a single polypeptide**
- Neuronal **cell death** induced by the cell's inability to remove peptide aggregates
- dementia and motor coordination problems as a result of neuronal degeneration

Prion diseases

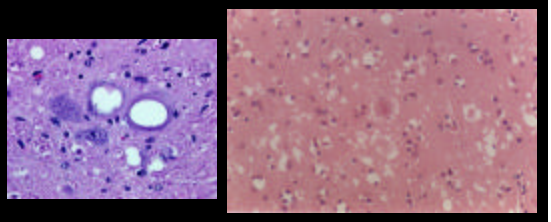
•Creutzfeld Jacob disease (CJD)
•Kuru
= "*laughing death*"
•Bovine Spongiform Encephalitis (BSE)
= "*mad cow* disease", scrapie
•Familial Fatal insomnia (FFI)
•Gerstmann-Straussler-Schenker S. (GSS)



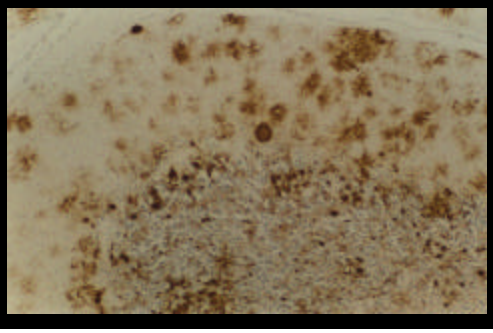
Prion diseases

- Disease is **both transmissible and heritable**
- infectious particles consist of **protein only**!
- Infectious particles are resistant to proteases and moderate concentrations of chaotropic agents

BSE Amyloid Plaque and spongiform degeneration in human neuronal Tissue



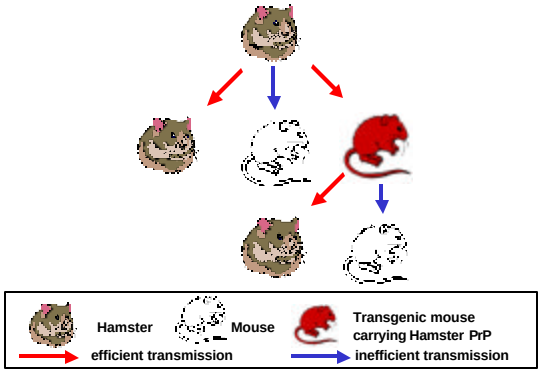
Immunocytochemical PrP detection in human neuronal Tissue



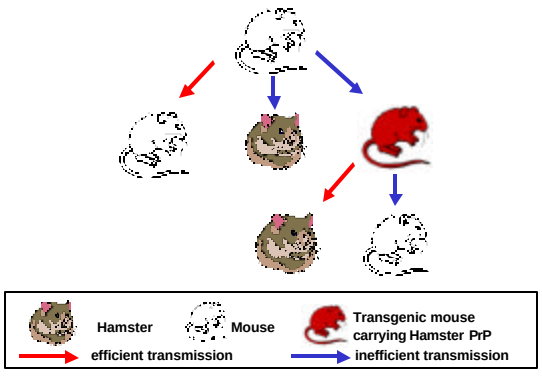
Plaques in prion diseases contain a small cellular protein

- PrP (prion protein) is a neuronal cell surface protein. PrP is believed to be involved in synaptic transmission
- carriers of inherited prion diseases (*Familial insomnia, Creutzfeld-Jacob*) display point mutations within the PrP gene
- gene *knockouts* in mice are viable and fertile
- lack of PrP renders the organism immune to prion infections

Inter-species prion transmission

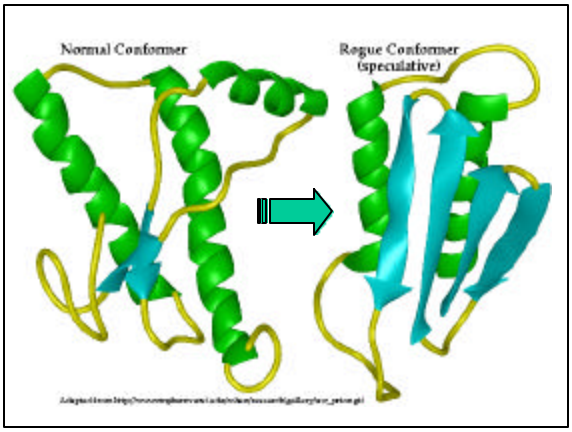


Inter-species prion transmission



Conformational changes in the *PrP* protein are thought to cause plaque formation

- PrP appears to exist as two alternative stable conformeres
- transition to the PrP^{scr} form is favored in a number of point mutations



Mutations within the PrP gene

- Mutations with the PrP gene predispose individuals to acquired and sporadic CJD
- unrelated families with CJD or GSS show the same mutations within the PrP gene
- mutations either confer sensitivity to infection OR mutations enhance the rate of spontaneous conversion of PrP to PrP^{SC}

Conclusions

- **Prion diseases** are caused by a misfolded cellular protein
- **misfolding** is promoted by specific amino acid replacements (result of mutation)
- prions catalyze the **refolding** of normal protein subunits = **rogue conformeres**
- **rogue conformeres** are highly resistant to proteolysis and denaturation
- **The species-specificity of the process is limited, providing the hypothetical basis for large-scale spread of the disease**