ELASTIN

BIOCHEMISTRY

Structure of Elastin

- It is a connective tissue protein
- Rubber like properties
- Elastin & glycoprotein microfibrils are present in lungs, walls of large arteries, elastic ligaments.

- Can be stretched to several times their normal length, but recoil back.

- Insoluble protein polymer
- Precursor is **Tropoelastin**--- it is a linear polypeptide composed of about 700 amino acids – small and non –polar AA.
- Rich in Proline and Lysine
- Very little hydroxy proline & hydroxy lysine.

- Tropoelastin is secreted by the cells into the extracellular matrix.
- There it interacts with specific glycoprotein microfibrils – called fibrillin.
- Fibrillin acts as a scaffold on which tropoelastin is deposited.

- In this case desmosine cross links are formed.
- This produces Elastin. Interconnected rubbery network.

- Mutations in fibrillin are responsible for Marfan's syndrome.
- Connective tissue supports the tendons, ligaments, blood vessels, cartilage and heart valves in the body.
- Affects three major organ systems of the body: the heart and circulatory system, the bones and muscles, and the eyes.

- Fibrillin is the primary component of the microfibrils that allow tissues to stretch repeatedly without weakening.
- fibrillin is abnormal, connective tissues are looser than usual, which weakens or damages the support structures of the entire body.
- The most common external signs associated with Marfan syndrome include excessively long arms and legs, arm span being greater than height.

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α1 antitrypsin

- α1 antitrypsin- it is a protein present in the blood and other body fluids.
- It inhibits a number of proteolytic enzymes called proteinases ---- that destroy proteins.
- It inhibits elastase ---- that degrades elastin of alveolar walls.

- Mutation in its gene leads to lung destruction---emphysema.

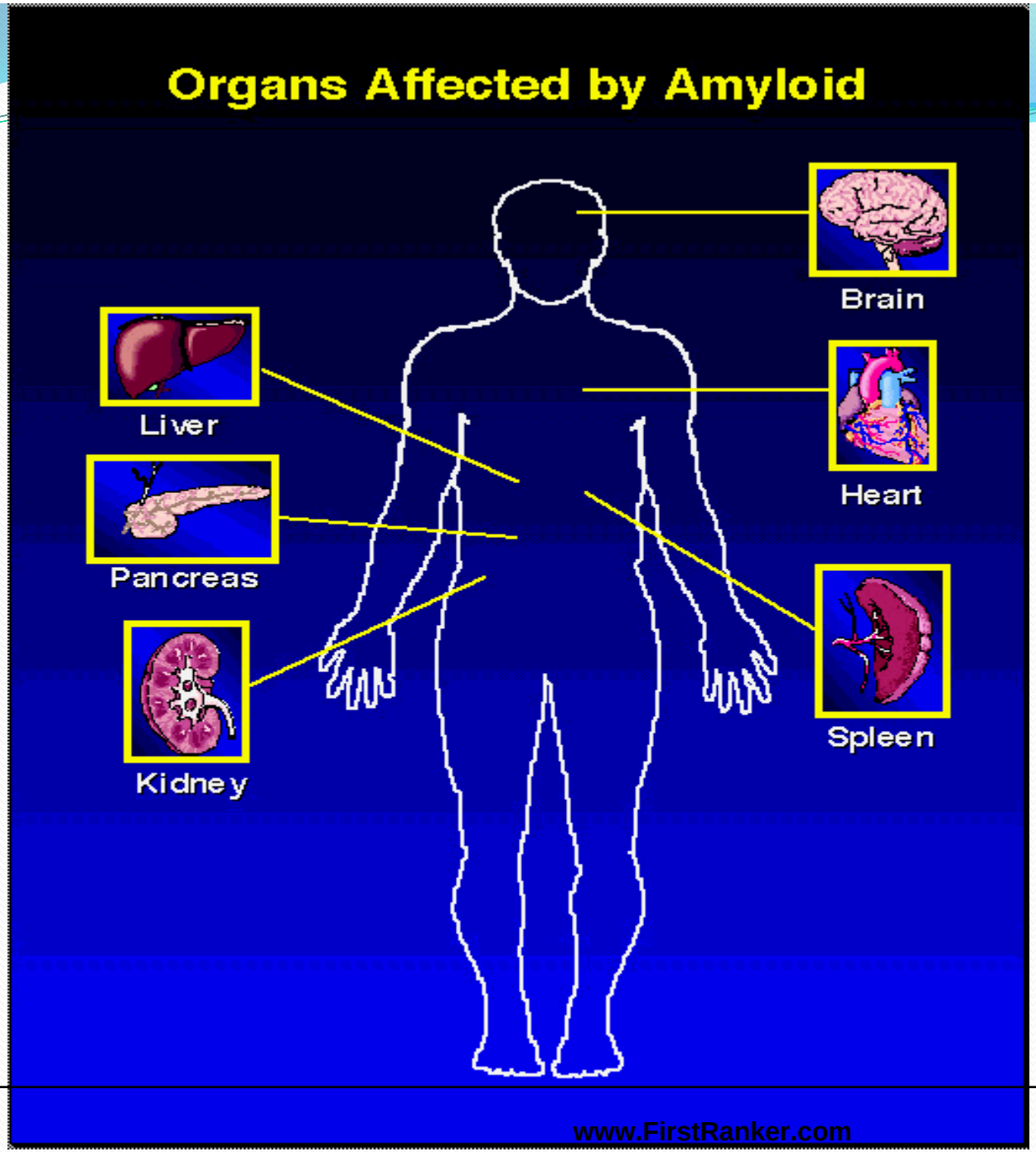
- Smokers more vulnerable.

Denaturation of Proteins

- **Protein folding**
- **Denaturation**
- **Chaperones**
- **Protein Misfolding**

- Folding is a complex process and can sometimes result in misfolded proteins.
- These proteins are tagged and degraded within the cell.
- Sometimes they are not removed properly and they then accumulate inside the body, particularly in old age.

- These misfolded proteins are responsible for a number of diseases including amyloidosis.

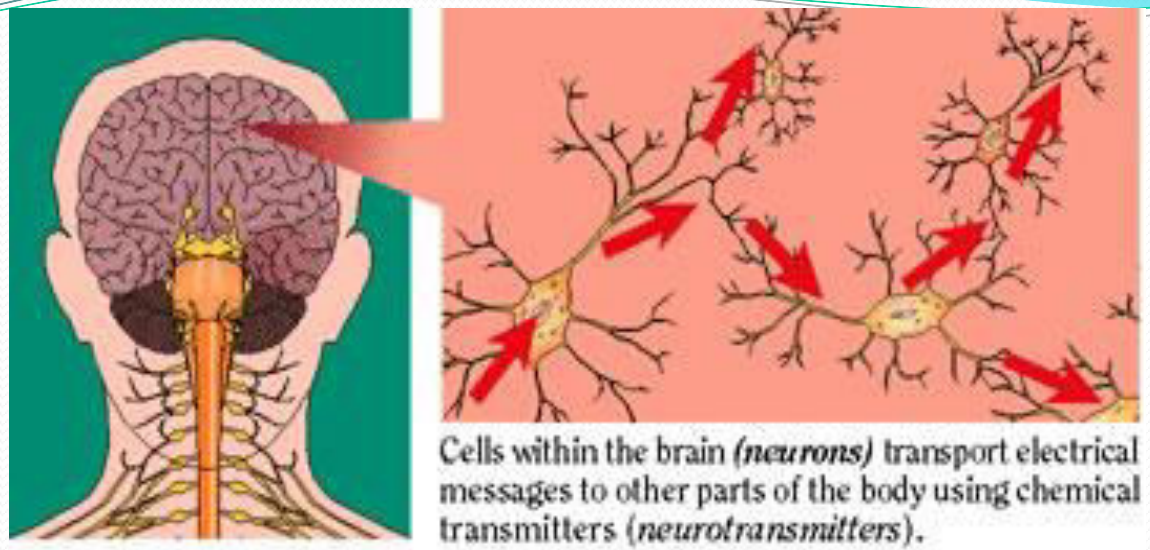


- Amyloid appears as rigid, non-branching ***fibrils***.

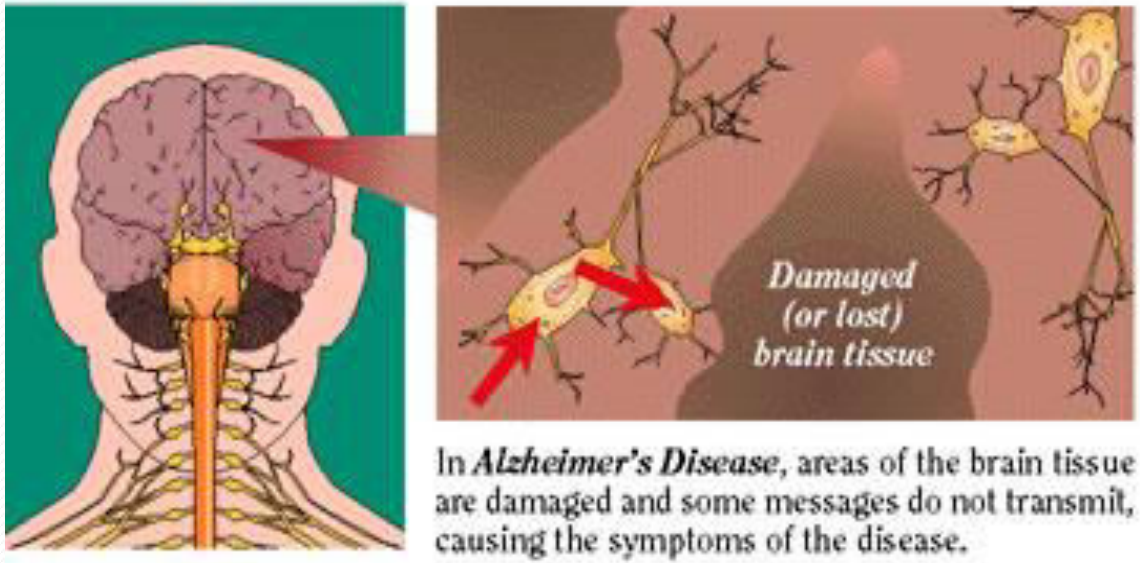
- Rigidity result from the protein conformation in the form of ***beta-pleated sheets***. This feature renders amyloid insoluble.
- Further, it is not viewed by the body as foreign thus, is protected from "attack" by natural defense mechanisms.

- The invasion of healthy tissue by amyloid interferes with normal body function; over time, this relentless process can lead to organ failure and death.

- Accumulation of these proteins called **amyloids** has been implicated in a number of neurodegenerative disorders, particularly **Alzheimer disease**.



Cells within the brain ***(neurons)*** transport electrical messages to other parts of the body using chemical transmitters ***(neurotransmitters)***.



In ***Alzheimer's Disease***, areas of the brain tissue are damaged and some messages do not transmit, causing the symptoms of the disease.

Very Early Alzheimer's

Mild to Moderate Alzheimer's

Severe Alzheimer's

As Alzheimer's disease progresses, neurofibrillary tangles spread throughout the brain (shown in blue). Plaques also spread throughout the brain, starting in the neocortex. By the final stage, damage is widespread and brain tissue has shrunk significantly.

Prion Diseases

- Prion proteins are implicated.
- Destroy brain tissue giving it a spongy appearance
- For these reasons prion diseases are also called **transmissible spongiform encephalopathies** or **TSEs**.

- Prions are molecules of a normal body protein that have **changed their three-dimensional configuration**.

PrP^C

- The normal protein is called **PrP^C** (for cellular)
- is a transmembrane glycoprotein normally found at the surface of certain cells (e.g., neural and hematopoietic stem cells)
- has its secondary structure dominated by alpha helices
- is easily soluble
- is easily digested by proteases
- is encoded by a gene located on chromosome 20.

PrP^{Sc}

- The abnormal, disease-producing protein is called **PrP^{Sc}**
- has the same amino acid sequence as the normal protein; that is, **their primary structures are identical** but
- its secondary structure is dominated by beta conformation
- is insoluble in all but the strongest solvents
- is highly resistant to digestion by proteases

- When PrP^{Sc} comes in contact with PrP^{C}, it converts the PrP^{C} into more of itself (even in the test tube).
- These molecules bind to each other forming aggregates.
- It is not yet clear if these aggregates are themselves the cause of the cell damage or are simply a side effect of the underlying disease process.

Inherited Prion Diseases

- **Creutzfeldt-Jakob Disease (CJD)**

Infectious Prion Diseases

- Scrapie
- Bovine Spongiform Encephalopathy (BSE) or "Mad Cow Disease“
- Creutzfeldt-Jakob Disease (CJD)

- Grafts of dura mater taken from patients with inherited CJD have transmitted the disease to more than 100 recipients.
- Corneal transplants have also inadvertently transmitted CJD.
- Instruments used in brain surgery on patients with CJD have transmitted the disease to other patients. Two years after their supposed sterilization, these instruments remained infectious.

- Over 100 people have acquired CJD from injections of human growth hormone (HGH) or human gonadotropins prepared from pooled pituitary glands that inadvertently included glands taken from humans with CJD.

  (By 2009, the death toll among French children receiving contaminated HGH reached 116.)