Causes of pathological conformation of proteins

A conformational change is a change in the secondary, tertiary, or quaternary **structure of a** protein, without altering its primary structure. Protein assembly is **a sequence of conformational transformations**, that allows a polypeptide chain to assume a biologically active structure. Packing occurs during translation and *in vitro* during renaturation. This **process is very complex** and there is not enough information about the laws of its course. While small single-chain proteins usually fold into their native structure spontaneously, when the packing process is determined by their primary structure, larger complex proteins sometimes need an auxiliary protein to properly fold. **chaperon**.

A common feature of diseases caused by the pathological conformation of proteins is the formation of β-sheet structures, which is usually stabilized by oligomerization and aggregation of the protein. As a result of this process, **deposits of**Amyloid -like aggregates are formed in various organs, they are **damaged and** protein functions are lost. A conformational defect causes disease.

Chaperones

 See the Chaperones page for more information. **Chaperones** are proteins involved in the **assembly** of other proteins. It protects them from the emergence of pathological conformations. Chaperones are **ATPs**, that are non-specific for their ligands. Their synthesis occurs during cellular stress, such as changes in temperature, cold, detergents, changes in pH, ionic strength, the effects of toxic substances and perhaps some foods. Thus, by synthesizing chaperones, the cell resists the denaturing effects of stress factors.

1. **Molekular**: They recognize a pathological protein, bind to a hydrophobic surface and inhibit aggregation. This mainly includes the so-called **heat shock proteins** (created during heat damage) - protects against denaturation.
2. **Chemical**: They regulate the conditions inside the cells, stabilize proteins against thermal and chemical denaturation (glycerol).
3. **Farmacological**: They bind to a specific conformation, stabilize it. Prevention of proteazomal degradation.

Application:

- help proteins to pack properly;
- they can even allow the protein to unfold;
- prevent proteins from packing prematurely;
- they prevent intermolecular interactions of still unpackaged proteins and thus their precipitation.

Problems of protein packaging

Today we know the primary structure of about 100,000 proteins, the tertiary structure is discovered in about a tenth of them. The problem of protein packaging is not a simple matter, because **the protein alternates several conformations**, before it becomes functional. **The principle of self-packaging** is not entirely simple, as it would take too long, and the products would probably react immediately with other substances in the cytoplasm, creating an inextricable mixture.

Anfinsen's postulate

The native spatial arrangement of a protein is determined by the order of the amino acids in its chain .[1] The rate of packing corresponds to how far apart the amino acids that interact are. When the amino acids that are adjacent to each other in the chain interact, the packing is faster. Conversely, if an interaction between distant amino acids is required for packaging, it will proceed slowly.

Levinthal's paradox

Protein packing is controlled **thermodynamically** – the protein packs into the most energetically advantageous conformation. However, this collapse cannot take place completely by chance, because there are a huge number of possible conformations; if the protein were to gradually go through many possible conformations, it would take much longer to pack than we actually observe[2].

The native structure is formed thermodynamically, but its formation is preceded by the formation of several intermediates. Packing begins in the so-called nucleation centers - parts of the polypeptide chain that have a more ordered structure. The nucleation centers pack first; this determines further packaging of the protein and significantly reduces the number of possible conformations that the protein may occupy during packaging.

Consequence of pathological conformation of proteins

1. **Formation of toxic protein : Neurodegenerative diseases**: **Neurodegenerativní onemocnění** –

chronic, progressive diseases; neuronal loss; accumulation of pathological proteins and formation of aggregates (Alzheimer's disease, Parkinson's disease, Hungtington's disease).
2. **Loss of function**: Cystic fibrosis - mutation - of the chloride channel gene.
3. **Storage : Amyloidosis** - fibrils are not toxic but insoluble. Storage causes tissue damage.

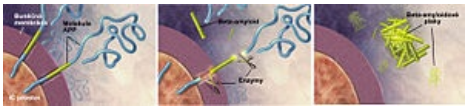
Diseases caused by pathological conformation of proteins

These include, for example, **Amyloidosis**, Alzheimer's disease nebo Parkinson's disease.

Pathological conformation of proteins in Alzheimer's disease

More detailed information on diagnosis, clinical picture and therapy can be found on the Alzheimer's disease page.

Alzheimer's disease is a **in which β-amyloid deposits are deposited extracellularly. The basis of the disease is genotic, poorly packaged proteins accumulate over time. The poorly cleaved precursor protein is**β-amyloid precursor protein **(β-APP). There are at least** two different protein aggregates**in the patient's brain:**


Amyloid-plaque formation-cs

1. misfolded Cytoskeletal **protein tau**;
2. plaques formed by fragments of membrane protein β-APP (β-amyloid, see below)

β-APP is a transmembrane protein of unclear function. It normally cleaves at another site, then its fragments have no pathological function. Near the N-terminus (see figure) of the protein there is an amino acid sequence (there are 42) called amyloid β-peptide. It is this fragment that forms the protein aggregates found in the brains of patients diagnosed with Alzheimer's disease. Amyloid β-peptide polymerizes easily to form insoluble fibrillar structures. These **neuritic plaques** also occur sporadically in healthy individuals, but are present in large amounts in patients with Alzheimer's disease. Of the brain structures, the hippocampus is mainly affected(highest incidence of plaques). Reactive microglial cells infiltrate plaques over time, and are also surrounded by astroglial cells. This results in the release of free O 2 radicals and cztokines, which manifests as aseptic inflammation. Eventually, the surrounding neurons die out. Because the largest accumulation of amyloid is in the hippocampus, patients have the greatest memory problems, are disoriented, and are unable to take care of themselves.

Alzheimer's disease therapy

- inhibition and correction of conformational changes;
- development of new peptides (β-sheet breakers);
- chaperones - experimentally studied.

Pathological conformation of proteins in Parkinson's disease

See Parkinson's Disease for more information on diagnosis, clinical presentation, and therapy.

Mutations in the parkin gene are the main causes of early autosomal recessive familial PD and isolated juvenile PD (occurring by the age of 20) . Genetic testing is necessary to confirm the diagnosis (clinical picture is not sufficient).

The pathogenetic basis is the loss of dopaminergic neurons in the brain (eg the substantia nigra).**The cells gradually wither and so-called Lewy bodies** gradually appear inside them . Their origin and significance are unclear, but they are characteristic of Parkinson's disease. The extinction of these neurons is not complete and is not the only basis for the disease. Also some other cell populations (cholinergic, serotoninergic, adrenergic) tend to be affected, although not as severely. It is not known what unites these populations and why the rest of the brain remains more or less intact. Parkinson's disease also affects some nerve cells outside the brain - nerve cells in the sebaceous glands of the skin (oily skin of Parkinson's, seborrheic dermatitis). There is also constipation, dysuria, impotence.

The place where the greatest disability occurs is the already mentioned **substantia nigra**. From this locality, the axons of the neurons emerge up to the cells of the bazal ganglia. They are involved in the process of regulating movements. They are not directly subject to degeneration, but are affected by a decrease in dopamine (and thus "bad" information) from the substantia nigra. The main consequence of various connections in the brain is ultimately **increased activity of the globus pallidus** – this leads to excessive stimulation of the thalamus. This explains the possibility of neurosurgical treatment - pallidotomy - when the symptoms of the disease may be partially corrected.

The first symptoms appear only when dopamine production in the substantia nigra cells is reduced by 80%. In practice, this means a loss of at least half of the dopaminergic neurons. Thus, the brain compensates for the significant depletion of dopamine without clinically occurring.

Prions and their diseases

Scrapie

Scrapie is undoubtedly the longest known prionopathy. The affected sheep will first show a decline, which will alternate with periods of excessive activity (all the devils "sew" with the animal). Severe itching may occur later. In the following stages of the disease, CNS damage occurs (coordination of movements is impaired) - the animals step on the ground as if it were trotting (hence the Czech folk name trotting). The disease ends in paralysis and death of the sheep. Humans do not become infected with the prion, it is probably not possible for the sheep prion to serve as a matrix for the transformation of human PrPC (unlike bovine prions, which can do this and humans get a new variant of Creutzfeldt-Jakob disease, see below).

Bovine spongiform encephalopathy

BSE („mad cow disease“) was first observed **in cattle in 1986**. Ten years later, a new variant of **Creutzfeldt-Jakob disease** (CJD). was also described. There is a growing body of evidence of similarity between BSE and the new variant of CJD. It is called mad cow disease because it causes strange behavior in animals in the late stages. The macroscopic finding on the brain (*poring*) in the later stages resembles a fungus (spongiform = fungal). A variant of BSE could be (as expected) a disease of sheep scrapie. The incubation period of the disease is several years. We do not yet have evidence (or a specific case) that transmission to humans is possible.

Pathogenesis: Prion cellular protein (**PrPC**) **occurs naturally** on the ganglion cell membranes of the brain. It participates in the regulation of sleep and wakefulness processes and in the maintenance of homeostatic mechanisms of the organism. PrPC can change its conformation to the pathological isoform of PrPSc (causes not clear). PrPC and PrPSc do not differ in the primary structure, but differences can be found in the spatial arrangement. PrPSc is 41% structurally β-sheet, while PrPC is 42% α-helix. As a result, PrPSc gains extreme resistance to the chemical, physical and protease effects.

Creutzfeldt-Jakob disease

CJD is a very **rare disease** belonging to the group of **transmissible spongiform encephalopathies**. The disease affects about 1 in a million people. The cause is the formation of a **pathological protein** in the brain of some people. In CJD, the prion protein enters the brain cells and remains as a virus. The affected cells are eventually so filled with prion proteins that they rupture and die. The disease begins to manifest itself in rapidly progressing **personality breakdown and dementia**.The process could be likened to rapid and very severe Alzheimer's disease, which is also associated with severe mobility impairment and tremor. From the onset of the first symptoms, the person **dies within a few months**.

{{{1}}}

1. ANFINSEN, C B. Principles that govern the folding of protein chains. *Science* [online] . 1973, vol 181, no. 4096, pp. 223-30, also available from < https://www.ncbi.nlm.nih.gov/pubmed/4124164 > . ISSN 0036-8075.
2. TOMPA, Peter and George D ROSE. The Levinthal paradox of the interactome. *Protein Sci* [online] . 2011, vol 20, no. 12, pp. 2074-9, also available from < https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3302650/?tool=pubmed > . ISSN 0961-8368 (print), 1469-896X.