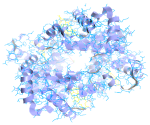


StarBiochem

Name_____

Amyloid Peptides and Alzheimer's Exercise

Learning Objectives

In this exercise, you will use StarBiochem, a protein 3D-viewer, to explore:

- the structure of the amyloid peptides that contribute to the development of Alzheimer's disease
- the process by which these peptides are produced

Background

Alzheimer's disease (AD), a neurodegenerative disease of the brain, is the most common cause of dementia. AD can be divided into two forms depending on the mode of inheritance: familial AD (FAD), the genetically inherited form, and sporadic AD (SAD), the form that shows no genetic inheritance. FAD is associated with early onset of the disease, affecting individuals as early as 30-60 years old, whereas SAD typically develops after age 65. AD is more common in women than men for any given age group.

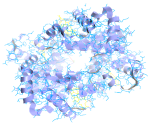
A molecular hallmark of AD is the formation of amyloid peptides which cluster together to form amyloid plaques in the brain. The density of these plaques shows a direct correlation with the progression of AD. Amyloid peptides are formed by the progressive cleavage of the amyloid precursor protein (APP) by secretase enzymes located in neuronal membranes. Amyloid peptides form inside neurons but exert their damaging effects when transported into the extracellular environment, a phenomenon that is observed only in AD patients.

Extracellular transport of amyloid peptides and the formation of amyloid plaques cause neuronal death due to inflammation and/or formation of neurofibrillary tangles (NFTs). NFTs are formed by the aggregation of phosphorylated tau proteins. The tau protein, in its unphosphorylated state, stabilizes microtubules which are required for transport of molecules along the length of neurons. Phosphorylated tau does not stabilize microtubules but instead binds to other tau proteins to form NFTs. Accumulation of NFTs results in neuronal cell death.

Getting started with StarBiochem

- To being using StarBiochem, please navigate to: **http://web.mit.edu/star/biochem**.
- Click on the **Start** button to launch the application.
- Click **Trust** when a prompt appears asking if you trust the certificate.
- In the top menu under File click on **Open/Import**, select "1IYT" and click **Open**.
- Repeat these steps to import the following structures in separate windows: "1BA4", "2ONA", "2OKZ" and "1HZ3" while keeping the other structures opened.

Amyloid peptides and plaques are represented among these structures. The current way you are viewing these structures is by seeing each bond in the protein drawn as a line ("bonds only" view).



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Practice changing the viewpoint of this protein in the view window:

	Mac	PC
TO ROTATE	**click** and **drag** the mouse	**left-click** and **drag** the mouse
TO MOVE UP/DOWN RIGHT/LEFT	**apple-click** and **drag** the mouse	**right-click** and **drag** the mouse
TO ZOOM	**option-click** and **drag** the mouse	**Alt-left-click** and **drag** the mouse

Take a moment to look at the structure of these amyloid peptides and plaques (1IYT, 1BA4, 2ONA, 2OKZ, and 1HZ3) from various angles in this "bonds only" view. Before proceeding to answer the questions, you can review the basic structures and terms on the next page which you can refer to during this exercise.

PROTEIN STRUCTURE BASICS

Each protein has the following three levels of protein structure:

Primary structure
Lists the amino acids that make up a protein's sequence, but does not describe its shape.

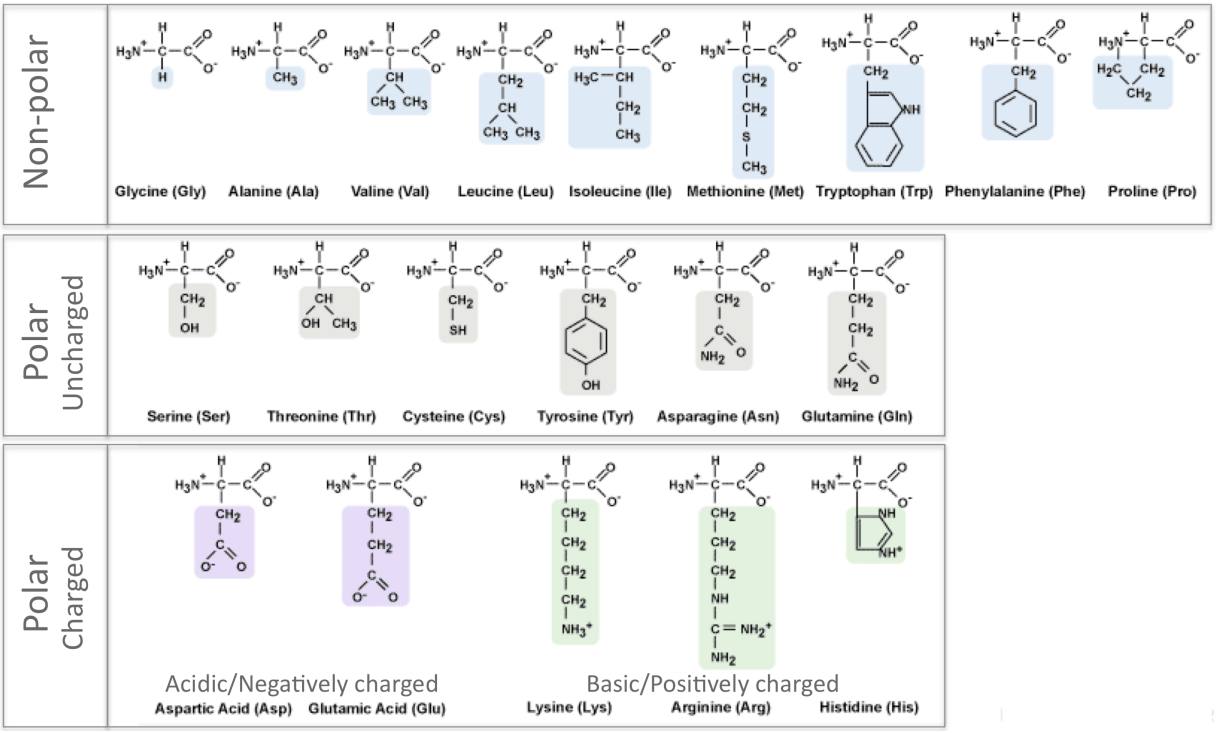
Secondary structure
Describes regions of local folding that form a specific shape, like a helix, a sheet, or a coil.

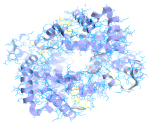
Tertiary structure
Describes the entire folded shape of a whole protein chain.

In addition, some proteins interact with themselves or with other proteins to form larger protein structures. How these proteins interact and fold to form a larger protein complex is termed **Quaternary structure**.

CHEMICAL STRUCTURES OF THE AMINO ACIDS

The 20 amino acids share a common backbone and are distinguished by different 'R' groups, highlighted in various colors below.





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1 ***How many monomers/chains do you see in the current view for each of these structures?***

- Click on **Structure**.
- Click on **Primary**. The amino acids of each polypeptide chain are highlighted by a specific color and can be distinguished from those of other polypeptide chains.
- To distinguish between the different monomers that together make up each of these structures, under **Structure** click on **Quaternary**. Click on **Chain**.

Answer

2 Carefully look at the amino acid sequence of each structure. ***Write down the sequence that is common among all four structures.***

*Hint: For each of these crystal structures, click on **Primary**.*

Answer

3 Biological reactions are multi-step cascades of events. The end product of one reaction step becomes the starting substrate of the next step. Each step in the cascade is catalyzed by a specific enzyme. The formation of amyloid plaques from amyloid peptides is an example of a multi-step biological reaction.

a) ***Based on the primary structures of these peptides, arrange these structures sequentially to reflect the cascade that leads to amyloid plaque formation.***

Hint: All of these structures are derived by the cleavage of amyloid precursor protein.

Answer

b) ***How many enzymes might be involved in catalyzing all the steps of this cascade*****?** Assume that each step in the cascade is catalyzed by only one specific enzyme.

Answer

c) ***Describe what happens at each step in the cascade.***

Answer

4 We will now analyze the secondary structure of these peptides.

- For each window, go to **View**.
- Click on **Reset Molecule**.
- Under **Structure**, click on **Secondary**.
- Explore the different secondary structures found within these crystal structures by individually clicking on the different choices that appear within the **Show Ribbons** box.

a) ***Which secondary structure is absent in all of these crystal structures?***

Answer

b) ***Which secondary structure is present in all of these crystal structures?***

Answer

c) ***Which is the only secondary structure present in the amyloid precursor peptide?***

Answer

d) ***Which secondary structure is present exclusively in the amyloid plaques?***

Answer

5 Let us analyze the nature of the amino acids that comprise these peptides to better understand the environment in which they reside.

- Go to **View**.
- Click on **Reset Molecule**.
- Within **Structure**, click on **Tertiary**.
- Click on the different options provided within the **Color by residue** box.

a) ***Arrange the peptides, in descending order based on their difference in polarity (polar >>>nonpolar).***

Answer

b) It is hypothesized that some of these peptides remain inside neurons after being produced. The presence of these structures in neurons is not regarded as an index of AD. ***Which of these structures represent the amyloid peptides that reside inside neurons? Explain your answer.***

Answer

c) The peptides that you have identified in question 5 (b) contain a central cluster: N-Leu-Val-Phe-Phe-Ala-C. ***Circle the option that best describes the nature of this cluster.***

Answer				
	Polar	Non-polar	Hydrophilic	Hydrophobic

d) ***Within this cluster identify the amino acid(s) that "Valine" interacts with and state the type of interaction between them.*** Your choices are 'hydrogen bond', 'ionic bonds', 'peptide bonds', 'hydrophobic interaction' OR 'van der Waals forces'.

Answer

e) In contrast to the structures you identified in question 5 (b), there are other types of amyloid peptides that are transported from the inside of brain neurons to the outside, where they form amyloid plaques. ***Identify this structure and provide an explanation for how these peptides can reside in the aqueous extracellular environment.***

Answer

f) What is the most common interaction that may exist between the peptides that make up amyloid plaques?

Answer

6 Besides amyloid plaque formation, another key feature observed in AD is the phosphorylation and clustering of the tau protein.

- Open a new window of Starbiochem.
- In the top panel, under **File** click on **Open/Import**.
- Type in "2Ol9."
- Click **Open**.

Of the twenty essential amino acid residues, indicate which ones can be phosphorylated in the tau protein.

Hint: you can refer to the amino acid chemical structure chart at the beginning of this exercise.

Answer

7 Based on what you have learned from this exercise, if you were to design a treatment strategy, ***what process would you target to prevent the onset and progression of AD? Propose three treatment strategies and explain how each will prevent the onset or progression of AD.***

Answer

Keywords

Cascade, familial, sporadic, type-II diabetes, dementia, enzymes, amyloid plaques, and amyloid peptides.

Thought questions

1 HIV patients are often reported to develop dementia with similar characteristics to that observed in AD. Propose an explanation for this observation.

2 What do the mechanism that leads to the onset of AD and the mechanism that leads to the onset of prion diseases have in common?

3 People with Down's syndrome develop AD at a much earlier age. Explain why.