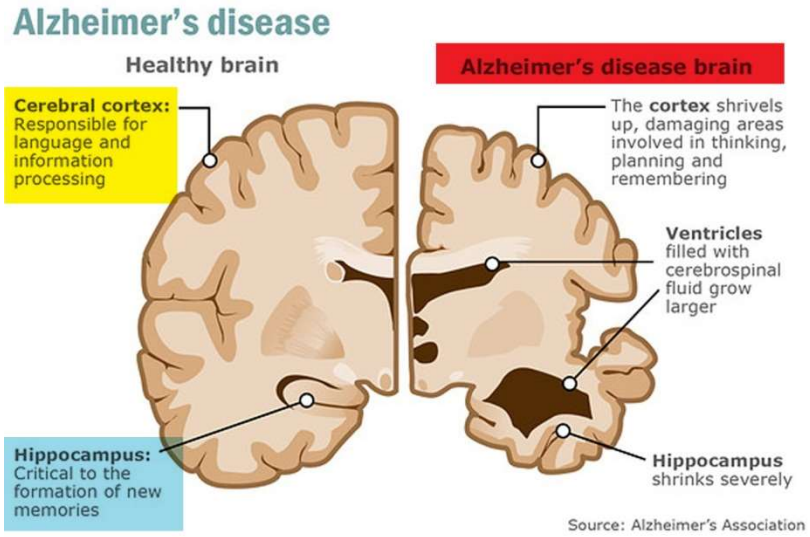

Scientists have found the "trigger" of Alzheimer's disease

A group of scientists from Moscow State University in collaboration with colleagues from the Institute of Molecular Biology of the Russian Academy of Sciences and King's College of London managed to understand the mechanism of development of Alzheimer's disease and, perhaps, point to the main cause initiating the process its occurrence. An article about this study was published in the journal Scientific Reports.

"Alzheimer's disease is a widespread degenerative disease of the central nervous system, leading to loss of mental abilities. The disease Alzheimer's was considered an incurable disease," says a leading researcher at the Faculty of Fundamental Medicine of Moscow State University Vladimir Polshakov. However, now scientists have managed to discover a mechanism that "triggers" the development of the disease, which means that it will be possible to develop new chemical compounds that can become an effective medicine.

Several hypotheses have been devoted to the mechanism of development of Alzheimer's disease. One of the most common and generally accepted is the so-called amyloid hypothesis.

Beta-amyloid peptides are a molecular structure of a protein type and in their normal, healthy state are engaged in protecting nerve cells of the brain.

Their term is short and having fulfilled their function they fall under the "knives" of proteases, cleaning proteins, cutting into small pieces everything that has become unnecessary and turning amyloids into safe "slags", which are then disposed of or excreted from the body.

But, according to the hypothesis, sometimes there comes a moment when something goes wrong and the defenders of nerve cells turn into their killers. Moreover, these peptides begin to combine with each other to form aggregates and become inaccessible to the "knives" of proteases. More or less in detail, this mechanism within the framework of the amyloid hypothesis is prescribed at the stages inherent in the disease already in the developed stage, when toxic aggregates appear, and further, when the brain is already covered with amyloid plaques. It was known very little about the initial stage of the process of converting beta-amyloid into products dangerous for nerve cells.

"It was known, for example, that transition metal ions, primarily zinc, play an important role in the initialization of these processes"- says one of the authors of the article Vladimir Polshakov.

Zinc, generally performs a lot of useful and important functions in the brain, but here it was suspected of "sabotage" for very serious reasons, in that it is one of the initializers of the cascade of processes leading to Alzheimer's disease.However, what exactly happens when beta-amyloid peptide molecules interact with zinc ions, with which amino acid residues these ions bind and how such binding stimulates the processes of peptide aggregation remained unclear. We have set ourselves the task of clarifying at least part of these issues."

Scientists have studied various pathogenic beta-amyloid peptides, or rather, their short sections, domains that bind them to metals. Various methods were used in the work, the main of which was nuclear magnetic resonance spectroscopy(NRS). The structures of the resulting molecular complexes were

determined with its help. Some aspects requiring increased sensitivity of the instrument were additionally measured in the UK.

According to Polshakov, the choice of the studied pathogens was “partly luck”. One of the pathogens was the so-called "English mutant", which differs from the normal beta-amyloid peptide by only one amino acid substitution. With the help of NMR, scientists were able to understand in detail the ongoing chemical processes and structural changes during the binding of the peptide with zinc ions and further aggregation.

The second pathogen studied was an isomerized beta-amyloid peptide. The chemical composition of the UN does not differ from a normal human peptide, but one of its amino acid residues, aspartic acid, is a molecule with a different arrangement of atoms.

Such isomerization occurs spontaneously, without the participation of enzymes, and therefore is associated with the aging process — another important factor in the development of Alzheimer's disease.

Colleagues from the Institute of Molecular Biology RAS recently showed that the administration of an isomerized peptide to transgenic mice quickly leads to the formation of amyloid plaques in them. In the presence of zinc ions, the metal-binding domain of this peptide aggregated so quickly that the resulting structures simply did not have time to detect.

Though scientists managed to distinguish that despite all the differences in processes occurring to the 'English mutant' and isomerized peptide in presence of zinc ions, initial stages of these transformations were similar.

In both cases, the trigger turned out to be the same — the role of pathogenic aggregation embryos in both cases was played by pathogenic peptide dimers formed at the very beginning, i.e. two peptide molecules bonded by a zinc ion.

The same dimers were observed in the case of a normal human peptide, and the differences for all the studied forms were associated with the rate of dimer formation and their tendency to further aggregation.

Based on this similarity, the researchers developed a proposed mechanism for the zinc ion-controlled procedure for converting a protective peptide into a killer peptide. As the scientists note, this mechanism explains many experimental facts obtained not only by them, but also by their colleagues in other laboratories studying Alzheimer's disease. Scientists also hope that their discovery due to the precise choice of the target will help to create new drugs that can block the aggregation of beta-amyloid peptides initiated by zinc ions.