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Currently, about 35 million people suffer from AD worldwide. Those afflicted are confronted with the loss of function and eventual death of their nerve cells, a process which leads to the progressive loss of memory and to dementia. Inheritable (familial) forms of AD are rare. "About 0.5 - 1 per cent, Professor Willnow estimates. Still, familial forms of the disease are informative for science as they provide insight into the diseases genetic causes, which probably also play a role in the sporadic form of AD. Sporadic AD is the common form of age-related dementia affecting the vast majority of patients, but its causes are still unclear.
The major culprit in the occurrence of AD is a short protein fragment called amyloid-beta peptide, or A-beta for short. A-beta is produced in the nerve cells from the amyloid precursor protein (APP), a larger protein that is cut into pieces by molecular scissors (secretases). The production of A-beta is a normal physiological process which occurs in the brain of every healthy human being. The reason for the production of A-beta is still a matter of debate, but recent findings suggest that this peptide reduces the activity of nerve cells in order to keep them from overreacting.
A-beta becomes a problem when too much is produced, as is the case in the brain of patients at risk of AD. Overproduction of this peptide impairs the communication between nerve cells, causing memory deficits and cognitive impairment. In addition, too much A-beta results in the deposit of plaques in the brain that damage nerve cells even further. "Since the amount of A-beta in the brain constantly rises with the age of the individual, the risk of developing AD increases dramatically in ageing societies, Professor Willnow explains.
Nerve cells produce protecting factor
Several years ago, Professor Willnows research group discovered that healthy neurons produce a factor which reduces the production of A-beta. This factor is the transport molecule SORLA (sorting protein-related receptor). They showed that mice that do not produce SORLA due to a gene defect accumulate more A-beta than normal mice. The researchers found the same phenomenon in humans: the amount of SORLA produced in the brain of AD patients was often lower than in the brain of individuals not suffering from dementia.
"Genetic studies by many research groups around the world support this hypothesis, says Professor Willnow. These studies show that specific gene variations of SORLA which cause reduced production of this protecting factor are more often seen in AD patients than in others. This observation suggests that the brain of some individuals produces too little SORLA. "Their risk of developing AD is higher, Professor Willnow points out. He assumes that high levels of SORLA in the brain slow down the process of AD, whereas low levels of SORLA increase the risk of the disease.
Proven: High levels of SORLA dramatically reduce A-beta
To test their hypothesis, Professor Willnow and his colleagues now wanted to find out if the brain really is protected from A-beta production when levels of SORLA are increased. For this purpose, they generated mice that carry an extra copy of the gene for SORLA in their genome. These transgenic mice not only produced four times as much SORLA in nerve cells as normal mice. Their increased levels of SORLA also drastically reduced the production of A-beta. With this experiment the researchers in Berlin were able to demonstrate that increased production of SORLA indeed protects the brain from too much A-beta.
Protecting factor already active within the nerve cells
In their studies Professor Willnow and his colleagues also uncovered how SORLA works. Normally, A-beta is released from producing cells in order to regulate the communication between the nerve cells. Now the researchers demonstrated that SORLA already gets hold of newly produced A-beta within the nerve cell. SORLA binds A-beta and transports it into a kind of cellular shredder, the lysosomes. "SORLA shuttles some A-beta into the lysomes and reduces the amount of A-beta that is released. Consequently, less A-beta accumulates in the brain and the damage to nerve cells is reduced, Professor Willnow points out.
Findings also important for familial AD
The importance of these findings in transgenic mice for the human disease was further underscored when Professor Willnows group studied one particular mutation in the human SORLA gene found by French researchers in a family suffering from an inheritable form of AD. "We were able to show that the mutation is located exactly where SORLA binds to A-beta. In patients who carry this particular mutation SORLA cannot bind A-beta and shuttle it to lysosomes for destruction. Too much A-beta makes its way out of the nerve cells and increasingly blocks their communication, Professor Willnow points out.
Screening for small molecules
"Now we are looking for small molecules which are able to increase the production of SORLA in the human brain. In the long run, those substances may be used to protect the brain of patients from overproduction of A-beta and slow down the progression of dementia, Professor Willnow hopes.
*Lysosomal Sorting of Amyloid-b by the SORLA Receptor Is Impaired by a Familial Alzheimers Disease Mutation
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gewonnenen Erkenntnisse möglichst rasch in die Anwendung zu überführen.