Researchers identify 'neurostatin' that may reduce the risk of Alzheimer's disease

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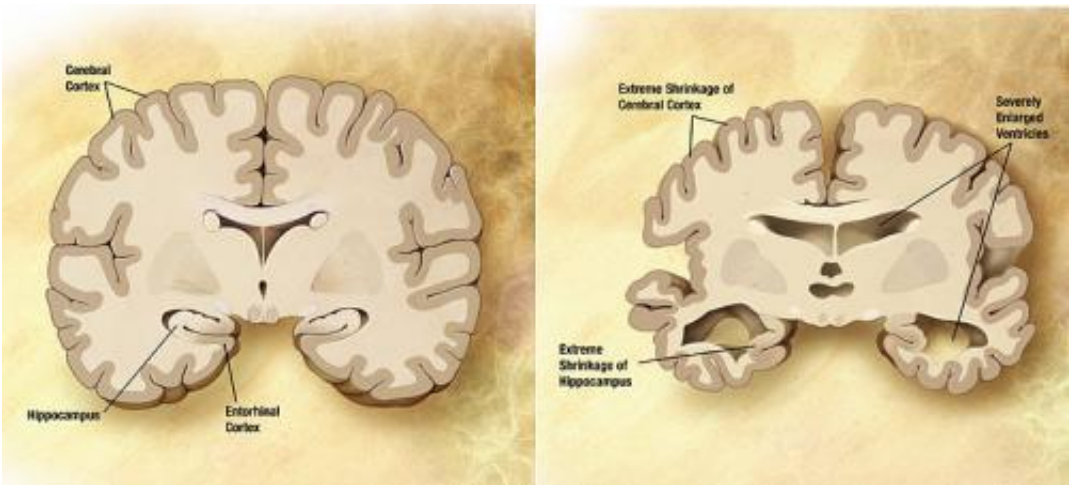

Diagram of the brain of a person with Alzheimer's Disease. Credit: Wikipedia/public domain.

Researchers have identified a drug that targets the first step in the toxic chain reaction leading to the death of brain cells, suggesting that treatments could be developed to protect against Alzheimer's disease, in a similar way to how statins are able to reduce the risk of developing heart disease.

The drug, which is an approved anti-cancer treatment, has been shown to delay the onset of Alzheimer's disease, both in a test tube and in nematode worms. It has previously been suggested that statin-like drugs - which are safe and can be taken widely by those at risk of developing

disease - might be a prospect, but this is the first time that a potential 'neurostatin' has been reported.

When the drug was given to nematode worms genetically programmed to develop Alzheimer's disease, it had no effect once symptoms had already appeared. But when the drug was given to the worms before any symptoms became apparent, no evidence of the condition appeared, raising the possibility that this drug, or other molecules like it, could be used to reduce the risk of developing Alzheimer's disease. The results are reported in the journal *Science Advances*.

By analysing the way the drug, called bexarotene, works at the molecular level, the international team of researchers, from the University of Cambridge, Lund University and the University of Groningen, found that it stops the first step in the molecular cascade that leads to the death of brain cells. This step, called primary nucleation, occurs when naturally occurring proteins in the body fold into the wrong shape and stick together with other proteins, eventually forming thin filament-like structures called amyloid fibrils. This process also creates smaller clusters called oligomers, which are highly toxic to nerve cells and are thought to be responsible for brain damage in Alzheimer's disease.

"The body has a variety of natural defences to protect itself against neurodegeneration, but as we age, these defences become progressively impaired and can get overwhelmed," said Professor Michele Vendruscolo of Cambridge's Department of Chemistry, the paper's senior author. "By understanding how these natural defences work, we might be able to support them by designing drugs that behave in similar ways."

For the past two decades, researchers have attempted to develop treatments for Alzheimer's that could stop the aggregation and proliferation of oligomers. However, these attempts have all failed, in

part because there was not a precise knowledge of the mechanics of the disease's development: Vendruscolo and his colleagues have been working to understand exactly that.

Using a test developed by study co-author Professor Tuomas Knowles, also from the Department of Chemistry, and by Professor Sara Linse, from Lund University, the researchers were able to determine what happens during each stage of the disease's development, and also what might happen if one of those stages was somehow switched off.

"In order to block protein aggregation, we need accurate understanding of exactly what is happening and when," said Vendruscolo. "The test that we have developed not only measures the rates of the process as a whole, but also the rates of its specific component sub-processes, so that we can reduce the toxicity of the aggregates rather than simply stopping them forming."

Johnny Habchi, the first author of the paper, and colleagues assembled a library of more than 10,000 small molecules which interact in some way with amyloid-beta, a molecule that plays a vital role in Alzheimer's disease.

Using the test developed by Knowles and Linse, the researchers first analysed molecules that were either drugs already approved for some other purpose, or drugs developed for Alzheimer's disease or other similar conditions which had failed clinical trials.

The first successful molecule they identified was bexarotene, which is approved by the US Food and Drug Administration for the treatment of lymphoma. "One of the real steps forward was to take a molecule that we thought could be a potential drug and work out exactly what it does. In this case, what it does is suppress primary nucleation, which is the aim for any neurostatin-type molecule," said Vendruscolo. "If you stop the

process before aggregation has started, you can't get proliferation."

One of the key advances of the current work is that by understanding the mechanisms of how Alzheimer's disease develops in the brain, the researchers were able to target bexarotene to the correct point in the process.

"Even if you have an effective molecule, if you target the wrong step in the process, you can actually make things worse by causing toxic protein assemblies to build up elsewhere," said study co-author Professor Chris Dobson, Master of St John's College, University of Cambridge. "It's like traffic control - if you close a road to try to reduce jams, you can actually make the situation worse if you put the block in the wrong place. It is not necessarily the case that all the molecules in earlier drug trials were ineffective, but it may be that in some cases the timing of the delivery was wrong."

Earlier studies of bexarotene had suggested that the drug could actually reverse Alzheimer's symptoms by clearing amyloid-beta aggregates in the brain, which received a great deal of attention. However, the earlier results, which were later called into question, were based on a completely different mode of action - the clearance of aggregates - than the one reported in the current study. By exploiting their novel approach, which enables them to carry out highly quantitative analysis of the aggregation process, the researchers have now shown that compounds such as bexarotene could instead be developed as preventive drugs, because its primary action is to inhibit the crucial first step in the aggregation of amyloid-beta.

"We know that the accumulation of amyloid is a hallmark feature of Alzheimer's and that drugs to halt this build-up could help protect nerve cells from damage and death," said Dr Rosa Sancho, Head of Research at Alzheimer's Research UK. "A recent clinical trial of bexarotene in

people with Alzheimer's was not successful, but this new work in worms suggests the drug may need to be given very early in the disease. We will now need to see whether this new preventative approach could halt the earliest biological events in Alzheimer's and keep damage at bay in in further animal and human studies."

Over the next 35 years, the number of people with Alzheimer's disease is predicted to go from 40 million to 130 million, with 70% of those in middle or low-income countries. "The only way of realistically stopping this dramatic rise is through preventive measures: treating Alzheimer's disease only after symptoms have already developed could overwhelm healthcare systems around the world."

The body has a number of natural defences designed to keep proteins in check. But as we get older, these processes can become impaired and get overwhelmed, and some proteins can slip through the safety net, resulting in Alzheimer's disease and other protein misfolding conditions. While neurostatins are not a cure for Alzheimer's disease, the researchers say that they could reduce its risk by acting as a backup for the body's natural defences against misfolding proteins.

"You wouldn't give statins to someone who had just had a heart attack, and we doubt that giving a neurostatin to an Alzheimer's patient who could no longer recognise a family member would be very helpful," said Dobson. "But if it reduces the risk of the initial step in the process, then it has a serious prospect of being an effective preventive treatment."

But is there hope for those already affected by the disease? The methods that have led to the present advance have enabled the researchers to identify compounds that, rather than preventing the disease, could slow down its progression even when symptoms have become evident. "The next target of our research is also to be able to treat victims of this dreadful disease," said Vendruscolo.

More information: An anticancer drug suppresses the primary nucleation reaction that produces the toxic Aβ42 aggregates linked with Alzheimer's disease , dx.doi.org/10.1126/sciadv.1501244