Abstract:
Researchers at Aarhus University, Denmark, have drawn up the most detailed 'image of the enemy' to date of one of the body's most important players in the development of Parkinson's disease. This provides much greater understanding of the battle taking place when the disease occurs - knowledge that is necessary if we are to understand and treat Parkinsonism. However, it also raises an existential question because part of the conclusion is that we do not live forever!

Know your enemy: Oligomers' role in the development of Parkinson's disease

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Parkinson's disease is one of the most common neurological disorders, with about 7000 people suffering from the disease in Denmark alone. There is no cure, and the symptoms continue to get worse. The disease occurs because different nerves in the brain die. These include the nerve cells that form dopamine, which is known as the brain's 'reward substance' and which also helps control our fine motor skills.

A group of researchers from Aarhus University, the University of Southern Denmark (SDU) and the University of Cambridge has just published two studies in the prestigious Journal of the American Chemical Society (JACS) and Angewandte Chemie. These studies provide the best insight to date into the behaviour of a particular protein state that plays an important role in Parkinson's disease. In other words, they have created a detailed image of what is presumed to be the arch enemy we are up against in our understanding of Parkinsonism. It is an advanced antagonist, and one that functions with a considerable degree of unpredictability. "Fighting the enemy is by no means a Sunday outing," say the main authors of the results - Professor Daniel Otzen, Aarhus University, and his colleagues Nikolai Lorenzen and Wojciech Paslawski, who recently defended their PhD dissertations on this subject at Aarhus University's Interdisciplinary Nanoscience Centre (iNANO).

Protein aggregation kills nerve cells

Knowledge about what actually takes place in the brain when Parkinson's disease occurs and develops is absolutely necessary, not only for the prevention and treatment of symptoms, but also for possibly developing a cure one day.

However, getting to know the enemy is no easy task when it comes to understanding Parkinson's disease. The more we find out, the more complex the image becomes.

We already know that the disease - as well as other neurological disorders - arises because some protein structures in the body start clumping together. They stack themselves on top of each other and gradually form what are known as fibrils - long, thin needle-shaped structures. From a biochemical point of view, this is quite a boring process because the protein structures simply pile themselves on top of each other and - in principle - can continue to do so forever.

It is far more interesting to look at the intermediate stages leading up to the aggregation. It turns out here that when the proteins form fibrils, a kind of intermediate aggregation process also takes place to form oligomers, which consist of a small number of protein molecules that clump together. It is presumably the oligomers that kill the nerve cells and cause the symptoms of Parkinson's disease. So oligomers are the enemy we want to control.

Ground-breaking new knowledge about the enemy

In their two studies, the researchers from Aarhus University, the University of Southern Denmark and the University of Cambridge provide the most well-documented description of oligomers to date. Until now, the general perception was that oligomers were precursors of the fibrils. As it turns out, however, it is rather the antagonists or competitors of the fibrils that are the precursors, and these are capable of slowing down the formation of fibrils.

The researchers discovered that there are different kinds of oligomers. If we look at the size, there are two types that are quite intimately connected. A somewhat small oligomer that is very well defined and a larger one that is virtually a chain composed of the smaller ones. The oligomers are thus capable of linking up in the same way as the fibrils, but in chains that inhibit the fibrils. "You could say that they put a spanner in the works regarding the formation of fibrils," says Professor Otzen. It could possibly be a help to shift the focus even further away from the fibrils, which are formed in a different process than the oligomers, and which should not be a target for pharmaceutical products on their own.

Description of the enemy
So what does our adversary look like? The researchers can now help provide us with a better answer. An oligomer consists of a very stable interior and a more diffuse sphere surrounding it, where the protein is not as compact and where it flaps around a little.

And yet the image is even more complicated than that! Because if you take a closer look at the little oligomer, there are also two types here. To study this, the researchers used very advanced mass spectrometric techniques carried out together by Associate Professor Thomas Jørgensen and PhD student Simon Mysling at SDU. Associate Professor Jørgensen's group consists of world experts in hydrogen-deuterium exchange (HDX), which can be used to study how flexible or loosely structured the different parts of a protein are. It turns out that two different oligomers with different degrees of flexibility can be present at the same time. One type admittedly 'flaps around' more than the other, but it is nevertheless very stable and does not turn into fibrils because it is unable to 'absorb' monomer proteins and thereby grow bigger. This oligomer simply clumps together to form larger oligomers, and is the dominating (and toxic) type, corresponding to the structure shown above. The other type (which only accounts for 10% of the total oligomer population) is capable of absorbing monomers and becoming (harmless) fibrils.

"You can't say that we've now solved the puzzle of Parkinson's disease. Of course we haven't," says Professor Otzen. "But we've come much further in our understanding of an important player in the disease. We know what it looks like, how it arises and how it affects the formation of other fibrils," he adds.

"Knowing what the enemy looks like provides us with better tools to fight it. It's a very shrewd and sneaky adversary because it combines a compact nucleus with a diffuse shell," says Professor Otzen. "We haven't yet found its Achilles heel, but we've gained a much better starting point for interpreting what happens, and understanding the substances that can bind to the oligomers. We'll be able to study whether there are substances that can jog the distribution of oligomers, for example, so that they 'suppress' the formation of the toxic oligomers and boost the formation of the harmless type that can go on to become fibrils," he concludes. This knowledge is useful in the work to develop pharmaceuticals and in the understanding of Parkinson's disease. The research can be better targeted, but based on the slogan that the more you know, the more complex things can often be. Even though we know the enemy, we do not yet know how to nail it.

The existential aspect

Back to the question of the existential aspect, because conditions like Parkinson's disease are to a great extent an expression of human progress and well-being.

What is so special about oligomers is that they have no purpose in the body. They are not designed to do anything in particular. Protein aggregation is basically an expression of a system error in the body that shows the system is getting old and tired. This means there is not necessarily a simple explanation of why the oligomers occur. In a way, they are the shady side of the proteins' ability to make beautiful structures because this also provides them with an opportunity to make wrong structures.

The fact that they start to be tricky is to a large extent a matter of getting older and older. We used to wear out earlier and we died much younger before the body's 'system error' started to play up. We can now grow to be very old, but our bodies are by no means designed to be so old. We should therefore not expect a simple explanation of why conditions like Parkinson's disease arise, even though we are now in better control of the oligomers. Parkinson's is a kind of 'wear and tear' situation and, just from our own car mechanic, we know that there are numerous different ways a car can be worn out - and the same applies here. "In a way, it's very existential. We can't live forever, and this is one explanation of why not," says Professor Otzen. "This type of thing just starts to happen when we get old, but we can hopefully postpone and minimise the consequences so that we can remain hale and hearty to an even greater extent when we reach a ripe old age," he adds.

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About the studies

The JACS study involves a collaboration between Daniel Otzen's Protein Biophysics Group, headed by Professor Jan Skov Pedersen, also from iNANO at Aarhus University, working with SAXS techniques, and a group headed by Tuomas Knowles and Chris Dobson from the University of Cambridge, who work with studies of protein aggregation. The study published in Angewandte Chemie involved very close collaboration with Associate Professor Thomas Jørgensen and PhD student Simon Mysling at the University of Southern Denmark.
For more information, please click here

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