Small error, dramatic effects

Proteins are vital: these complex biomolecules ensure the smooth operation of our metabolism and immune defence, for example. However, small deviations in their molecular structures can lead to severe diseases such as Parkinson's or Alzheimer's. In our Interview, Jülich biochemist Prof. Dieter Willbold talks about the dramatic effects of these small errors.

Loss of memory due to Alzheimer's, impaired movement caused by Parkinson's, high blood sugar levels from diabetes – these ailments don't have an immediately obvious connection. And yet, they are often mentioned in the same breath at your institute, Prof. Willbold – why is that?
The symptoms are different, but the causes are similar on the molecular level: the molecules of certain – generally harmless – proteins accumulate and form aggregates which then have damaging effects on the body. These aggregations are the beginning of the respective disease. Different proteins and organs are affected, but the underlying phenomenon of aggregation is always the same. We want to understand why proteins produced by the body itself thus become disease triggers.

Are there other diseases where this plays a role?
Yes, we know of many such diseases. Neurodegenerative conditions, which damage the brain and nervous system, are particularly prominent among them. Apart from Alzheimer's and Parkinson's, from which many millions of people suffer, there are also very rare but severe diseases caused by these conditions. Examples include amyotrophic lateral sclerosis (ALS) – the disease that physicist Stephen Hawking suffers from – as well as Huntington's and Creutzfeldt-Jakob disease.

↑ American actor Michael J. Fox has suffered from Parkinson's since 1991. A foundation he established raises and awards funding for Parkinson's research.

← Prof. Dieter Willbold heads the Institute of Complex Systems – Structural Biochemistry.

Is it known what causes these protein aggregations?
They're connected to malformed molecular structures. Proteins are precision tools in the body, with precisely defined functions and complex, three-dimensional structures suited to their exact purpose. Even very small deviations can cause an aggregation. What's fatal is that the proteins not only lose their original function in their aggregated form, but frequently acquire new, damaging properties – for example, they can become toxic and then damage nerve cells. In order to understand what distinguishes the structures of healthy, correctly working proteins from that of pathologically altered ones, we need ultrahigh-resolution images of their molecular structures. At Jülich, we use methods such as NMR spectroscopy for this purpose, which – ideally – shows us the position of every single atom in a molecule.

In research, the connection between Alzheimer's disease and diabetes is discussed intensively; some scientists even call Alzheimer's "type 3 diabetes". Why is that?
There are observations that patients suffering from type 2 diabetes mellitus, the form that makes up around 90 percent of all diabetes cases, far more frequently also develop Alzheimer's disease than other people. Conversely, patients suffering from Alzheimer's often develop diabetes. Statistically, these two diseases are risk factors for each other. The cause remains unknown – perhaps permanently raised blood sugar levels make a person more susceptible to Alzheimer's, or maybe other lifestyle factors promote both diseases. In the past few years, it has been shown, however, that the proteins responsible for the respective disease can also interact directly.

Could this mean that there is a connection between the two diseases on a molecular level?
We know too little so far to identify conclusive connections. But needless to say, indications such as these should be further pursued nonetheless. It's important that interactions between the various disease-specific proteins now gain increasing importance in research – also for very practical questions on dealing with these diseases.

For example?
For example the early diagnosis of neurodegenerative diseases. Unlike diabetes, where we can measure the higher blood sugar levels, we have yet to identify a biomarker for Alzheimer's and Parkinson's – a reliable indicator for the disease, measurable at an early stage. We are forced to go by the diseases' symptoms – and they are not very reliable, especially in the beginning. This is why we have developed an extremely sensitive procedure for the detection and analysis of protein aggregates, with the aim of using them as diagnostic biomarkers.

And protein interactions would be a problem?
Unknown interactions or overlaps between the aggregates could actually be detrimental. We have recently received funding from a joint initiative of the American Alzheimer's Association and the Michael J. Fox Foundation for Parkinson's Research to investigate these issues using our system.

If the basic principle of these diseases is similar, is it then conceivable that one drug could show effects on several of them?
If the drug were to affect the process of aggregation itself, and not only the symptoms, then yes. Wolfgang Hoyer's research group at our institute, for example, has developed a molecule which can shield certain areas of protein molecules. At least in laboratory experiments, the aggregation of the proteins relevant to Alzheimer's, Parkinson's, and type 2 diabetes was successfully inhibited. We are hoping that a new drug candidate against Alzheimer's which we are developing at Jülich will also exhibit this effectiveness across diseases.

How far is this drug candidate in development?
We know that the substance eliminates the particularly toxic aggregate forms and we have collected a lot of information on its tolerability and effectiveness in various model organisms. We are about to apply for the first clinical trials, during which its safety will be tested in humans. If it can later be confirmed in patients that our molecule is indeed effective against Alzheimer's, then we'll try to transfer the principle to Parkinson's, Huntington's, and ALS.

THE INTERVIEW WAS CONDUCTED BY PETER ZEKERT.